An economic analysis of safe surgery in low- and middle- income countries: a case study of surgical site infection

by

Mark Monahan

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Health Economics Unit
Department of Applied Health Sciences
College of Medicine and Health
University of Birmingham

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Abstract

Introduction

Surgical Site Infection (SSI) is a common postoperative complication and is associated with substantial financial and quality of life consequences. Numerous logistical challenges make accurate quantification of SSI-related costs and outcomes difficult. SSI has a higher incidence rate in low- and middle- income countries (LMICs) relative to high income countries. This along with efforts to increase the volume of surgeries to address unmet surgical need in LMIC settings gives a more pressing focus on postoperative surgical outcomes. The reduction of postoperative complications is a key outcome measure for safe surgery. For decision makers in resource-constrained environments, it is important to know whether investments in safe surgery represent a worthwhile use of health care resources given the opportunity cost of those healthcare resources.

Thesis aim

The thesis uses primary and secondary research sources to answer the research question: What is the economic rationale for investing in safe surgery interventions to reduce SSI in LMICs?

Methods

Separate systematic reviews on the costs and utility decrement of SSI were undertaken to populate a preliminary economic model to assess the cost-effectiveness of SSI prevention interventions using 'best guess' estimates. The model was further refined using cost and quality of life estimates from a re-analysis of an SSI Randomised Control Trial (RCT). Next, the cost and quality of life implications of SSI were ascertained from primary research by i) generating health state valuations associated with SSI, and ii) collecting costs associated with SSI in a sub study of a multinational RCT. The preliminary economic model was then

updated with the primary research data to assess the economic rationale of safe surgery interventions to reduce SSI in LMICs.

Results

The base case results of the preliminary decision analytic model indicated that both exemplar interventions were cheaper and more effective than Usual Care and the results were robust to sensitivity analyses across the examined settings. Refining the preliminary model-based economic evaluation with the RCT re-analysis did not change the decision recommendation. For the primary data collection, an SSI was associated with additional postoperative costs in patients undergoing abdominal surgery across Ghana, Mexico, Nigeria, and India. Specially constructed vignettes to describe different severity levels of SSI were successfully valued with the general public remotely using different health state valuation techniques.

For the final updated model with one exception, one or more of the SSI prevention interventions were cost-effective versus Usual Care but these varied by wound contamination. For the patient group in Mexico with Clean-Contaminated wounds, the results varied by outcome measure with Alcoholic Chlorhexidine being the most cost-effective strategy under the Cost per DALY averted approach and Usual Care being the most cost-effective strategy under the Cost per QALY approach.

Conclusion

An economic rationale in investing in safe surgery interventions to reduce SSI in LMICs was uncovered. Despite possible transferability issues with the cost, utility and treatment effectiveness data, the decision recommendations of preliminary economic modelling did not change when the model was iteratively refined with more suitable LMIC data.

Declaration

This is to certify that:

i. This thesis comprises only my original work towards the Degree of Doctor of Philosophy;

ii. Due acknowledgement has been made in the text to all other material used;

iii. The thesis is fewer than 80,000 words in length, exclusive of tables, figures, references, and appendices.

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Chapter 3

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Chapter 7

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List of abbreviations

AIC	Akaike information criterion	ICER	Incremental Cost-effectiveness Ratio
ASA grade	American Society of Anaesthesiologists grade	IMF	International Monetary Fund
ASCOT	Adult Social Care Outcomes Toolkit	IPD	Individual Participant Data
BMI	Body Mass Index	IQR	Interquartile Range
BNF	British National Formulary	ITU	Intensive Therapy Unit
CABG	Coronary Artery Bypass Graft	LMIC	Low- and Middle- Income Countries
CBA	Cost Benefit Analysis	LOS	Length of stay
CCA	Cost Consequence Analysis	MRSA	Methicillin-resistant Staphylococcus aureus
CDC	Center of Disease Control	NHS	National Health Service
CEA	Cost-effectiveness Analysis	NMB	Net Monetary Benefit
CEAC	Cost-effectiveness Acceptability curve	NNIS	Nosocomial Infection Surveillance System risk index
CHEC	Consensus on Health Economic Criteria	OECD	The Organisation for Economic Co-operation and Development
CI	Confidence Interval	PI	Prediction Intervals
COI	Cost of Illness	PPP	Purchasing Power Parity
CRF	Case Report Form	PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
CUA	Cost-utility Analysis	PSA	Probabilistic Sensitivity Analysis
DAIR	Debridement and implant retention	PSSRU	Personal Social Services Research Unit
DALY	Disability Adjusted Life Year	QALM	Quality Adjusted Life Month
DCE	Discrete Choice Experiments	QALY	Quality Adjusted Life Year
DES	Discrete Event Simulation	QWB	Quality of Wellbeing
DRG	Diagnosis-related group	RCT	Randomised Control Trial
DSA	Deterministic Sensitivity Analysis	Redcap	Research Electronic Data Capture
ENBS	Expected Net Benefit of Sampling	SD	Standard Deviation

EVPI	Expected value of perfect information	SDG	Sustainable Development Goals
EVPPI	Expected Value of Perfect Parameter Information	SE	Standard Error
EVSI	Expected Value of Sample Information	SF-36	Short Form Thirty Six
GBD	Global Burden of Disease	SF-6D	Short Form Six dimensions
GDP	Gross Domestic Product	SG	Standard Gamble
GNP	Gross National Product	SSI	Surgical Site Infection
GP	General Practitioner	THA	Total hip arthroplasty
GRADE	Grading of Recommendations Assessment, Development and Evaluation	TTO	Time Trade Off
HAI	Hospital Acquired Infection	VAS	Visual Analogue Scale
HDU	High Dependency Unit	VOI	Value of Information
HIC	High Income Countries	WHO	World Health Organisation
HPA SSISS	Health Protection Agency SSI surveillance system	WTA	Willingness to Accept
HRQOL	Health related Quality of Life	WTP	Willingness to Pay
HTA	Health Technology Assessment	YLD	Years Lived with Disability
HUI	Health Utility Index	YLL	Years of Life Lost

Chapter 1:

Introduction

Surgery is an essential component of comprehensive healthcare and plays a critical role in averting mortality and morbidity. It is a crucial treatment modality for a wide range of diseases and medical conditions. Many life-threatening or debilitating conditions, such as cancer, heart disease, appendicitis, and trauma-related injuries, often require surgical intervention for effective treatment and management. However, complications after surgery can delay recovery, consume additional scarce health care resources and have a detrimental impact on a patient's length of life and quality of life [1,2]. The most common hospital acquired infection is surgical site infection (SSI). SSI is a particular problem in Low- and Middle- Income Countries (LMIC) due to a higher incidence rate [3,4] coupled with a greater share of patient out-of-pocket health care expenditure [5] compared to High Income Countries (HIC). LMIC and HIC are World Bank classifications which group countries by their gross national income per capita [6] with LMICs being an combination of low, lower-middle, and upper-middle income country categories.

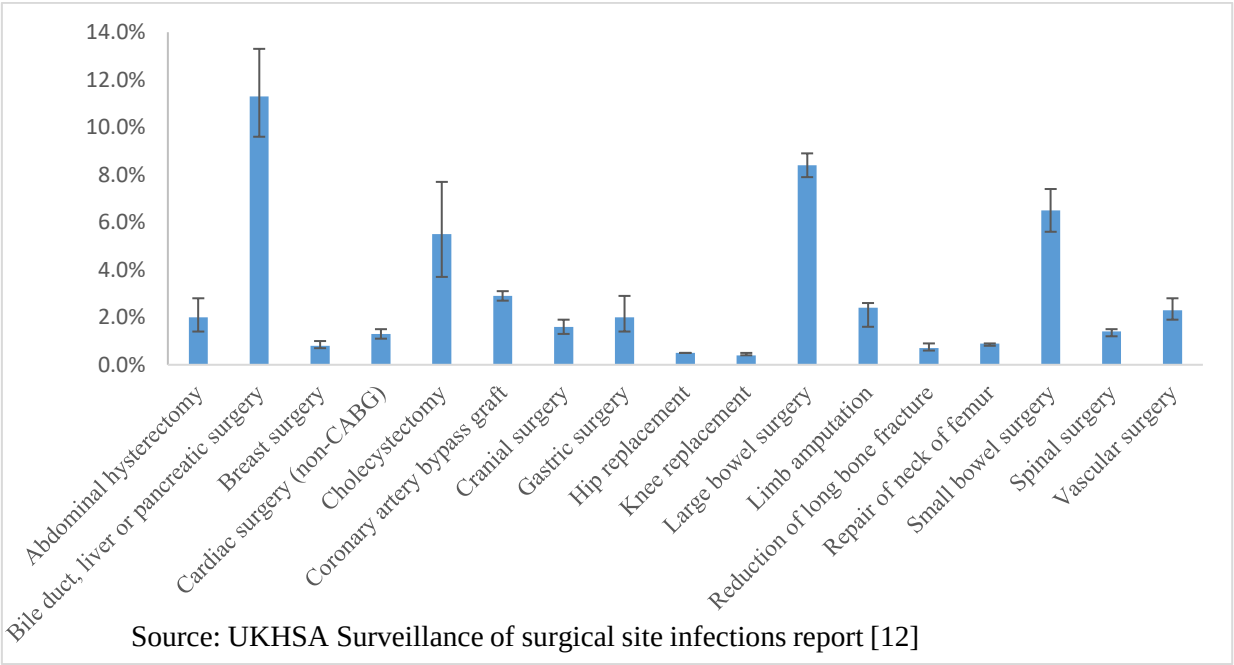
This thesis seeks to investigate the economic rationale for reducing complications after surgery in LMICs and uses SSI as a case study. The rest of this chapter describes SSI and the current surgical challenges faced by many LMICs. This is followed by an outline of the thesis' aims and objectives and concludes with an outline of the structure and content of the subsequent chapters.

1.1 Description of surgical site infection

SSI is a wound infection that arises at, or close to the site of, the surgical incision following a surgical procedure. SSI is caused by microorganisms that contaminate the surgical site either during or after the surgery. These microorganisms may come from the patient, the surgical team, the surgical instruments, or the environment. SSI can delay healing of the wound and is associated with increased morbidity and mortality [7].

There are opportunities to decrease the risk of an SSI: (i) before surgery (preoperative stage), (ii) during surgery (intraoperative stage), and (iii) after surgery (postoperative stage). Preoperative interventions to reduce the development of SSI include Methicillin-resistant Staphylococcus aureus (MRSA) screening and decolonization procedures for carriers; prophylactic antibiotics; bathing; hair removal at surgical site, and skin antiseptic preparation [8]. Intraoperative interventions include sterilization of surgical instruments; antimicrobial skin sealants; optimising tissue oxygenation; different surgical wound closure techniques, and protective coverings worn by surgical staff to maintain a sterile operative environment [9]. Postoperative interventions include wound dressing strategies [10], and continuing prophylactic antibiotics [11].

The type of surgical procedure has an impact on the risk of developing an SSI. SSI surveillance data for NHS England are illustrated in Figure 1.1. The reported risk of SSI in knee (0.4%) or hip (0.5%) replacement surgery is significantly lower than large bowel surgery (8.4%), or bile duct, liver or pancreatic surgery (11.3%) [12].



Source: UKHSA Surveillance of surgical site infections report [12]

Figure 1.1 SSI risk spanning April 2016 to March 2021 in NHS hospitals in England

A reason for the disparity in SSI risk across procedures is likely to be the degree of wound contamination at time of surgery. Using a standard ordinal grading system (Table 1.1) developed by the Centers for Disease Control and Prevention (CDC) to identify patients preoperatively at risk of an SSI [13], orthopaedic surgeries are generally associated with lower grades of wound class contamination compared to general surgery cases [12]. While subjectivity in these classifications can mean that the wound grading applied depends on which of the surgical theatre staff is making the assessment [14], surgical patients with a higher wound contamination are associated with a higher incidence of SSI [15,16]. Correlated to the wound contamination system, patients who present as an emergency case versus those who present as an elective case are associated with a higher risk of SSI [17].

Table 1.1 Surgical wound grade classifications

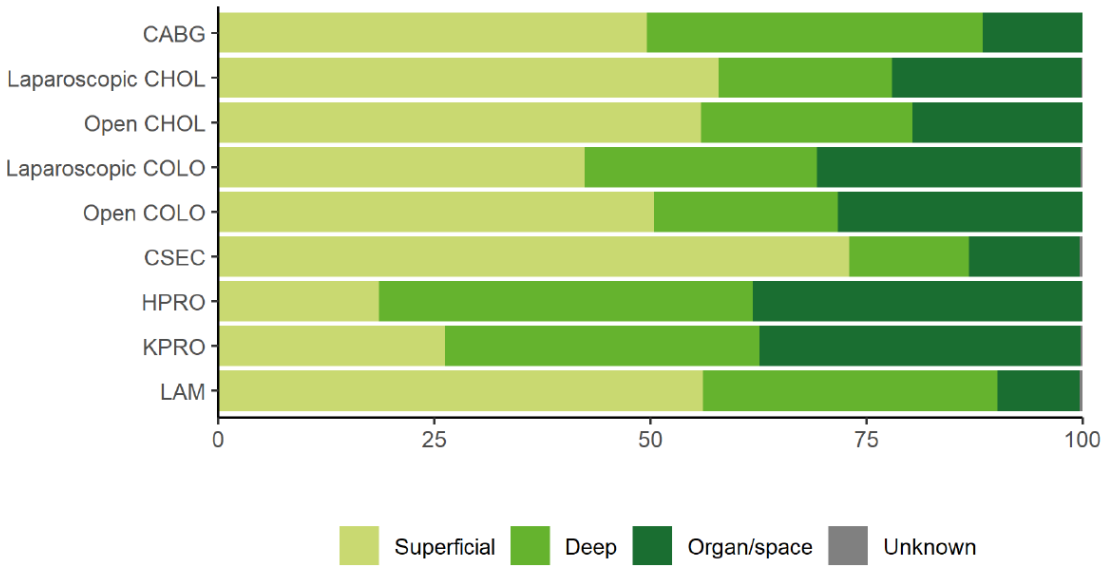
Wound Classification	Description
Class I / Clean	An uninfected operative wound in which no inflammation is encountered and the respiratory, alimentary, genital, or uninfected urinary tract is not entered. In addition, clean wounds are primarily closed and, if necessary, drained with closed drainage. Operative incisional wounds that follow nonpenetrating (blunt) trauma should be included in this category if they meet the criteria.
Class II / Clean-Contaminated	An operative wound in which the respiratory, alimentary, genital, or urinary tracts are entered under controlled conditions and without unusual contamination. Specifically, operations involving the biliary tract, appendix, vagina, and oropharynx are included in this category, provided no evidence of infection or major break in technique is encountered.
Class III / Contaminated	Open, fresh, accidental wounds. In addition, operations with major breaks in sterile technique (e.g., open cardiac massage) or gross spillage from the gastrointestinal tract, and incisions in which acute, non-purulent inflammation is encountered are included in this category.
Class IV / Dirty-Infected	Old traumatic wounds with retained devitalized tissue and those that involve existing clinical infection or perforated viscera. This definition suggests that the organisms causing postoperative infection were present in the operative field before the operation.
Source: CDC severity criteria for surgical site infection [13]	

Another risk factor for SSI relates to the duration of surgery. A longer surgical procedure time increases the exposure time and the potential for microorganisms to contaminate the surgical site. A systematic review found that procedure time increments of 15 minutes, 30 minutes, and 60 minutes increased the likelihood of SSI by 13%, 17%, and 37%, respectively [18].

1.1.1 Severity levels of surgical site infection

Not all SSIs are alike, so they are typically classified into one of three categories of the Centers for Disease Control and Prevention (CDC) severity criteria (Appendix Table A1.1): (i) superficial incisional SSI, (ii) deep incisional SSI, and (iii) deep incisional organ/space SSI. A more severe SSI has a greater depth of infection. Compared to superficial SSI, the risk of morbidity and mortality is higher for the patients diagnosed with either deep incisional SSI or organ/space SSI [7,19].

The distribution of the three SSI severity types varies across surgical procedure. This is borne out in a European SSI surveillance report across nine procedures (Figure 1.2). The report found that the highest proportion of superficial incisional SSI were for caesarean sections, whilst the highest proportion of deep incisional SSI, and organ/space SSI was for hip prosthesis surgery where the hip is replaced with a surgical implant [20].



Source: EU/EEA SSI surveillance report 2018-2020 [20]

CABG: coronary artery bypass graft; CHOL: cholecystectomy; COLO: colon surgery; CSEC: caesarean section; HPRO: hip prosthesis; KPRO: knee prosthesis; LAM: laminectomy

Figure 1.2 Distribution of SSI types by surgical procedure

The onset of an SSI differs and can occur before or after hospital discharge. For example, the median time to infection with NHS surveillance SSI data ranged from 6 to 23 days across reported procedures [12]. By the latest CDC definitions, they need to present within 30 days after surgery in in most cases or within 90 days after surgery for some procedures (Appendix Table A1.1). Previously, the detection window for SSI for operations without implants was stipulated to be up to 30 days post-surgery or up to 1 year post-surgery for operations with implants [21]. In terms of wound healing time, SSI resolution varied by severity with a superficial SSI taking a median 28 days (Interquartile range: 13 to 73.5 days) to completely heal versus a median 76.5 days (Interquartile range: 39 to 166 days) that it took for patients with a deep incisional or organ/space SSI in a fracture-related study [22].

1.1.2 Surgical site infection treatment

Treatment of an SSI depends on the severity of the infection and the causative microorganism. Antibiotics are the primary treatment, and the choice of antibiotic depends on the specific bacteria involved and its susceptibility to different antibiotics [23]. In more severe cases of SSI, debridement may also be necessary. Debridement is a medical procedure performed to remove dead, damaged, or infected tissue from a wound. The goal of debridement is to promote wound healing by creating an environment that supports tissue regeneration [24]. Where there is a collection of pus (abscess) from the surgical site, drainage may be required. This can involve a minor procedure to open the abscess, allowing the pus to then drain and the procedure can be also combined with a debridement [25].

1.1.3 Associated costs of SSI

SSI carries an additional financial burden. In the US alone, the annual attributable costs to SSI was estimated to be nearly $3.3 billion (2012 cost year) [26]. The healthcare resource use associated with SSI typically entails additional hospital length of stay, investigations, antibiotics, wound dressing changes, clinic visits, analgesic medication, hospital readmission and reoperations. Costs to patient and their wider family include productivity losses, travel costs, and informal caring [27]. Given that the first line of treatment of an SSI is antibiotics, there is an associated economic cost of contributing to the antibiotic resistance [28].

1.2 Surgery in a low- and middle- income countries context

While surgical care is an important consideration for health systems, with nearly 313 million operations estimated worldwide in 2012 [29], nearly five billion people are estimated to not have access to surgery [30]. Many countries fail to meet the basic surgical needs of their populations [31]. Most surgical provision is carried out in HICs and typically there is not enough surgery capacity to address demand in many LMICs [32–34]. In LMICs, shortfalls in surgical labour [35–38] and surgical infrastructure [39–42] limits the number of operations that can be performed; threatens the effectiveness of surgery, and can lead to adverse patient outcomes [43]. Patients that do undergo surgery in LMIC settings face higher levels of postoperative complications compared to high income settings [44]. The risk of acquiring an SSI substantially increases the overall risk of financial catastrophe- a situation in which health care spending is greater than 10% annual proportion of household expenditure [45]. Compounding the problem is that there is a higher antimicrobial resistance in LMIC settings [3] which makes it challenging to prevent and treat SSI.

Identifying appropriate solutions to combat SSI is of global interest [3,46,47]. Recently completed and ongoing research studies to find the most cost-effective prevention strategies for SSI, have had mixed success [10,48]. The majority of this research has been via randomised controlled trials (RCTs) with a parallel economic evaluation based in HIC [49,50]. Significant challenges hamper clinical trials in LMICs relating to lack of infrastructure and limited human resources [51]. This limits the data that can be feasibly collected in contrast to trials in HICs settings.

Population attitudes and behaviours towards surgeries

The cost of surgical treatment alone is not the sole barrier to patients. Attitudes and beliefs towards surgeries in LMICs can affect timely healthcare seeking. In Uganda, low rates of health literacy along with negative perceptions and fears of surgery being unsafe can delay healthcare seeking from patients [52]. When cataract surgery was provided for free, commonly identified barriers affecting the uptake of surgery to those who fear of surgery and complications in studies in Nigeria [53], rural Kenya, Zambia and Uganda [54]. Superstitious beliefs were another factor that can dissuade patients from undergoing surgery in the multi-country study based in rural Kenya, Zambia and Uganda [133], and this was also cited as a theme in Sierra Leone prospective surgical patients [134]. Distrust of the local surgery team was cited in a study based in rural Mexico [55], and Benin [56]. Linked to the surgical complications fear, perceptions on the expected improvement of health following surgery influenced a patient's decision to proceed with cataract surgery in the Kenya, Zambia and Uganda qualitative study [133]. Family support was an important surgery enabler in the Kenya, Zambia and Uganda qualitative study [133], and the Sierra Leone [57].

1.3 Safe surgery

Monitoring improvements of surgical care is part of the World Health Organisations (WHO) 100 Core Health Indicators [58], a list of global health metrics that tie into the Sustainable Development Goals (SDGs). SDGs are a set of 17 goals adopted by the United Nations in 2015 as part of the 2030 Agenda for Sustainable Development and serves as a framework for addressing major social, economic, and environmental challenges globally [59]. Specifically, surgical care is linked to SDG 3 which is to "ensure healthy lives and promote well-being for all at all ages" [59:pg14]. Strengthening surgical systems is acknowledged as a key consideration by the WHO in achieving the SDG 3 and the indicators relate to surgical timeliness, capacity, quality and affordability [60]. These indicators originated from the Lancet Commission on Global Surgery and call for increases in the surgical workforce, surgical procedures, protection against impoverishing or catastrophic expenditure for accessing surgical and anaesthesia care, and the tracking and setting of national targets for perioperative mortality [39]. However, even at current quality standards, the efforts to increase the volume of surgery will increase the absolute number of SSI cases which in turn weakens protection against catastrophic expenditure for accessing surgical and anaesthesia care.

Safe surgery refers to the implementation of comprehensive measures and protocols aimed at enhancing patient safety throughout the surgical process [61]. Reducing postoperative complications is a key outcome measure for safe surgery. However, for decision makers in resource-constrained environments, it is vital that they know whether investing in safe surgery represents a worthwhile use of health care resources. As there are alternative uses of healthcare resources instead of investing in improvements of patient outcomes in surgery, a

careful assessment of the costs and benefits associated with reducing postoperative complications is necessary to assess the economic merits of safe surgery.

1.4 Thesis aims and objectives

The overall thesis aim is to make an assessment of the economic rationale for investing in safe surgery to reduce postoperative complications in LMICs with SSI as a case study.

Specifically, the objectives are to:

1. Ascertain the costs and quality of life implications of SSI from the best available estimates in secondary sources;
2. Build a decision analytic model populated with the best available estimates from secondary sources to preliminarily assess the economic rationale for investing in safe surgery;
3. Ascertain the costs and quality of life implications of SSI from primary research by generating health state valuations associated with SSI and collecting costs associated with SSI;
4. Update the decision analytic model with the primary research data to assess the economic rationale of interventions to reduce SSI in LMICs.

1.5 Structure of the thesis

The rest of the thesis is organised into the following chapters:

Chapter 2 sets out the necessary groundwork with a background on the relevant theories and concepts pertaining to economic evaluations with a specific focus on undertaking them in LMICs, which serves to guide the understanding of the empirical literature and primary research in the Chapters which follow.

Chapter 3 and Chapter 4 present two systematic reviews of the literature on the costs and quality of life estimates associated with SSI respectively, and highlight the methodological challenges faced when quantifying the economic impact of SSI. With the cost and quality of life estimates obtained in the preceding Chapters, a preliminary economic model evaluates the costs and outcomes of implementing interventions to reduce SSI from a UK, Ghana, India and Mexico setting and is reported in Chapter 5. In Chapter 6, more robust estimates are developed from a re-analysis of a large SSI Randomised Control Trial in the UK. This Chapter concludes by assessing the impact of using these estimates within the preliminary model-based economic evaluation.

Chapter 7 presents the first stage of the primary research phase with the primary research collection of costs by SSI status in a multinational LMIC surgical trial. Chapter 8 reports the development and generation of quality of life estimates associated with SSI. Combining the information derived from Chapters 7 and 8, the model-based economic evaluation in Chapter 6 is refined a final time to assess the costs and outcomes of implementing an intervention to reduce SSI in LMICs using primary research and presented in the final section of Chapter 9. In Chapter 10 the objectives set out in Chapter 1 are revisited in order to present a discussion of the main findings and contribution of the thesis along with strengths, limitations, and policy recommendations.

Chapter 2:

Background

2.1 Introduction

The overall aim of this thesis is to assess the economic rationale for investing in safe surgery to reduce postoperative complications in Low- and Middle- Income Countries (LMICs) based on a case study of Surgical Site Infection (SSI). This chapter will provide the necessary context and background information for the various terms, concepts and theory related to an economic analysis of safe surgery in LMICs. An overview is provided on the health economic aspects, including the theoretical underpinnings behind economic evaluations and different methodological approaches that can be used to assess cost-effectiveness. An overview of preliminary economic evaluation modelling, which sheds light on both their use and helpfulness for informing decision making. Specifically, the role of decision analytic modelling in economic evaluations is highlighted. Issues specifically pertinent to surgical research and LMIC settings are highlighted where applicable.

2.2 Health economics and economic evaluations

Health economics is a subdiscipline within economics that seeks to understand how individuals, healthcare providers, insurers, and governments make decisions with respect to health and health care [62]. Figure 2.1 is an adapted version of the seminal "plumbing diagram" by Alan Williams [63]. This schematic illustrates the breadth of research areas within Health(care) Economics and the interactions between sections. The research focus of the thesis occupies Section B (What is Health? What is its Value?) and Section E (Micro-Economic Evaluation at the Treatment Level).

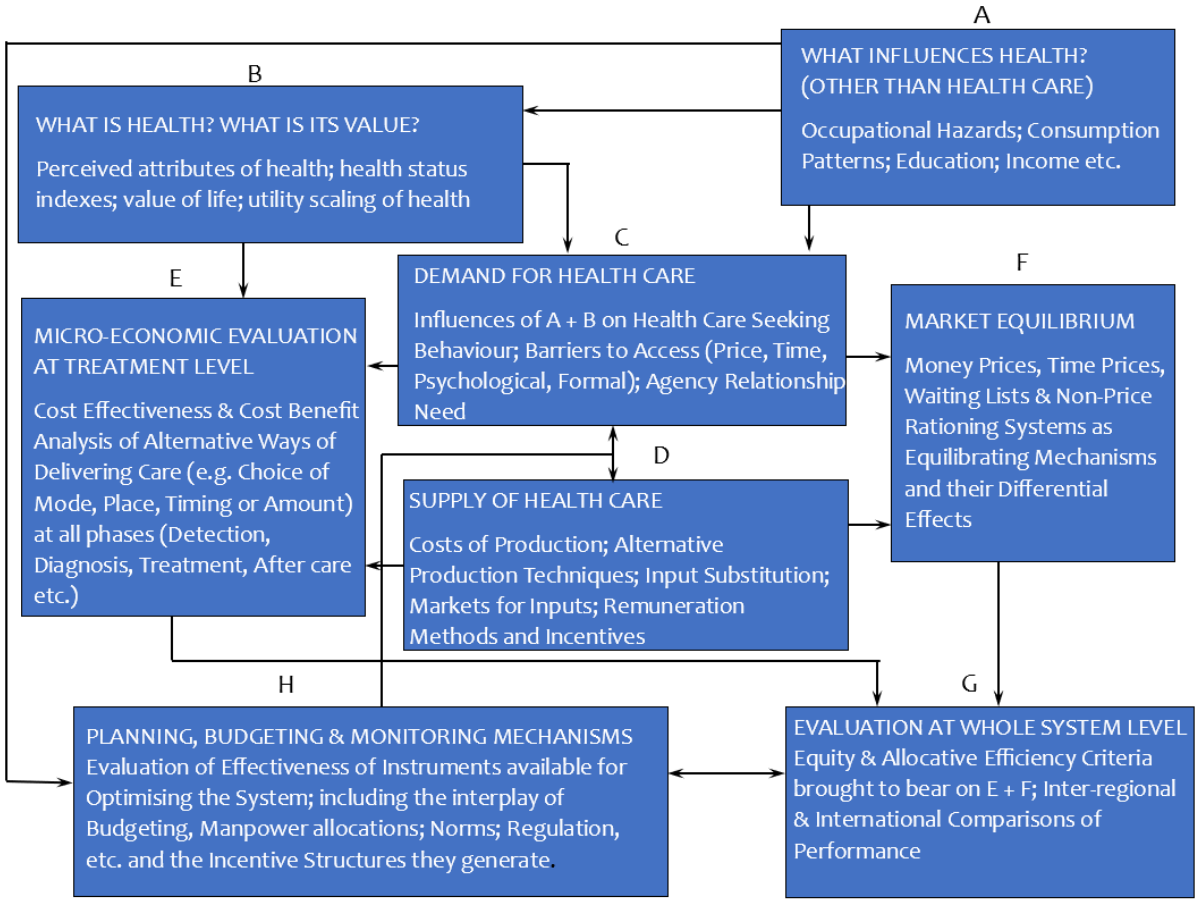


Figure 2.1 Plumbing Diagram adapted from Williams (1987)

A key dilemma for decision making with respect to health and health care is the presence of scarcity [64]. Unlimited provision of healthcare is impossible with finite resources. Resources here include financial, human capital, time, and infrastructure. Electing to deploy finite resources one way means that the finite resources are not deployed in an alternative way. Opportunity cost is a value attributed to a resource had it been deployed in its highest valued alternative use [65].

In healthcare resource allocation decision making, economic evaluations are used to assess the merits of competing alternatives. An economic evaluation is the "comparative analysis of alternative courses of action in terms of both their costs and consequences" [66:pg4].

The relevance of an economic evaluation type for resource allocation decisions depends on the school of thought that is subscribed to. The following section offers an overview of the two main schools of thought for resource allocation decision making in health economics: welfarism and extra-welfarism.

Welfarism

In decision making, the principles of welfarism relate to a sole focus on outcomes that maximise the sum of individuals' economic welfare in society [65]. The aggregation of each individual's welfare is referred to as social welfare [67]. In the welfarism paradigm, an individual's economic welfare or utility, not to be confused with a health-related quality of life utility, are the only outcomes with intrinsic value. Under a welfarism approach, two decisions with the same utility outcomes but dissimilar non-utility outcomes would be treated as equally good [68]. Welfarism is a type of consequentialism where the consequences or outcomes relating to social welfare and how it can be best maximised is the sole evaluation criteria that matter for decision making [69]. An individual is assumed to know best in judging how much utility is gained from different options and they will rationally select options that maximise their utility [67].

Extra welfarism

Extra welfarism is derived from welfarism and considers non-utility outcomes in addition to welfare. Non-utility outcomes can contribute to human flourishing above and beyond the utility generated to individuals [65], and can encompass wide ranging attributes such as equity, health, environmental sustainability, justice, and community cohesion. In contrast to welfarism, extra welfarism does not rely solely on an individuals' preferences solely and permits value judgements on behalf of individuals instead [67]. Within health economics,

health is commonly selected as the outcome to be maximised within healthcare decision making rather than individuals' utility [65].

2.3 Economic evaluation types

Types of economic evaluation differ in the measurement and valuation of benefits arising from the deployment of resources. For all types of economic evaluation, a course of action is compared against the opportunity cost of the course of action.

A cost benefit analysis (CBA) is a type of economic evaluation that attaches a monetary value on both the costs and consequences associated with each course of action. CBA has its foundations in the welfarism framework [70]. The course of action or strategy associated with the highest net benefits (that is, total benefits minus total costs) is the optimal choice in a cost-benefit analysis assuming that all relevant comparators have been included.

A cost-effectiveness analysis (CEA) is a type of economic evaluation where one single outcome measure is used and expressed in natural units (for example, cardiovascular events avoided, changes in systolic blood pressure, cancers detected). CEA is associated with an extra-welfarism approach given that non-welfare outcomes (health) are assessed as part of the resource allocation decision. The restriction of selecting just one outcome out of many possible outcomes to reflect the benefits of a strategy is a notable weakness. For a CEA, a strategy would be considered cost-effective if it had lower costs and higher effectiveness compared to its next best alternative course of action. However, where a strategy has increased costs and improved outcomes compared to the next best option, it is challenging to know whether it is worthwhile adopting the strategy relative to competing course of actions in different disease areas due to outcome incompatibility and the lack of established cost-effectiveness thresholds.

A cost consequence analysis (CCA) is a type of economic evaluation where the costs and multiple outcome measures of a course of action are compared to those of other possible courses of action in a disaggregated manner. CCA is associated with an extra-welfarism approach given the evaluation of multiple outcomes and not the sole evaluation of individuals' utility. There is no weighing on the relative importance of outcomes in a CCA. A strategy in a CCA would be the most cost-effective option where it had the lowest costs and the best performance in all outcomes compared to the other strategies. Where this is not the case, it is left up to decision makers to judge which strategy they would choose, based on the disaggregated costs and multiple outcomes.

A cost minimization analysis a type of economic evaluation where the single outcome of interest between courses of action are assumed to be identical or to only have negligible differences. Here, only costs would be compared across different strategies. Thus, the strategy with the lowest cost is considered the most cost-effective option. This type of economic evaluation is rarely undertaken in recent times due to advancements in statistical methods and computing demonstrating that the strong assumption on equivalent effectiveness between strategies, especially when the costs and outcome are jointly subjected to a parameter uncertainty assessment is not robust [71].

A cost-utility analysis (CUA) is a type of economic evaluation where the single outcome of interest is typically a generic health related quality of life measure such as a Quality-Adjusted Life Year (QALY) or a Disability Adjusted Life Year (DALY). The utility outcome does not equate to an individual's utility in the welfarist definition; rather, it considers an expression of health gain that instead falls under the non-utility outcomes of the extra-welfarism approach. CUA is like CEA in many respects except on the choice of outcome. With the use of a generic health related quality of life measure, CUA results have the advantage of comparability across

disease areas. Where a strategy has increased costs and improved outcomes compared to the next best option, there are existing cost-effectiveness thresholds that can indicate if a strategy may be cost effective based on their incremental cost-effectiveness ratio (ICER). An ICER comprises the cost difference and outcome effect difference of two strategies on the numerator and denominator, respectively [65]. Different analytic choices within a CUA can affect the ICER and this methodological uncertainty can hamper cross-comparability of ICERs across different economic evaluations. Thus, reference cases with a set of recommended methods in economic evaluations are used to provide methodological guidance, ensure consistency in approach and comparability of ICERs across different economic evaluations, and increase the applicability of the cost-effectiveness threshold in resource allocation decisions.

2.3.1 Recommended economic evaluation approaches

In the UK reference case [72], the recommended type of analysis to inform healthcare resource allocation decisions is for economic evaluations to be CUA. For LMICs with published guidance, the majority of guidelines had CUA as the preferred analytical method [73]. Where no published LMIC guidance exist, the Bill and Melinda Gates Foundation developed a reference case for economic evaluations within these countries to adhere to consistent methods and minimise methodological uncertainty [74]. Again, CUA was the recommended analytical method in their reference case.

2.4 Methodological considerations in economic evaluations

Resource use and costs

With each course of action, there are implications for resource use and consequently costs. These can fall upon the healthcare system, patients, and wider society. Examples of healthcare system resource use include treatment drugs, hospital length of stay, primary care visits, staff

time, and theatre time. Examples of patient resource use include travel time for healthcare visits, medical consumables not covered by the healthcare system, and convalescent days off work. An example of wider society resource use would be changes in productivity as result of the course of action.

The costs from each course of action arise from valuations of the associated resource use. Resource use is multiplied by their respective unit costs to calculate costs. In theory, the unit costs should reflect the marginal opportunity cost of the resource use and this economic cost can differ from the accounting cost (resource use acquisition financial cost) in healthcare systems [65]. In practice, the challenges associated with valuing context-specific opportunity costs means that country-specific economic evaluation guidelines recommend the use of standardized unit costs that reflect the accounting cost for consistency purposes [75].

There are different cost categories that can be included in an economic evaluation. Direct costs are medical and non-medical costs that can be traced back to a course of action [76]. Direct medical costs are healthcare labour, infrastructure, and medical consumables costs attributable to a strategy under evaluation. Direct non-medical costs are non-healthcare expenses incurred by the patient and their family including travel costs, informal care costs and social services costs. Indirect costs are medical and non-medical costs incurred that do not have a direct relationship to a strategy under evaluation [76]. Indirect medical costs are unrelated future medical costs as a result of increased life expectancy from a strategy under evaluation [77]. However, indirect medical costs have rarely been considered in economic evaluations to date [78]. Indirect non-medical costs are patient productivity costs associated with a strategy under evaluation and is commonly valued using either the human capital method or the friction cost method [79].

Health system financing

The way in which health care systems are funded varies by country. Sources of health system financing can include one or more of government taxation, social insurance contributions, private insurance, and out-pocket-payments. In Europe, tax financed and social insurance contributions are the main sources of health system financing [80]. A progressive health financing system is when the health care cost paid by an individual as a share of their income increases as their income increases. A regressive health financing system is when the health care cost paid by an individual as a share of their income decreases as their income increases. A health system predominately financed by government taxation can be considered progressive or regressive depending on whether the overall tax being levelled is progressive or regressive. A progressive health financing system is preferred by decision makers wanting to reduce population health inequities.

User charges for healthcare are a common feature in many LMIC settings where the provision of healthcare cannot be funded from taxation and/or social insurance contributions alone. Higher levels of out-of-pocket payments has been shown to be correlated with worse health outcomes [81]. In near end of life care, out-of-pocket payments costs in LMIC setting was found to be represent an significant driver of impoverishment for patients and their families [82]. It is estimated that 81.3 million people are driven to financial catastrophe (defined as greater than 10% of overall household expenditure) as a result of surgery every year, 40% of those from the direct medical costs attributable to the surgery alone [45]. In a study in Uganda where the government hospital was technically free at point of use, patients had to pay for medical consumables, and provide informal payments to staff in some cases [83]. Combined with the indirect costs faced with the medical episode, a third of patients faced catastrophic expenditure, and half of households had to borrow to pay for care [83]. In a scoping review of

empirical studies measuring indicators of financial risk protection in healthcare from out-of-pocket spending, current estimates of healthcare financial risk protection were shown to vary considerable among the LMIC studies[84]. A systematic review on the equity in health care financing found that the burden of health care financing was progressive and the distribution of health care benefits was regressive in both sub-Saharan Africa and Asia-Pacific countries[85].

As a measure to promote financial protection when accessing essential health care, universal health coverage has been adopted as a WHO Sustainable Development Goal for 2030 that would aim for patients to be able to access essential healthcare without the risk of incurring impoverishing costs [59]. Implementation requires health care financing that is increasingly progressive in nature to improve health equity[85]. Globally, effective health coverage has increased since 2015 although it has been disrupted by COVID-19 and it is unlikely to reach the set target on current trajectories[86].

Perspective

The scope of costs included in an economic evaluation depend on the perspective of the decision maker. A healthcare perspective includes direct medical costs and indirect medical costs for each strategy under evaluation. A societal perspective covers indirect costs as well as costs from a healthcare perspective. The healthcare perspective is recommended in the UK reference case [72]. For LMICs with published guidance, there is no consensus on the perspective to be used with half recommending the healthcare perspective, and the other half recommending the societal perspective [73]. The Gates Foundation recommend a disaggregated societal perspective where healthcare and societal costs are listed separately in the cost-effectiveness results [74].

Time horizon and discounting

The choice of timeframe over which the costs and consequences are considered in an economic evaluation can have an impact on the cost-effectiveness results. An insufficiently short time horizon will exclude longer term costs and consequences that could otherwise change decision recommendations. A sufficiently long enough time horizon to capture all relevant costs and consequences is recommended in both the UK reference case [72], LMICs with published guidance [73] and the Gates Foundation reference case [74].

As the timing of when the costs and consequences occur does not happen all at once, another consideration is how to treat long-term costs and consequences relative to short-term costs and consequences. Acknowledging the preference towards present benefits compared to future benefits, a discount rate calculates the present day value of future costs and consequences by reducing their value in relation to how far in the future they accrue. Costs and health effects can be discounted at a common rate or they can have differential discount rates [87]. The same annual discount rate is applied for both costs and health effects in the UK reference case [72], the Gates Foundation reference case [74], and in ten of the eleven LMIC economic evaluation guidelines [73]. The discount rate used varied across the reference cases with the UK reference case using 3.5%, the Gates Foundation reference case opting for 3%, and the LMIC economic evaluation guidelines specifying either 3%, 3.5% or 5%.

Outcomes and their valuation

In CUA, outcomes are typically expressed using a QALY or a DALY. Both are generic health outcome measures that can be used to compare health status across disease areas and have been elicited in a variety of ways.

Quality Adjusted Life Year

A QALY combines length of life and quality of life within one generic health measure [65]. A year in perfect health corresponds to a QALY score of 1 and a year equivalent to death corresponds to a QALY score of 0. States worse than death (that is, negative QALYs) are possible with some health state instruments. A QALY is a recommended CUA outcome in the UK reference case [72]. For LMICs with published guidance, QALYs are specified as one of the preferred outcomes in nine out of the thirteen countries. QALYs can be developed using direct and indirect health state valuation approaches. Quality of life adjustments are referred to as health-related quality of life or utilities.

The main ***direct health state valuation*** approaches include the (i) standard gamble, (ii) time trade off (TTO), and (iii) the visual analogue scale (VAS) [88].

(i) Standard gamble measures quality of life derived from participants choices on the selection of a health state with certainty or the selection of an improved health state with uncertainty (the gamble) [88]. The probability associated with obtaining the improved health state is varied until the participant is indifferent between choices. The probability at which there is an indifference between choices is inferred to be the utility.

(ii) TTO compares the choice of two health states with certainty but the full health state has a reduced life expectancy in the pairwise comparison [88]. The duration of the full health state is varied until the participant is indifferent between the choice of the health state under evaluation and the full health state at their different specified durations. The duration at which there is an indifference between choices is divided by the total duration of the comparator health state to get the associated utility value of the comparator health state [65].

(iii) In a VAS, a respondent indicates a value within a rating scale that best represents their judgement of a health state where it resides in relation to defined endpoints of health on the top and bottom of the scale [88] . Unlike the previous two approaches, VAS does not offer a pairwise comparison of health states for the participant to choose from. Instead, it represents a visual way to rate a health state [65]. A commonly used VAS in economic evaluations is the EQ-5D VAS [89]. It has defined boundaries on the top and bottom of the scale to indicate the best and worst imaginable health state, respectively. Participants indicate on the scale where the health state would be within these boundaries and this value is then used as the utility. The lack of choice to measure strength of preference has attracted criticism for the VAS technique in that it does not have the same theoretical grounding as the time trade off and standard gamble techniques [90].

Both standard gamble and TTO are rooted in Expected Utility Theory where individuals try to maximise their anticipated utility under uncertainty [88]. All three direct health state valuation approach are listed as methods to derive utility in two of the LMICs for which there is published guidance (China, Thailand) [73].

The presence of death and life expectancy within the Standard gamble and TTO exercises have been considered challenging for valuations of temporary health states where there is only minor impairment to quality of life over a short period of time and/or it is difficult to disentangle subsequent future health states from the current health state being valued [91]. A chained TTO is a variation of the conventional TTO which uses an anchor health state in two stages so participants do not directly trade off life expectancy for the temporary health state [92].

Indirect health valuation approaches typically use a combination of value judgements (tariff values) and a health-related quality of life measure to derive utilities. The tariff values ascertain preferences of a target population with respect to each attribute of health-related quality of life using methods such as time trade off or standard gamble. Tariff values are uncommon in LMICs [93] which can result in resource allocation decisions that are contrary to a countries preferences with respect to health.

One of the main health related quality of life measures used to derive utilities for QALYs is the EQ-5D [94]. The EQ-5D asks a participant about their health on the day it was administered by selecting the most applicable response across five domains of health (pain, mobility, usual activities, pain/discomfort and anxiety/depression). There are two versions of the EQ-5D; the EQ-5D-3L is the older version with three levels of responses and the newer EQ-5D-5L has five levels of responses. Tariff values for the two versions are available across many countries which provide values to convert EQ-5D responses into utilities that reflect country-specific preferences across the health domains [94]. The EQ-5D-5L is the recommended method to generate utilities in the UK reference case [72]. Seven LMICs with published guidance listed the EQ-5D as a method to generate utilities [73]. All seven of these LMICs have country-specific tariff values of EQ-5D-3L or EQ-5D-5L to convert the responses into utilities.

The short form six dimensions (SF-6D) is another common measure used to generate utilities. SF-6D versions are derived from either the short form 36 (SF-36) health outcome measure or the short form 12 (SF-12) health outcome measure [88]. The SF-6D derived from the SF-36 has four to six response levels across six dimensions (Physical Functioning, Role Limitations, Pain, Mental Health, Social Functioning, and Vitality). The SF-6D derived from the SF-12 and the health instrument has three to five response levels across six dimensions. A newer

version of SF-6D has been developed (SF-6Dv2) which is in turn derived from a newer version of the SF-36 (SF-36v2) [95]. The SF-6Dv2 uses different response wording and four to six response levels across the same domains compared to the original SF-6D. Four LMICs with published guidance listed the SF-6D as a method to generate utilities [73], although only two of these countries have their own tariff values [96].

Other preference-based health outcomes measures include the Health Utility Index (HUI) and the Quality of Wellbeing (QWB). Four LMICs with published guidance listed the HUI and the QWB as methods to generate utilities [73].

Disability Adjusted Life Year

DALYs comprise the summation of Years of Life Lost (YLL) and Years Lived with Disability (YLD) due to a health condition [65]. Unlike a QALY where a higher QALY indicates more health gain, fewer DALYs are preferred as it reflects more health burden averted. With LMICs with published guidance, DALYs averted is specified as one of the preferred outcomes in one country (Indonesia) [73]. The Gates Foundation reference case also recommends DALYs averted as the outcome measure to use in CUA [74].

DALYs comprise the summation of Years of Life Lost (YLL) and Years Lived with Disability (YLD) due to a health condition [97]. YLL is the life expectancy had the individual not died from the disease under evaluation. Life tables can be used to estimate the average population life expectancy at the age where the individual had not suffered a premature death [98]. Where the life expectancy is greater than a year, a discount rate can be applied to obtain the present value of the YLL [99].

YLD is calculated as the duration of the onset and resolution of health condition adjusted by a disability weight. A disability weight reflects a quality of life severity of being in the health

state and is analogous to a QALY utility except the 0-1 scale is reversed as a lower disability weight value indicates less morbidity. Disability weights across 440 health states to date have been elicited by the Global Burden of Disease study [97]. Disability weights are assumed to provide the same preferences with respect to health regardless of country.

Disability weights are valued using a paired comparison of short health state descriptions of diseases where participants were asked to judge which health state would be considered healthier [97]. A variation of the person trade off method (population health equivalence) is then used to anchor the responses to a 0-1 scale [97]. The person trade off method presents two groups which have their own health condition and sample size. Participants are then asked to choose which group they would cure. One of the groups size is then varied to assess the point of indifference between choosing to cure either group [65]. The population health equivalence method presents two health programmes with the first one preventing a thousand people from receiving a disease that causes a swift death, and the second one preventing a randomly allocated higher number of people suffering a lifetime non-fatal described health state [100]. The same method is used for both temporary and chronic health states.

Evidence sources for economic evaluations

Economic evaluations are usually conducted alongside a randomised control trial (RCT) because they are excellent vehicles for data collection with a direct comparison built into the design. Another approach is to use decision analytic modelling framework which can combine and draw on data from a range of sources when it not obtainable from one vehicle such a trial.

A Phase 3 RCT is a study design that compares the clinical effectiveness of two or more interventions that allocation of patients in each intervention determined randomly [65]. RCTs within a surgery setting can have methodological challenges around the learning curve of a

new technique [101], the lack of equipoise for non-surgery comparators [102], and the effectiveness of an intervention being confounded by a surgical team's collective proficiency [103]. Whether or not to collect the operative experiences of surgeons learning a new intervention technique for inclusion in the treatment effectiveness of the RCT measure is a matter of debate [104]. The learning effect would be relevant to initial implementation of the new surgical technique, as treatment effectiveness without operations with the learning would be overstating any cost-effectiveness results.

For some interventions, their underlying characteristics and how it operates within the healthcare system can mean that establishing effectiveness can prove challenging. In the complex interventions guidance, a complex intervention is typically described having one or more of the following traits: multiple interacting components, involving behaviour change, spanning multiple groups or organisational tiers, multiple outcomes, and/or tailoring to different contexts[105]. In updated guidance, complex interventions can be thought to share similar properties as complex adaptive systems with features such as emergence, system feedback loops, adaptation, and self-organisation [106]. As the interventions to reduce SSI considered in the thesis consist of substitutions within existing surgical procedures and are not relating to behavioural change nor health service level changes, the complex interventions framework was assessed to have low applicability to the economic evaluation work.

Trial-based economic evaluation

A trial-based economic evaluation exploits the opportunity of a RCT to simultaneously assess the clinical effectiveness and cost-effectiveness of interventions [107]. The measurement of costs and utilities can represent additional information to collect in a RCT and can align with other clinical measurement timepoints to minimise patient burden. Different RCT study designs can necessitate different analytic approaches for the accompanying economic

evaluation [108–110]. For example, for economic evaluations alongside factorial RCTs, the non-interaction effect for clinical effectiveness (allowing for a more efficient sample size for the study) may not hold for resource use and outcomes. The two analytic approaches vary on the assumption of an interaction effect: (1) an at-the-margins analysis assumes no interaction effect, and considers the costs and outcomes of all those within a given intervention; (2) and inside-the-table analysis assumes an interaction effect and treats each intervention combination as separate comparators when evaluating the costs and outcomes [108]. Economic evaluations alongside multinational RCTs also require careful consideration on analytic approach as the assumption of clinical effectiveness being transferrable across the participating countries rarely extends to the economic data [111].

An advantage of a trial-based economic evaluation is that the cost and outcome data benefit from standardized processes and follow-up for each patient randomised. However, disadvantages include the representativeness of the evaluation results to the patient population many only reflect the underlying representativeness of the patients recruited to the RCT, only the RCT interventions can be compared which may not include the best alternative, and the primary clinical endpoint may not be long enough to capture all relevant costs and consequences [62].

Model-based economic evaluation

To overcome some of the noted criticisms of trial-based economic evaluations, economic evaluations using a decision analytic modelling framework can be used to more appropriately incorporate the costs and effects of strategies under evaluation. Economic evaluations using decision analytic modelling offer several advantages compared to trial-based economic evaluations. Model-based economic evaluations can synthesise data from multiple sources; include interventions that were not directly compared together; make predictions from

extrapolations beyond which data is available; link intermediate endpoints to final health outcomes, and inform resource allocation decisions in the absence of trial data [112].

In making predictions on the cost-effectiveness of interventions, different model types can be used to represent the patient pathway for each intervention. A decision tree is a diagrammatic representation of a decision problem where patients are assigned different pathways depending on underlying probabilities and different costs and consequences are assigned based on the specific pathway a patient has ended up [65]. Decision trees are particularly suited to short-term time frames and acute health care conditions where recurrence is not an issue [112]. A decision tree is typically depicted from left to right where a decision node at the trunk of the decision tree details the starting point of each comparator being evaluated; chance nodes branch off two or more possible pathways that a patient can follow; and terminal nodes (denoted by leaf shaped triangles) have the costs and consequences associated with the specific pathway [62]. To obtain the expected costs and outcomes of each strategy, a rollback calculation multiplies the costs and consequences of each terminal node by the proportion of patients who have ended up at each terminal node.

A Markov cohort model represents a decision problem with a cohort of patients with identical characteristics in a sequence of time periods across constructed health states where the cohort of patients can transition between [65]. Markov models are suited to diseases with recurrence and can easily account for patients moving between health states repeatedly that would make the representation in a decision tree rapidly unwieldly in branch requirements [112].

A discrete event simulation is another form of patient level simulation where a series of health state changes are represented using distributions, and the events occur in chronological order to a patient [113]. Capacity constraints and patient interaction can be assessed in a discrete

event simulation where the probability of events are affected by the presence of other patients [112]. A transmission dynamic model can also allow for patient interaction, is typically divided up into different compartments that patients reside in, and are mainly used to represent communicable diseases where the risk of infection is affected by the number of other infectious people [114].

Data synthesis for model inputs

When choosing an input across multiple data source options for a model-based economic evaluation, there are statistical methods available to combining data sources. Synthesising data can improve the precision of the estimate compared to relying on one data source [115]. A meta-analysis is a quantitative data synthesis with different approaches available depending on the nature of the data and assumptions around the inter study variance [116]. As studies that feed into a meta-analysis can vary in quality, there are tools available to assess the risk of bias within included studies [117].

Meta-analysis for model inputs can be done at the aggregate or Individual Participant Data (IPD) level. Whereas aggregate level meta-analysis uses summary information published from studies, IPD level meta-analysis uses patient-level data requested from the study publications. IPD level meta-analysis is considered to take longer to undertake compared to aggregate level meta-analysis given the greater time and cost commitments required to access and analyse the patient-level data [115]. While IPD level meta-analysis enhances precision relative to aggregate level meta-analysis, a systematic review of IPD meta-analyses compared with meta-analyses based on aggregate data determined that they reach broadly similar results and conclusions in many cases [118].

For economic evaluations, treatment effectiveness data is the most common model input type to have data synthesis compared with other model inputs such as health utility data, and cost/resource use data [119]. One reason for the lack of data synthesised health utility data is due to poor study reporting of the uncertainty of the estimates [120]. For resource use and cost data, generalisability issues, non-normality of data, and large methodological study heterogeneity have been posited as barriers to undertaking a data synthesis in this area [119].

Characterizing uncertainty in economic evaluations

Uncertainty is inherent in economic evaluations. There are different sources of uncertainty that are present in trial-based economic evaluations [107], and model-based economic evaluations [121] which can affect decision recommendations on whether or not an intervention can be considered cost-effective. Both types of economic evaluations are affected by methodological uncertainty where there is no consensus agreement on the correct method(s) to use when undertaking an economic evaluation [121].

For trial-based economic evaluations, stochastic uncertainty is the likelihood that the cost-effectiveness results change if the RCT was repeated with different patients within the population [122]. Stochastic uncertainty can be quantified using confidence intervals, generated from non-parametric bootstrapping, for the costs and effectiveness results [122]. The Net Monetary Benefit (NMB) is the monetary value attached to an outcome minus the total cost of a strategy [65]. Cost-effectiveness acceptability curves (CEACs) summarises the uncertainty of the most cost-effective strategy by graphing the proportion of each strategy that has the highest NMB across a range of WTP thresholds [123].

For model-based economic evaluations, there is parameter uncertainty on the true value of the model inputs, and structural uncertainty on how best to model the health condition under

evaluation [121]. Where the evidence base is limited for one or more model inputs, their relative importance on the cost-effectiveness results be assessed in the decision analytic modelling framework through the use of sensitivity analysis on the parameters. Parameter uncertainty can be assessed using both deterministic sensitivity analysis (DSA) and probabilistic sensitivity analysis (PSA). A DSA varies one or more of the model inputs to assess the impact on the point estimate results. A PSA attaches statistical distributions to the model inputs in order to make the decision model probabilistic and reflects the joint parameter uncertainty in the outputs of interest (costs, effects) [124].

The results of a PSA can be summarised in a table with the mean results of the iterations accompanied by prediction intervals, plotted on an incremental cost-effectiveness plane, and displayed using a CEAC. An incremental cost-effectiveness plane is a four quadrant graph of costs (Y axis) and effects (X axis) where the costs difference and effects difference between two strategies across all the PSA iterations is plotted and visually shows how many of the iterations would be considered cost effective based on their position in the graph [65].

Both the Gates foundation and UK reference cases recommend that an overall assessment of the uncertainty (parameter, structural) associated with an economic evaluation should be reported [72,74]. For LMICs with published guidance, all required some form of sensitivity analysis to characterise the uncertainty in the economic evaluation [73].

Timing of intervention adoption decision

Based on the outputs of an economic evaluation, the choice to adopt or not adopt the intervention can be made by decision makers. With uncertainty on whether or not the intervention is the most cost-effective option, there is a risk of making a wrong decision on adoption or non-adoption which is commonly referred to as decision uncertainty [66].

Decisions to adopt a new intervention in healthcare settings also have a degree of irreversibility in that resources to implement the intervention become sunk costs [125] and rowing back later on the adoption decision can be challenging for political reasons[126]. Interventions undertaken at a service level are known to be difficult to reverse once implemented [127]. The impact of an intervention adoption can also affect the healthcare landscape by influencing the availability of future potential interventions[128]. For example, the decision to increase the volume of surgery will invariably increase the number of SSI cases which require antibiotic treatment. Increasing use of antibiotics will contribute to antibiotic resistance and restrict the future number of effective antibiotics available. For decisions that do not have to made immediately, there may be value in deferring the timing of the decision [125]. Delaying the decision can allow time to gather more evidence to reduce the decision uncertainty. The value of reducing the decision uncertainty can be explored using a Value of information analysis (VOI).

Value of information analysis

Using information from the PSA, a VOI analysis can be used to inform and prioritize research. Guiding research to collect more information on the basis of the most influential parameter alone is not sufficient, due to the opportunity cost of research. Obtaining more robust estimates of an influential parameter is not worthwhile in cases where the research costs outweigh the benefits from reducing uncertainty. A less influential parameter with cheaper research costs may represent a more optimal use of resources.

A VOI analysis is a formal assessment of the value of undertaking research to acquire better information versus the costs associated with the information acquisition [129]. Acquiring more information inevitably delays the decision on adopting the intervention versus taking an immediate decision based on the current available evidence and uncertainty. Thus, the costs

associated with generating further evidence to inform the decision includes any forgone benefits from not adopting the intervention immediately [130]. With decision uncertainty, there is always a risk of making the wrong decision on the cost-effectiveness of an intervention resulting in suboptimal resource allocations.

Value of Information can be quantified in a variety of ways depending on its intended purpose. The first way VOI analysis can be used is to quantify the value of removing all or some the uncertainty from the cost-effectiveness decision. The expected value of perfect information (EVPI) measures the additional value of resolving all decision uncertainty compared to the current level of decision uncertainty [129]. The absence of decision uncertainty is derived from the removal of parameter uncertainty from all model inputs. Parameter uncertainty here refers to the variability of output from the PSA rather than the results from a DSA. The EVPI can be seen as a first step to judge if there is any value at all with generating additional information to inform the decision problem. Even with a large possible benefit from future research, elimination of all decision uncertainty could be infeasible. Instead, future research may realistically focus on the reduction or removal of parameter uncertainty from one or more model inputs. The expected value of perfect parameter information (EVPPI) measures the additional value generated from complete information of specified model inputs, compared to the imperfect level of information we have currently have on these parameters [130].

The second way VOI analysis can be used is to quantify the value and/or costs of future research to reduce decision uncertainty. The expected value of sample information (EVSI) is calculated from the additional value gained from undertaking specific types of research designs to decrease decision uncertainty of specific parameters (e.g., randomised control trial

to ascertain treatment effectiveness) compared to the current level of decision uncertainty[129]. Once the likely costs of the future research study is subtracted from EVSI, we get the Expected Net Benefit of Sampling (ENBS)[130]. These costs include the financial costs of undertaking the research study and the opportunity costs from delaying the decision to adopt the intervention to patients who would have benefited from the intervention in the intervening time [131].

Preliminary modelling

Preliminary health economic evaluation modelling (also called early economic modelling) has origins in pharmacoeconomic evaluations of early development drugs to inform decisions on whether the drug had sufficient economic value potential to progress to further research development [132]. This type of economic evaluation shares the same methods and analyses as a traditional conventional model-based economic evaluation, however the data sources for model input parameters tend to be less robust as characterised by its preliminary label. Model input parameters can take the form of treatment effectiveness, resource use, event costs, health state utilities, and patient movements.

The purpose of a preliminary economic evaluation is not limited to a signal to proceed or stop drug development. From the assessment of parameter uncertainty, preliminary modelling can inform design decisions on prioritizing data collection on key parameters identified as important drivers of cost-effectiveness [132]. In addition, structural uncertainty assessment can direct future research to ascertain the plausibility of structural assumptions that underpin the model results. With an evidence base that is inevitably limited, the preliminary modelling can indicate what parameter(s) would benefit from additional evidence collection to inform the cost-effectiveness decision making. The motivation to guide future research interwines the concepts of preliminary economic modelling with VOI. With imperfect model inputs, a VOI

analysis is a powerful tool in guiding the expected best path forward in the face of inherently higher parameter uncertainty in a preliminary model-based economic evaluation.

Iterative modelling framework

VOI analysis explores the merits of going beyond a single model-based economic evaluation to one taking a approach of updating the model-based economic evaluation with new information to improve the precision of the results and reduce decision uncertainty. An iterative model-based decision making framework has been proposed by Kunst et al [133] informed by existing ISPOR guidelines on VOI [129,134] and good research practice[135–138]. The framework offers guidance on how the use of VOI in the assessment of decision uncertainty and the need for additional evidence from a conventional economic evaluation can feed iteratively into rerunning the model with the newly acquired information prioritized by the VOI. The evidence can be sythesed with the original model inputs where appropriate [133]. The updated model results can signal an additional iteration where its VOI suggests the need for further additional evidence.

Transferability of economic evaluations

The majority of economic evaluations are skewed towards high income countries with a bibliometric analysis finding that lower middle income countries and upper-middle-income countries account for 4% and 14% of all published economic evaluations, respectively [139]. Reasons that hinder the development of economic evaluations in LMICs include challenges associated with acquiring data and the lack of analytical expertise required to carry out economic evaluations [140]. One way to reduce the burden from building an economic evaluation from scratch is to adapt an existing economic evaluation to become more applicable to the current setting. Transferability is the extent to which the results of an economic evaluation can generalise to another setting [66]. The level of transferability of an

economic evaluation can depend on the similarity of the two settings in terms of methodological guidance, the patient population demographics, treatment patterns, and healthcare systems [141].

One approach to assess the suitability of an economic evaluation's transferability is to compare its performance against Welte's knock-out criteria model [142]. General knock-out criteria include where the technology under evaluation or comparator in the economic evaluation are not comparable to ones available in the decision country or the economic evaluation of low methodological quality. The low quality has been operationalised by other authors as a study scoring ≤10 out of the 19 items on the Consensus on Health Economic Criteria (CHEC) criteria, a methodological quality of economic evaluations checklist [143,144].

Passing the general knock-out criteria then progresses to a checklist of specific knock-out criteria. These criteria are based on the estimated relevance of transferability factors that determine the economic evaluation results. Transferability factors reflect methodological choices (e.g., discounting, perspective, measurement and valuation of resource use and health outcomes), patient population (e.g., case-mix, disease incidence and/or spread, treatment adherence, life expectancy), and practice variation [142]. The results are said to be transferrable where there is high comparability between settings in relevant transferability factors. An economic evaluation can be ruled out if there are low comparability in relevant transferability factors. However, modelling adjustments to reconcile the model structure, model inputs or other methodological choices can improve comparability in relevant transferability factors.

In an interview survey of decision-making bodies representatives in twelve middle-income countries, treatment effectiveness data was thought to have better transferable properties compared to unit costs or prices, and it commonplace to have economic evaluations which had been first developed in a High Income Country [145].

2.5 Conclusion

This chapter has provided an overview on of the various terms, concepts and theory related to an economic analysis of safe surgery in LMICs. To assess the economic rationale of safe surgery in LMICs, an iterative modelling framework described in the chapter is adopted for the thesis. This was selected as it provides the iterative role of modelling in terms of addressing the limitations of the current evidence base on the economic considerations of SSI in LMIC settings. Cost and utility evidence relating to SSI will be collected in systematic reviews (Chapters 3 and 4) to populate a preliminary economic model assessing the cost-effectiveness of SSI reduction. Where model input information comes from different country settings, the transferability of model input is assessed using Welte's knock-out criteria model [142]. Value of information analysis is then undertaken to assess the value of reducing decision uncertainty. The preliminary economic model is then updated with information from a HIC RCT re-analysis with a further Value of information analysis. Then the preliminary model is updated for one more iteration with more applicable LMIC data collected as part of the thesis. The iterative model then conducts a final Value of information analysis to see if there is value in reducing decision uncertainty further.

The next chapter begins to address the thesis's first objective in searching for the best available estimates on the costs associated with SSI by reporting a systematic review on the cost burden of SSI in LMICs.

Chapter 3:

Systematic Review on the costs of SSI in LMICs and methodological comparison with European studies

To ascertain the cost implications of Surgical Site Infection (SSI) from the best available estimates in secondary sources, this Chapter reports a systematic review on the cost burden of SSI in Low- and Middle- Income Countries (LMICs), using European High Income Countries (HIC) as a methodological comparison. The systematic review results in a thorough understanding of the existing literature on the costs associated with SSI across High Income Countries (HIC) and LMIC settings, data collection methods on the SSI costs, what type of costs are being collected, and highlight any important potential data gaps and methodological considerations in each setting.

The results presented here have been adapted from the following peer-reviewed paper:

Monahan, M., Jowett, S., Pinkney, T., Brocklehurst, P., Morton, D.G., Abdali, Z. and Roberts, T.E., 2020. Surgical site infection and costs in low-and middle-income countries: A systematic review of the economic burden. *PloS one*, 15(6), p.e0232960.

The chapter is structured as follows: first, the main challenges associated with estimating the additional costs of SSI are outlined. Then, the methods of the systematic review are detailed including eligibility criteria, study categorisations, database specific search terms, and reporting checklists applied to each included study. The results are grouped by HIC and LMIC studies with methodological aspects appraised separately and then compared together. A cost value robustness assessment completes the results section by comparing the merits of the reported cost values from each study to obtain the best available estimate to use in the preliminary model in Chapter 5. The main findings from the review in relation to the outlined challenges are discussed and the chapter is then concluded.

3.1 Background

A cost of illness (COI) study quantifies how much society is spending on a particular disease and represents the cost burden averted if the disease was eradicated [146]. Understanding the additional cost burden imposed by the complications of surgery such as those caused by an SSI, helps to strengthen the case for identifying interventions to reduce such complications [147]. This in turn provides the justification for undertaking economic evaluations to present relevant evidence to inform the prioritization of resource allocation decisions for interventions to reduce SSI complications.

There are five main challenges in measuring the additional costs associated with an SSI. First, the lack of an internationally agreed definition for SSI results in baseline variability in who is diagnosed with the condition [148]. Second, as an SSI can manifest beyond hospital discharge, approaches for post-discharge SSI assessment or confirmation will impact SSI detection rate [149,150]. Follow-up difficulties can be exacerbated for surgical patients in low income settings due to high out-of-pocket transportation costs in accessing healthcare [151].

Third, estimating the additional cost of SSI relies on the choice of the comparator, which is patients without SSI. Studies with a case-control design try to address potential confounding with an adjusted comparison where each of the exposure and control patients have matching confounding variables (e.g., same age, gender, surgical procedure). Yet, the choice of matching variables should be considered carefully in case-control studies because of its impact on the efficiency and validity of the results [152].

Fourth, SSI costs are only as representative as the hospital settings used. Resource use and costs are known to differ across urban and rural settings and different patient population mixes from different surgical procedures can influence the cost of SSI, limiting the generalisability across procedures. Finally, SSIs vary in severity, and those SSIs that are severe can substantially increase costs and inpatient length of stay compared to more minor ones [153]. However, the distinction between SSI severity levels is open to further subjective interpretation by the clinical team [25].

The objective of this study is to critically appraise and assess how the cost of SSI has been estimated in a range of LMIC studies and compare with a selection of high income European studies which explored similar SSI costs. European studies are included in the review to provide a reference standard for the LMIC studies. The aim of the comparison is to examine the costs associated with SSI (presented in international dollars) across the different settings and identify potential data gaps, and methodological considerations in each setting. A secondary aim is to assess the robustness of these cost values for use in a preliminary model-based economic evaluation in Chapter 5.

This chapter is structured so that the review of the selection of European studies is presented first. An analogous review of the LMIC studies is then presented. Lastly, a comparison between the main finding of the reviews for the HIC and LMIC settings is presented before the main discussion.

3.2 Methods

The review followed the UK Centre for Review and Dissemination [154] guidelines and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [155].

3.2.1 Search strategy

The following electronic databases were searched from inception to 20th February 2019: EMBASE and MEDLINE In-Process & Other Non-Indexed Citations. Additional references were found using hand searching of relevant journal articles and Google scholar searches. Search terms used for each database are detailed in Appendix A3.1.

3.2.2 Eligibility criteria

Studies were included if they considered the costs associated with SSIs in European Organisation for Economic Co-operation and Development (OECD) countries [156]. For the analogous review of LMIC, studies were included if they considered the economic impact of SSIs in LMICs. For both settings, costs could be borne by the healthcare providers, patients, wider community and/or society. Eligible articles included cost analysis, partial or full economic evaluations (trial-based and model-based) and cost of illness studies in a European country or LMIC setting. Multi-country studies were included if at least one eligible country was included, and the study's findings were reported separately for that country. Non-eligible studies were those that were not published in English, conference proceedings, protocols, commentaries, and editorials.

Stage I categorisation for European or LMIC studies

A. The study reports primary data on the costs of SSI
B. The study may have useful economic information on aspects of SSI (e.g., Hospital Acquired Infections), but does not obviously fall into (A)
C. The study discusses aspects related to the costs of SSI, but neither (A) nor (B) above;
D. The study mentions the costs of SSI but the full text is not English
E. The study is a conference abstract or letter.
F. The study has no relevance to the costs of SSI in Europe or LMIC

Stage II categorisation for European or LMIC studies

1. Cost of illness study looking at the economic burden of SSI
2. Cost study or effectiveness study with financial information on SSI
3. Study does not disaggregate SSIs from other complications or treatment group
4. Study is not in European or LMIC setting
5. Study is not relevant to the costs of SSI
6. Study cannot be accessed

3.2.3 Study selection

The titles and abstracts of the databases' search results were screened against the eligibility criteria. A three stage categorisation process was used to determine relevant studies appropriate for inclusion, using methods described elsewhere [157]. Two investigators carried out study screening and data extraction for the LMIC search (MM & ZA). One investigator (MM) carried out all study screening and data extraction for the European literature search, and another investigator (ZA) undertook screening of a random 20% to assess agreement. Disagreements were resolved through discussion; a third independent investigator (TR) was sought where agreement could not be reached.

For each included study, data were extracted on the study characteristics, country setting, costs and resource use included, use of adjusted analyses, and the main results reported. The information was tabulated, and the issues faced by the individual studies in estimating the additional costs of SSI were compared narratively. For consistency across studies, costs were converted to international dollars and inflated to 2017, where appropriate. To improve comparability of cost findings, costs were adjusted by their country's Purchasing Power Parity (PPP) conversion factor [158]. Where a country did not have a PPP conversion factor, an implied PPP conversion factor from the Internal Monetary Fund (IMF) was used instead [159]. For inflation purposes, studies without a specified cost year were assumed to be the last year of data collection.

All included studies were assessed by a modified reporting Müller checklist (translated into English) for Cost of Illness studies and scored by their inclusion of relevant items [160]. A study scored one point on each aspect they had described or justified out of a possible maximum score of 36. The checklist for each study is available in Appendix Table 3.1.

To aid the selection of a suitable model input for the associated cost of SSI for the preliminary economic evaluation in Chapter 5, a de novo quality checklist was created to appraise the aforementioned robustness of the cost values found in both the current and previous review and is presented in the last section of the results. The quality criteria was at follows: (1) whether or not the data collection was in the 21st century as the costs in older studies may not be representative of present day healthcare patterns even after inflation adjustment; (2) whether or not the cost by SSI severity was presented; (3) whether or not patients were followed up beyond their index hospital stay; (4) whether or not the CDC definition of SSI was used; (5) whether or not the costs were adjusted for patient covariates; (6) whether or not the sample size of SSI was greater than 100; (7) whether or not the study was across multiple

centres; (8) whether or not the study had prospective data collection; and (9) whether or not primary care costs were included. As the preliminary economic evaluation will have an abdominal surgery patient population, an extra criterion that (10) the additional cost of an SSI was applicable to this population was also added.

3.3 Results

3.3.1 European literature search

The electronic database search for the European studies yielded 588 citations. Figure 3.1 presents a flow diagram of the selection process. Sixteen studies met the inclusion criteria.

General study characteristics

The sixteen studies were published from 1992 to 2018 and data collection spanned 1987 to 2016. Studies were based in England (n=6) [161–166],Spain (n=2) [27,167], Scotland (n=2) [168,169], Finland (n=1) [170], France (n=1) [171], Switzerland (n=1)[172], Belgium (n=1) [173], Denmark (n=1) [174] and Germany (n=1) [175]. Table 3.1 shows general characteristics of each study included in the review.

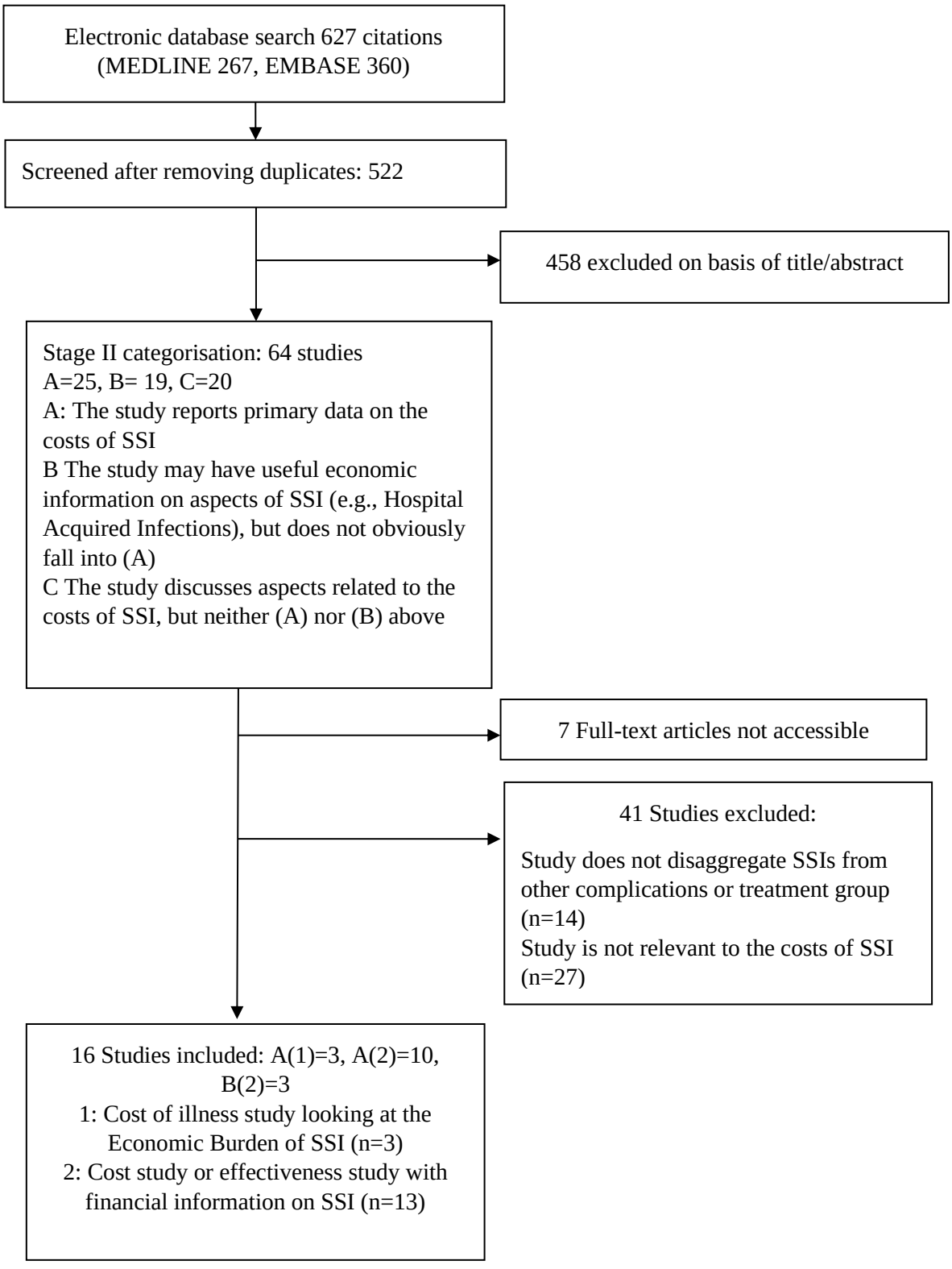


Figure 3.1 PRISMA diagram of European Search

Table 3.1 European study characteristics

Lead author (Year)	Country	Patient population	Setting	Study aim	Study Type	Sample size	Period of data collection
Cardiothoracic surgery							
Graf (2010) [175]	Germany	CABG patients	University hospital	Calculate the costs of deep sternal wound infection	Case-control study	SSI: n=17; No SSI: n=34	2006-2008
Colorectal surgery							
Tanner (2009) [163]	England	Adult colorectal patients	University hospital	Provide an accurate cost for treating patients with SSI	Surveillance study	SSI: n=29; No SSI: n=76	2008
Turtiainen (2010) [170]	Finland	Vascular surgery patients	Four secondary referral hospitals	Calculate the extra cost of services needed to treat SSI	Prospective observational study	SSI: n=49; No SSI: n=136	2007-2008
Gynaecological surgery							
Hyldig (2018) [174]	Denmark	Obese women after caesarean section	5 obstetric departments across 2 tertiary & 3 teaching hospitals	Evaluate the cost-effectiveness of incisional negative pressure wound therapy in preventing SSI	Trial based CEA	SSI: n=57; No SSI: n=780	2013-2016

Lead author (Year)	Country	Patient population	Setting	Study aim	Study Type	Sample size	Period of data collection
Multiple surgical categories							
Alfonso (2007) [27]	Spain	Adult patients	General, tertiary hospital	To identify overall costs generated by SSI patients	Cost of illness study	SSI: n=30; No SSI: n=52	2001-2005
Defez (2008) [171]	France	Acute care patients	University hospital	Calculate the additional costs of nosocomial infection:	Prospective cohort study	SSI: n=21; No SSI: n=21	2001-2003
Jenks (2014) [161]	England	Patients who underwent major surgical procedures	University hospital	Determine the clinical and economic burden of SSI	Cost analysis	SSI: n=282; No SSI: n=14,018	2010-2012
Lynch (1992) [168]	Scotland	Adult surgical patients	Teaching hospital	Study the cost of SSI	Cost analysis	SSI: n=513; No SSI: n=2,969	1987-1989

Lead author (Year)	Country	Patient population	Setting	Study aim	Study Type	Sample size	Period of data collection
Reilly (2001) [169]	Scotland	Surgery patients	Unspecified hospital	Quantify the cost of SSI to the hospital, community, and patient	Prospective cohort study	SSI: n=220; No SSI: n=1,982	1995-1999
Vegas (1993) [167]	Spain	General surgery and digestive surgery patients	University hospital	Estimate the length of stay of SSI patients	Prospective cohort study	SSI: n=106; No SSI: n=212	1990
Vrijens (2012) [173]	Belgium	Acute care patients	Acute care hospitals in Belgium	Estimate the total economic cost of infection to the public healthcare provider	Retrospective cohort study	SSI: n=77; No SSI: n=261	2007
Weber (2008) [172]	Switzerland	Traumatology, visceral and vascular surgery patients	University hospital	Quantify the economic burden of SSI	Retrospective cohort study	SSI: n=168; No SSI: n=168	2000-2001

Lead author (Year)	Country	Patient population	Setting	Study aim	Study Type	Sample size	Period of data collection
Orthopaedic surgery							
Edwards (2008) [166]	England	Hip fracture patients	University hospital	Estimate the cost of treating SSI	Retrospective cohort study	SSI: n=80; No SSI: n=80	1999-2004
Pollard (2006) [162]	England	Proximal femoral fracture surgery patients aged over 65 years	Tertiary teaching hospital	Assess the financial burden of deep SSI	Retrospective cohort study	SSI: n=61; No SSI: n=122	1998-2003
Parker (2018) [164]	England	Lower limb open fracture patients	24 specialist trauma hospitals	Estimate economic outcomes associated with deep SSI	Costing analysis of RCT	SSI: n=35; No SSI: n=423	2012-2015
Thakar (2010) [165]	England	Proximal femoral fracture patients	Tertiary teaching hospital	Calculate the additional hospital costs due to complications	Prospective cohort study	SSI: n=46; No SSI: n=92	2003-2008

All costs were inflated and converted to 2017 international dollars where appropriate

CABG, Coronary artery bypass graft ; CEA, Cost-effectiveness Analysis; NNIS, Nosocomial Infection Surveillance System risk index; SSI, Surgical Site Infection; RCT, Randomised Control Trial

Definition of SSI

SSI was defined using the Center of Disease Control (CDC) guidelines in most of the studies [27,161,163,164,167,170,171,175]. Other strategies for SSI confirmation included using a microbiological test [162,165] or if a patient required antibiotic treatment for wound problems [166,174]. Lynch et al. [168] defined an SSI based on pus discharge or a wound with a score of greater than ten on ASEPSIS, a scoring mechanism for postoperative SSI [176]. Reilly et al. [169] defined an SSI as pus or painful skin inflammation indicative of cellulitis.

Patients were followed-up for the occurrence of SSI for at least 30 days [27,161,168,169] with two studies following up SSI patients until the wound had healed [163,170]. Approaches to diagnose post-discharge SSI included outpatient clinics or primary care visits [27,169,170], surveys/questionnaires [161,168], or a home visit [163].

Patient matching

An imbalance of patient characteristics can bias and confound the cost calculation of SSI patients. This is analogous to an observational non-RCT setting where the difference in outcomes may be partially or wholly explained by factors other than the presence of SSI. Some form of patient matching in the analysis to adjust for confounding variables was used in most studies [27,161,162,164,165,167,171–173,175]. However, justification for the selected matching variables was given in less than half of these studies [27,162,164,165,173].

Setting and procedure

Public teaching hospitals [27,161–163,165–168,171,172,175] were the setting for majority of the studies with one hospital setting unclear [169], and another study referring to unspecified referral hospitals [170]. Study settings were mostly restricted to a single site with only four studies involving multiple hospitals [164,170,173,174]. Surgical procedures ranged from

general surgery or multiple surgery categories (n=8), cardiothoracic (n=1), colorectal (n=2), gynaecological (n=1), and orthopaedic (n=4). The patient population were all adult patients.

Half the studies that assessed SSI across surgical categories reported surgery category-specific costs associated with SSI [161,168,169,172]. All of these studies showed variation of SSI costs across surgical categories. Severity of SSI was always associated with increased costs. A deep SSI was more costly compared to a superficial SSI in all studies that had severity-specific SSI costs [161,165,172,174]. Yet, the stated approaches to classify the superficial versus deep SSI differed. Approaches to define superficial SSI included CDC criteria [174], or a treatment for an infection at the surgical site within 30 days postoperatively [172], or were not defined [165]. Approaches to classify a deep SSI included a microbiological confirmation of tissue from a further surgery [165], or an SSI requiring surgery [172] or using CDC criteria [174]. The sample size of SSI patients in the European studies ranged from as low as 17 patients to as high as 513 patients.

Cost components

The type of costs included and considered in each of the studies is shown in Table 3.2 and Table 3.3. All studies considered at least some form of direct medical costs in their cost calculations. However, there was a considerable variation in the description and the number of direct medical cost items included in each study. In terms of the costs arising from the initial hospitalization of patients, the description of the included cost components ranged from an unspecified cost per bed day to a comprehensive bottom up costing of the hospital length of stay, consumables, diagnostics, overhead, reoperation and staffing costs. Non-hospital costs were also considered in some of the studies including post-discharge costs from general practitioner/ nurse visits [27,163,168,169], and patient/community costs of wound dressings.

Table 3.2 Costs of surgical site infection in European studies

Lead author (Year)	Adjusted group comparison	Costs included	Mean cost of SSI patients (dispersion statistic)	Mean costs of no SSI patients (dispersion statistic)	Mean additional cost of SSI (dispersion statistic)	Mean Length of Stay (dispersion statistic)
Cardiothoracic surgery						
Graf (2010) [175]	Age, sex, DRG, preoperative LOS	Surgery, lab tests, hospital LOS	$50,912* (95% CI: $43,565-$67,479)	$18,751* (95% CI: $16,933-$25,175)	$32,161† (not stated)	SSI: 34.4 days* (95% CI: 30.1-38.6); No SSI: 16.5 days* (95% CI: 14.0-17.5);
Colorectal surgery						
Tanner (2009) [163]	Unadjusted analysis	Hospital stay, nurse & GP visits, outpatient clinic, wound dressing, readmissions, antibiotics, wound swab	Not stated	Not stated	$18,101 (not stated)	SSI: Extra 22.72 days (not stated); No SSI: not stated
Turtiainen (2010) [170]	Unadjusted analysis	LOS, Outpatient clinic and rehabilitation	Not stated	Not stated	$4,237 (not stated)	Not stated
Gynaecological surgery						

Lead author (Year)	Adjusted group comparison	Costs included	Mean cost of SSI patients (dispersion statistic)	Mean costs of no SSI patients (dispersion statistic)	Mean additional cost of SSI (dispersion statistic)	Mean Length of Stay (dispersion statistic)
Hyldig (2018) [174]	Unadjusted analysis	Inpatient stays, outpatient care, antibiotic treatment, postoperative dressing, primary care visits	Not stated	Not stated	Superficial SSI: $21 (not stated); Deep SSI: $9,527 (not stated)	Not stated
Multiple surgical categories						
Alfonso (2007) [27]	Age, sex, diagnosis, surgery duration, comorbidity, and procedure	Hospital Stay, readmission, diagnostics, antibiotics informal care, primary care, productivity loss	Not stated	Not stated	Health care costs: $15,263; Informal care: $15,734; Societal costs: $145,336; (not stated)	SSI : 21.43 days (SD: 20.54); No SSI: 7.63 days (SD: 3.89)
Defez (2008) [171]	Age, sex, ward type, principal diagnosis	Hospital stay, laboratory tests, radiology, surgery, diagnostics, & antibiotics	Not stated	Not stated	$2,780 (SD: $6,477)	Not stated
Jenks (2014) [161]	Surgery, age and NNIS risk index	Overhead, staffing costs, readmission, reoperation, hospital stay, diagnostics, consumables	$19,480* (95% CI: $16,863 - $21,564)	$8,795* (95% CI: $8,654 - $8,928)	$7,894* (95% CI: $6,965- $10,124)	SSI: 19 days* (95% CI 17-21); No SSI: 5 days* (95% CI: 5-15)

Lead author (Year)	Adjusted group comparison	Costs included	Mean cost of SSI patients (dispersion statistic)	Mean costs of no SSI patients (dispersion statistic)	Mean additional cost of SSI (dispersion statistic)	Mean Length of Stay (dispersion statistic)
Lynch (1992) [168]	Unadjusted comparison	GP visits, wound dressings, antibiotic costs, hospital stay	$3,678 (not stated)	$2,116 (not stated)	$1,563 (not stated)	No overall figures reported
Reilly (2001) [169]	Unadjusted comparison	Hospital stay, readmissions, GP and nurse visits, wound dressings, antibiotic prescriptions	Not stated	Not stated	$541 (not stated)	Not stated
Vegas (1993) [167]	Diagnosis, procedure, age	Hospital stay	Not stated	Not stated	$10,688 (not stated)	SSI: extra 14.33 days (SE: 2.53)
Vrijens (2012) [173]	Destination after discharge, hospital, comorbidity, ward, Age, DRG	Hospital stay	Not stated	Not stated	$3,149 (95% CI: -$148.4 – $4,526)	SSI: 35.2 days (not stated); No SSI: 29.2 days (not stated)

Lead author (Year)	Adjusted group comparison	Costs included	Mean cost of SSI patients (dispersion statistic)	Mean costs of no SSI patients (dispersion statistic)	Mean additional cost of SSI (dispersion statistic)	Mean Length of Stay (dispersion statistic)
Weber (2008) [172]	Age, procedure, and NNIS risk	Antibiotic use, postoperative LOS, hospital costs and patient charges	$45,196 (95% CI $36,807-$53,585)	$28,137 (not stated)	Overall: $17,060 (95% CI: $7,377 - $26,742); Superficial SSI: $2,226 (95% CI: -$4,209- $9,335); Deep incisional SSI: $3,801 (95% CI: $10,626-$19,378); Organ space SSI: $34,001 (95% CI: $17,220-$61,060)	SSI: 29 days; No SSI: 12.3 days
Orthopaedic surgery						
Edwards (2008) [166]	Unadjusted analysis	Inpatient stay, equipment, surgery consumables and staff salaries, medication, investigations, antibiotics	$49,290 (range: $8,336-$178,565)	$17,060 (range: $6,555 - $137,879)	$32,229 (not stated)	SSI: 76 days (not stated); No SSI: 22 days (not stated)

Lead author (Year)	Adjusted group comparison	Costs included	Mean cost of SSI patients (dispersion statistic)	Mean costs of no SSI patients (dispersion statistic)	Mean additional cost of SSI (dispersion statistic)	Mean Length of Stay (dispersion statistic)
Parker (2018) [164]	Age, sex, trial site, wound grade, diabetes, height, weight, and smoking status	Hospital inpatient & outpatient services, community health & social care, medication, aids and adaptations	Complete case analysis unadjusted: $22,255 ($978)	Complete case analysis unadjusted: $20,429 ($2,567)	SSI multiple imputation: $2,866 (95% CI:-$2,032 - $7,765); SSI complete case analysis adjusted: $299 (95% CI - $6,249-$6,847)	Not stated
Pollard (2006) [162]	Sex, age, fracture type, ASA grade, pre-fracture residence type, operation, social dependency & mobility scores	Hospital LOS, Antibiotics, outpatient treatment, theatre time, prosthetic costs, radiology, physiotherapy	$44,157* (IQR: $27,370-$69,952)	$13,043* (IQR: $7,760-$19,501)	$31,114† (not stated)	SSI: 80 days* (IQR: (43-146); No SSI: 28 days* (IQR: 13-53)

Lead author (Year)	Adjusted group comparison	Costs included	Mean cost of SSI patients (dispersion statistic)	Mean costs of no SSI patients (dispersion statistic)	Mean additional cost of SSI (dispersion statistic)	Mean Length of Stay (dispersion statistic)
Thakar (2010) [165]	Sex, age, fracture type, ASA grade, operation, pre-fracture residence type, social dependency & mobility	Theatre time, prosthetic costs, radiology, and pharmaceuticals	Superficial SSI: $30,193 (range $11,610 – $72,533) Deep SSI: $39,299 (range: $19,623 – $104,631)	Superficial SSI control: $13,987 (range: $5,460– $44,173); Deep SSI control: $13,631 (range: $7,247– $77,253)	Superficial SSI: $16,206 (not stated); Deep SSI: $25,669 (not stated)	Superficial SSI: 62.5 days; Superficial SSI control: 35 days; Deep SSI: 79.3 days; Deep SSI matched control: 34.3 days

All costs were inflated and converted to 2017 international dollars where appropriate.

*Median; † Difference in Medians calculated from paper;

ASA grade, American Society of Anaesthesiologists; CI, Confidence Interval; DRG, Diagnosis-related group; GP, General Practitioner; HAI, Hospital Acquired Infection; IQR: Interquartile range; LOS, Length of stay; NNIS, Nosocomial Infection Surveillance System risk index; SD, Standard Deviation; SE: Standard Error; SSI, Surgical Site Infection

Table 3.3 Cost information included in each European study

Lead author	Cost year	Cost subdivided	Hospital stay	Diagnostics	Medication excluding antibiotics	Antibiotics	Hospital Readmission	Outpatient	Patient or Family costs	COI reporting checklist score
Alfonso [27]	Y	Y	Y	Y	N	Y	Y	Y	Y	21
Defez [171]	N	Y	Y	Y	N	Y	N	N	N	15
Edwards [166]	N	Y	Y	Y	N	Y	N	N	N	13
Graf [175]	N	Y	Y	Y	N	N	N	N	N	12
Lynch [168]	Y	Y	Y	N	Y	Y	N	Y	Y	19
Jenks [161]	N	N	Y	Y	N	N	Y	N	N	18
Hyldig [174]	Y	N	Y	Y	Y	Y	Y	Y	N	18
Parker [164]	Y	Y	Y	Y	Y	Y	Y	Y	N	20
Pollard [162]	Y	N	Y	N	N	Y	N	Y	N	10
Reilly [169]	Y	N	Y	N	N	N	Y	Y	Y	14
Tanner [163]	Y	Y	Y	Y	N	N	Y	Y	N	15
Thakar [165]	Y	N	Y	Y	Y	Y	N	N	N	14
Turtiainen [170]	N	N	Y	N	N	N	N	Y	N	11
Vegas [167]	Y	NA	Y	N	N	N	N	N	N	13
Vrijens [173]	Y	NA	Y	N	N	N	N	N	N	17
Weber [172]	Y	N	Y	N	Y	Y	N	N	N	16

COI=Cost of illness; Y= Yes; N= No; NA= Not applicable; UC= Unclear

To facilitate a cost comparison across studies, a specified year for which the costs are applicable allows for the findings to be inflated correctly. The cost year was not stated in six studies [161,166,168,170,171,175]. Transparency on the amount that each cost component is contributing to the additional cost of SSI clarifies which aspects of medical care are driving the additional cost burden. However, the additional cost of SSI was not broken down into their cost components in seven studies [162,164,167,170,172,174].

All but one study restricted costs to the perspective of the health care payer. Alfonso et al. [27] widened the perspective to societal and looked at direct and indirect costs associated with SSI including hospital, primary care, informal care, and productivity loss.

Resource use

The reporting of resource use of SSI and no SSI patients was inconsistent across studies. Beyond the main resource item of hospital length of stay, there was little detail on the differential resource use of SSI and no SSI patients. A Spanish study [27] reported that patients with an SSI had significantly longer durations of use for hospital consumables (catheters, and antibiotics) compared with patients without an SSI. However, resource use details were omitted on general practitioner/ nurse visits and the level of informal care needed. Reilly et al. [169] (UK) presented a breakdown of resource use for SSI patients only.

Cost of surgical site infection

Overall, there was a lack of detail in the reporting of costs for SSI and no SSI patients. Average costs of both the respective SSI and no SSI patients groups were omitted for the majority of studies [27,163,167,169–171,173,174].

The variability of costs within studies is also of interest to indicate how dispersed postoperative costs are for the patient population and if the costs variation between patients is

similar by SSI status. Where a dispersion statistic was reported (e.g. Interquartile range, 95% Confidence Interval, range), the cost variability was higher in the group of patients with an SSI compared to the group of patients without an SSI in most studies [161,162,165,166,175].

Lynch et al. [168] had the lowest relative magnitude of cost difference with SSI costs being 1.73 times higher than no SSI costs. The authors had estimated the costs of SSI and no SSI patients as $3,678 and $2,116 respectively [168]. They had also broken results down by inpatient SSI and outpatient SSI, and the inpatient SSIs were 3.83 times more expensive than outpatient SSIs on a per-patient basis.

Pollard et al. [162] reported the highest relative magnitude of cost difference with SSI costs being 3.39 times higher than no SSI costs. For elderly proximal femoral fracture surgery patients, they had estimated the costs of SSI and no SSI patients to be $44,157 and $13,043 respectively. Their inclusion criteria meant that the SSI patients were those who specifically needed further surgery, representing an upper estimate of the additional costs of an SSI.

While all eligible studies had to present a cost difference between SSI and no SSI patients, there was a lack of reporting of the average costs for the SSI and no SSI patient groups used to calculate the difference (Table 3.2). All studies showed an elevated cost of SSI relative to no SSI patients. In the four studies where 95% confidence intervals were reported with the mean additional cost of SSI, the range included a zero in half of these studies[164,173]. The additional medical costs of SSI, which included costs incurred by the hospital and health system, ranged from $21 to $34,001 per patient.

The lowest additional cost associated of SSI was estimated in a Danish study assessing the cost-effectiveness of incisional negative pressure wound therapy in obese women after caesarean section [174]. In addition to the cost-effectiveness results, the study also provided a

per-patient cost of superficial SSI and deep SSI compared with patients who did not suffer an SSI. The superficial SSI was defined as requiring antibiotic treatment for an infection at the surgical site within the first 30 days after the caesarean section and not requiring further surgery. The highest additional health care cost associated with SSI was estimated by Weber et al. [172]. While the average additional cost of all SSI patients was $17,060, an organ space SSI approximately doubled the additional cost of an SSI in their case-control designed study.

Alfonso et al. [27] (Spain) was the only study to adopt a broader societal perspective and included the cost of productivity loss, informal care and health care costs. They estimated the cost associated with SSI to be an additional $145,366 per patient. This estimate comprised productivity costs (78.7%) with carer costs (10.8%) and health costs (10.5%) making up the remainder. Including only the health care costs made the additional cost of SSI $15,733 per patient.

Checklist

All studies were compared against a modified reporting Müller Cost of Illness study checklist (see Table 3.3 for scores). Alfonso et al. [27] achieved the highest number of items (23 points) in the checklist with detailed descriptions of the methods used to estimate the additional costs of SSI. Turtainen et al. [170] achieved the lowest score (11 points) in the checklist with little to no description in the study on what was included in the SSI cost estimate and how it was derived. In general, studies scored relatively poorly in the evaluation methods and presentation of results section of the checklist but highly in the discussion and conclusions sections.

3.3.2 LMIC search

The LMIC studies electronic database search yielded 2,557 citations. Five additional records were identified through hand searching references of included papers. Figure 3.2 presents a flow diagram of the selection process. Fifteen studies met the inclusion criteria.

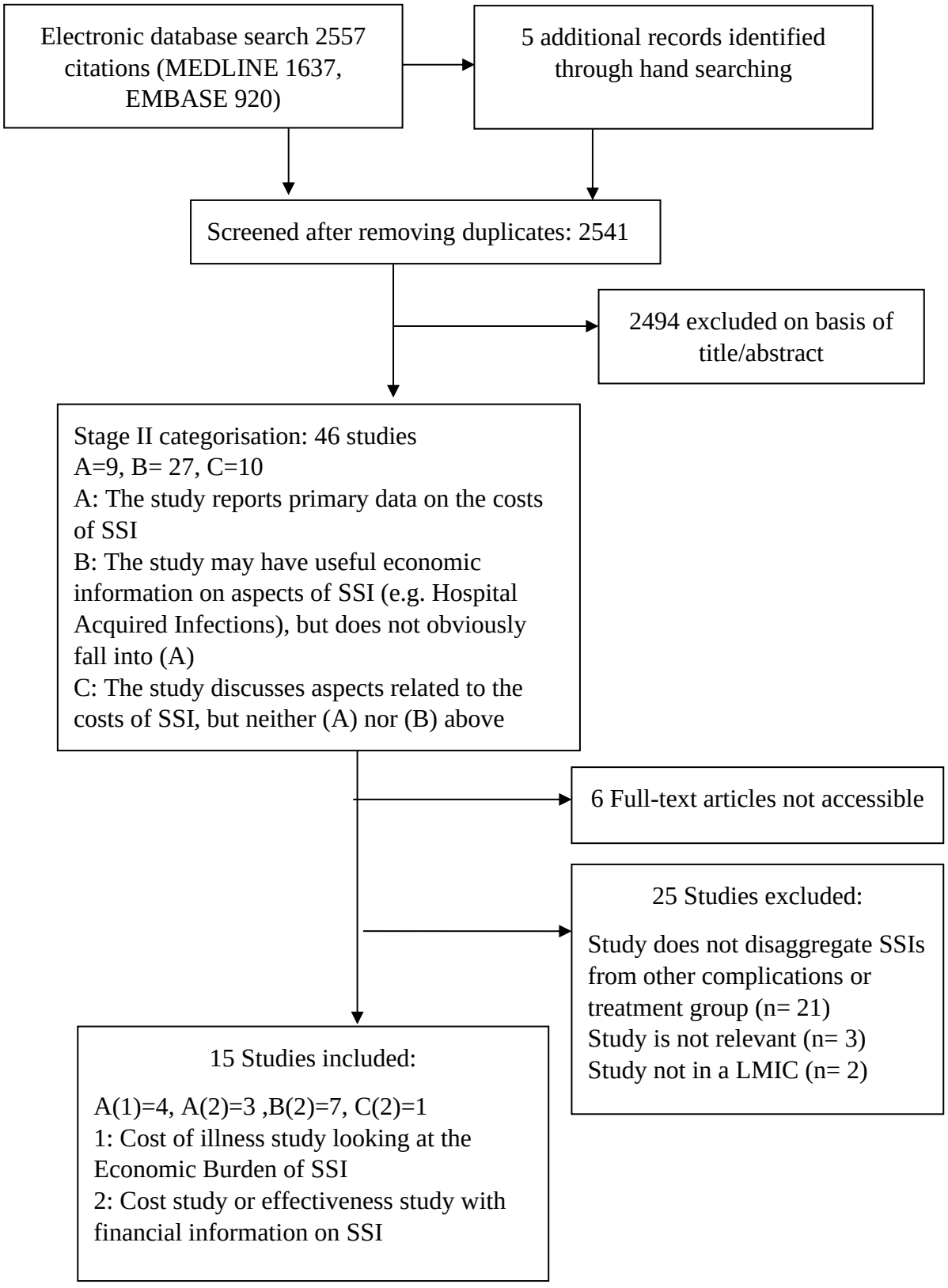


Figure 3.2 PRISMA Diagram of LMIC search

General study characteristics

The fifteen studies were published from 2003 to 2018 and data collection spanned 1999 to 2015. Studies were based in Turkey (n=3) [177–179], China (n=2) [180,181], Jordan (n=2) [182,183], Thailand (n=2) [184,185], Brazil (n=1) [186], Egypt (n=1) [187], India (n=1)[188], Mexico (n=1) [189], Rwanda (n=1) [190], and South Africa (n=1) [191]. According to the World Bank classifications, the studies were part of the following income groups: Low Income Country (n=1) [190], Lower Middle Income (n=2) [187,188] and Upper Middle Income (n=12) [177–186,189,191]. Table 3.4 shows general characteristics of each study included in the review.

Definition of SSI

The Center of Disease Control guidelines were used in the majority of the studies to define an SSI [177–182,186–189,191]. However, three studies lacked a definition of what constituted an SSI [184,185,190]. One study classified an SSI based on the wound discharge culture or other SSI suggestive signs and symptoms but these were not elaborated further [183].

Post-discharge SSIs cannot be detected where there is no follow-up. In this review, patients were not followed up after hospital discharge or it was not indicated in many of the studies [180,181,183–186,188,190,191]. Where follow-up was specified, it was only recorded if the patient happened to return to the index hospital in two studies [177,182]. The only specified method of follow-up in the studies was attendance of an outpatient clinic attendance a month after the patient's operation [177,179,187,189].

Table 3.4 LMIC Study characteristics

Lead author (Year) [Income Group]	Country	Patient population	Setting	Study aim	Study Type	Number of SSI & No SSI	Period of data collection
Cardio-thoracic surgery							
Al-Zaru (2011) [182] [Upper Middle Income]	Jordan	CABG adult patients	Teaching hospital	Assess clinical and economic impact of SSIs	Retrospective cost comparative study	SSI: n=106; No SSI: n=525	2005-2008
Coskun (2005) [177] [Upper Middle Income]	Turkey	CABG adult patients referred back with Sternal SSI	Private hospital	Evaluate costs and outcomes for Sternal SSI	Prospective surveillance	SSI: n=88; No SSI: n=88	1999-2002
Cardiac & Neurological surgery							
Zhou (2015) [181] [Upper Middle Income]	China	Patients who had a craniocerebral operation	Tertiary care hospital	Cost-benefit analysis of SSI control	Prospective economic analysis study	SSI: n=12; No SSI: n=588	2009-2012
Hweidi (2018) [183] [Upper Middle Income]	Jordan	Adult patients who underwent a craniocerebral operation	Teaching hospital	Estimate the additional healthcare costs attributable to SSI	Retrospective Case Control study	SSI: n=32; No SSI: n=32	2009- 2015

Lead author (Year) [Income Group]	Country	Patient population	Setting	Study aim	Study Type	Number of SSI & No SSI	Period of data collection
Gastrointestinal surgery							
Liu (2018) [180] [Upper Middle Income]	China	Colorectal cancer adult patients who had tumour surgically removed	Tertiary public hospital	Economic burden caused by HAIs	Retrospective SSI surveillance cost analysis	SSI: n=20; No SSI: n=38	2015
Özmen (2016) [179] [Upper Middle Income]	Turkey	Elective gastric surgery cancer patients	Teaching hospital	Factors affecting SSI rate	Prospective observational cohort study	SSI: n=10; No SSI: n=42	2013
Phothong (2015) [184] [Upper Middle Income]	Thailand	Patients with sigmoid cancer	Teaching hospital	Outcomes and treatment costs following a sigmoidectomy	Retrospective review and economic analysis	SSI: n=6; No SSI: n=44	2008-2013
Silverstein (2017) [190] [Low Income]	Rwanda	Biliary disease surgery patients	Referral military hospital, secondary and tertiary care	Laparoscopic cholecystectomy versus an open approach	Economic analysis of a Cohort study	Not stated	Not stated

Lead author (Year) [Income Group]	Country	Patient population	Setting	Study aim	Study Type	Number of SSI & No SSI	Period of data collection
General Surgery or multiple surgical categories							
Dramowski (2016) [191] [Upper Middle Income]	South Africa	Paediatric surgery, orthopaedics and urology patients	Teaching Children hospital	Investigate burden & risk factors of HAI	Prospective surveillance	SSI: n=21; No SSI: n=1022	2014 -2015
Galal (2011) [187] [Lower Middle Income]	Egypt	Surgery patients aged 21-60 years	Teaching hospital	Compare different sutures for SSI reduction	Prospective randomised double blind study	SSI: n=50; No SSI: n=400	Not stated
Porras-Hernández (2003) [189] [Upper Middle Income]	Mexico	Neurological, cardiovascular & general surgery patients, younger than 18 years	Tertiary teaching paediatric hospital	Determine the incidence of SSI	Prospective study	SSI: n=80; No SSI: n=348	1998-1999
Siribumrungwong (2015) [185] [Upper Middle Income]	Thailand	Varicose Vein patients	Teaching hospital	Economic evaluation of interventions for great saphenous vein ablation	Prospective economic analysis cohort study	SSI: n=4; No SSI: n=73	2011-2013
Tiwari (2013) [188] [Lower Middle Income]	India	Adult patients with at least 48 hours hospital stay	Private tertiary care hospital	Assess the costs associated with HAIs	Retrospective comparative cost analysis	SSI: n=4; No SSI: n=104	2008-2009

Lead author (Year) [Income Group]	Country	Patient population	Setting	Study aim	Study Type	Number of SSI & No SSI	Period of data collection
Gynaecological Surgery							
Köşüş (2009) [178] [Upper Middle Income]	Turkey	Caesarean surgery patients	Private hospital	Trial on the prevention of post-caesarean wound infection	Randomised prospective study	SSI: n=38; No SSI: n=76	2004-2007
Orthopaedic surgery							
Dal-Paz (2010) [186] [Upper Middle Income]	Brazil	Total knee arthroplasty patients	Tertiary level teaching hospital	Estimate the additional cost of nosocomial infections	Retrospective observational cohort study and cost analysis	SSI: n=34; No SSI: not stated	2006-2007

CABG, Coronary Artery Bypass Graft; HAI, Hospital Acquired Infection; SSI, Surgical Site Infection;

Patient matching

When estimating the additional cost burden of SSI, most of the studies did not make any adjustments in the comparison with no SSI patients or it was unclear if adjustment had been used (Table 3.5). Justification on the inclusion of the patient matching variables was only given in one of the six studies where patient matching was utilised [180].

Setting and Procedure

The setting where the findings are derived from were mainly public teaching hospitals [179,182–187,189,191] with three based in private hospitals [177,178,181,188]. All the studies were based in single centres. Surgical procedures ranged from general surgery or multiple surgical categories (n=5), oncological procedures (n=4), cardiothoracic (n=2), orthopaedic (n=1), gastric (n=1), general, cardiac and neurosurgery (n=2). The patient population was broader in the LMIC studies and varied from children (n=2), adults (n=12) and pregnant women (n=1). For the studies with SSI patients taken from multiple surgical categories, none reported costs of SSI by surgical category.

SSI severity increased the additional cost of SSI [177,180]. A subgroup analysis of one study had low sample sizes for the superficial (n=13), subcutaneous (n=6) and deep soft SSIs (n=1)[179]. Another study compared the severity of infections in three different types of surgical procedure, however, the reported cost was for all cases [189].

In general, studies tended to have a low number of SSI patients with the sample size of SSI patients in each study ranging from 4 patients [185,188] to 106 patients [182]. Six studies had twenty or fewer SSI patients [178–180,184,185,188].

Cost components

All studies estimated direct medical costs (Table 3.5). The lack of follow-up of patients beyond discharge limited most of the studies to report only inpatient hospital costs. One study had attempted to measure the direct non-medical costs, however the authors did not report it as a cost of an SSI [190]. Most studies did not report the relevant year for the cost estimation (Table 3.6). Most studies did not break down the extent to which each cost component makes up the costs of SSI and no SSI patients. Where cost components were reported in studies, it either included both SSI and no SSI patients [181,184,188] or was limited to only SSI patients [177,178,186].

Resource use

There was no reporting of resource use of SSI and no SSI patients beyond hospital length of stay in any of the studies. There was partial reporting on the additional procedures or investigations for SSI [177,186] but no detail on the total resource use by SSI and no SSI patients.

Cost of surgical site infection

The additional cost of SSI varied considerably across the studies. All but one study showed an elevated cost of SSI relative to no SSI patients. The study by Özmen et al. [179] (Turkey) study looked at outcomes of patients after elective gastric cancer surgery and found that the unspecified hospital costs were non-significantly lower for superficial SSI patients compared to no SSI patients. The calculation behind the lower SSI cost was unclear given that overall hospital costs were higher than either of the mean costs of the patient groups (SSI and no SSI).

Table 3.5 Costs of SSI in LMIC studies

Lead author (Year)	Adjusted group comparison	Costs included	Mean cost of SSI patients (dispersion statistic)	Mean costs of no SSI patients (dispersion statistic)	Mean additional cost of SSI (dispersion statistic)	Mean Length of Stay (dispersion statistic)
Cardio-thoracic surgery						
Al-Zaru (2011) [182]	Unadjusted comparison	Hospital stay, medications, radiology, microbiological & lab tests	$31,666 (not stated)	$22,329 (not stated)	$9,337 (not stated)	SSI: 16.7 days (not stated); No SSI: 7.8 days (not stated)
Coskun (2005) [177]	Age & sex	Medication, examination and lab test, hospital stay, additional operation	Not stated	Not stated	Deep SSI: $23,408 (not stated); Superficial SSI: $12,782 (not stated)	Deep SSI: Extra 35 days (not stated); Superficial SSI: Extra 21 days (not stated)
General surgery						
Dramowski (2016) [191]	Age, ward, preoperative length of stay	Hospital length of stay, laboratory investigations, radiology and pharmacy cost	Not stated	Not stated	$1,546 (not stated)	SSI : 11 days* (IQR: 5-25); No SSI: 7 days* (IQR: 5-14)
Galal (2011) [187]	Unadjusted comparison	Hospital stay	$2,465 (not stated)	$610 (not stated)	$1,855 (not stated)	SSI: 7.10 days (SD: 3.92); No SSI: 3.39 days (SD: 1.48)

Lead author (Year)	Adjusted group comparison	Costs included	Mean cost of SSI patients (dispersion statistic)	Mean costs of no SSI patients (dispersion statistic)	Mean additional cost of SSI (dispersion statistic)	Mean Length of Stay (dispersion statistic)
Porras-Hernández (2003) [189]	Unadjusted comparison	Hospital stay (excluding antibiotics)	Not stated	Not stated	$2,164 (not stated)	SSI: 13 days (not stated); No SSI: 6 days (not stated)
Siribumrungwong (2015) [185]	Not stated	Unspecified hospital costs	Not stated	Not stated	$174 (not stated)	Not stated
Tiwari (2013) [188]	Matched groups of HAI and non-HAI by age, diagnosis, illness severity	Consumables, hospital room, medications, investigations, blood components, consultation	$37,295 (SE: $4,583)	$7,685 (SE: $3,893)	$29,610 (not stated)	SSI: Not stated; No SSI: 9 days (not stated)
Gastrointestinal surgery						
Liu (2018) [180]	Age, sex, comorbidity, disease, and prior surgeries	Medication, equipment & supplies, diagnostics	Not stated	$11,691* (not stated)	Overall: $1,410* (not stated); Superficial: $462* (not stated); Subcutaneous SSI: $2,386* (not stated); Deep soft SSI: $17,094* (not stated)	SSI: Not stated; No SSI: 22 days* (not stated)

Lead author (Year)	Adjusted group comparison	Costs included	Mean cost of SSI patients (dispersion statistic)	Mean costs of no SSI patients (dispersion statistic)	Mean additional cost of SSI (dispersion statistic)	Mean Length of Stay (dispersion statistic)
Özmen (2016) [179]	Unadjusted comparison	Hospital stay	$4,195 (SD:$1,528)	$4,872 (SD: $2,123)	SSI patients had lower costs	SSI: 5.27 days (SD:3.24); No SSI: 5.40 days (SD: 2.22)
Phothong (2015) [184]	Unadjusted comparison	Room charges, theatre time, medication, anaesthesia, equipment & laboratory charges & nursing	$12,109 (range: $6,085-$32,051)	$5,960 (range: $3,840 - $17,481)	$6,149 (not stated)	SSI: 23.5 days (SD: 9.8); No SSI: 9.8 days (SD: 3.8)
Silverstein (2017) [190]	Not stated	Unclear	Not stated	Not stated	$483 (not stated)	Not stated
Cardio & Neurological surgery						
Zhou (2015) [181]	Age, sex, operation type, incision type, operation date, & physical status	Medication, equipment, lab test, treatment, exams, and additional surgeries	$16,979* (not stated)	$10,240* (not stated)	$6,739† (not stated)	SSI: 29 days* (IQR: 25-37.25); No SSI: 17.25 days* (IQR: 14.75-26.38)
Hweidi (2018) [183]	Age, sex, index diagnosis, admission month	Length of stay, antibiotics, reoperation	$34,872 (SD:$17,525)	$15,974 (SD: $7,315)	$18,899 (not stated)	SSI: 30.15 days (SD: 17.28); No SSI: 6.98 days (SD:1.75)

Lead author (Year)	Adjusted group comparison	Costs included	Mean cost of SSI patients (dispersion statistic)	Mean costs of no SSI patients (dispersion statistic)	Mean additional cost of SSI (dispersion statistic)	Mean Length of Stay (dispersion statistic)
Gynaecological surgery						
Köşüş (2009) [178]	Unadjusted comparison	Preventative antibiotics, hospital readmission and out-patient	$1,736 (not stated)	$0	$1,736 (not stated)	Two out of twelve SSI patients had 7 days readmission. No SSI: 0 days
Orthopaedic surgery						
Dal-Paz (2010) [186]	Unadjusted comparison	Hospital stay, lab and imagining test, additional operations, and antibiotics	Not stated	Not stated	$3,865 (not stated)	SSI: Extra 29.7 days (not stated); No SSI: not stated

All costs were inflated and converted to 2017 international dollars where appropriate.
*Median; † Difference in Medians calculated from paper;
CABG, Coronary Artery Bypass Graft; HAI, Hospital Acquired Infection; IQR: Inter Quartile Range; SD: Standard Deviation; SE, Standard Error; SSI, Surgical Site Infection;

Table 3.6 Cost information included in each LMIC study

Lead Author	Cost year	Costs subdivided	Hospital stay	Diagnostics	Antibiotics	Other Medication	Readmission	Outpatient	Patient or Family costs	COI reporting checklist score
Al-Zaru [182]	NR	N	Y	Y	Y	N	N	N	N	10
Coskun [177]	NR	Y	Y	Y	Y	N	N	N	N	11
Dal-paz [186]	Y	Y	Y	Y	Y	N	Y	N	N	11
Dramowski [191]	Y	N	Y	Y	Y	UC	N	N	N	16
Galal [187]	NR	NA	Y	N	N	N	N	N	N	9
Hweidi [183]	NR	N	Y	N	Y	N	Y	N	N	13
Köşüş [178]	NR	N	Y	N	Y	N	N	Y	N	11
Liu [180]	NR	N	Y	Y	N	Y	N	N	N	14
Özmen [179]	NR	N	UC	UC	UC	UC	N	N	N	7
Phothong [184]	NR	Y	Y	Y	Y	Y	N	N	N	11
Porras-Hernández [189]	NR	NA	Y	N	N	N	N	N	N	6
Silverstein [190]	Y	N	N	N	N	N	N	N	N	12
Siribumrungwong [185]	N	N	N	N	N	N	N	N	N	9
Tiwari [188]	NR	Y	Y	Y	Y	Y	N	N	N	12
Zhou [181]	N	N	Y	Y	Y	Y	N	N	N	17

COI=Cost of illness; Y= Yes; N= No; NA= Not applicable; UC= Unclear

The additional cost of SSI ranged from $174 (Thailand) [185] to $29,610 (India) [188]. None of the studies reported a confidence interval or other dispersion statistic to indicate the variability associated the mean additional cost of SSI. The lowest additional cost of SSI was from a study by Siribumrungwong et al. [185]. Their SSI cost was made up of undefined hospital costs of four SSI patients with no detail of the no SSI comparator group. The highest additional cost of SSI was from a study by Tiwari et al. [188]. For their four patients who suffered an SSI, drug acquisition costs, length of stay and antimicrobial drugs were the main cost drivers.

Clarity on the relative magnitude of difference in cost between SSI and no SSI patients was mixed. Half of studies did not present average costs of both SSI and no SSI patients. For the average costs by SSI status, a dispersion statistic was reported (e.g. standard deviation, standard error, range) in four studies [179,183,184,188], and the cost variability was found to be lower in the group of patients with an SSI compared to the group of patients without an SSI in one of these studies [179].

The lowest relative magnitude of difference in reported costs was in Jordan where SSI costs were 1.4 times higher than no SSI costs [182]. However, it is unclear what cost items are the major contributors of the additional costs. They had estimated the costs of SSI and no SSI patients as $31,666 and $22,329, respectively. The highest relative magnitude of difference in costs was in India where Tiwari et al. [188] found that SSI costs were 4.8 times higher than no SSI costs. The authors had estimated the costs of patients with SSI and patients without SSI to be $37,295 and $7,685, respectively.

Checklist

For the Cost of Illness checklist, the studies achieved on average a score of 11.07 out a maximum of possible score of 36. The lack of a stated perspective and cost year reduced the scores of many of the LMIC studies. Dramowski et al. [191] scored the highest number of items (16) in the discussion and conclusion. The lack of description of pertinent study items meant that Porras-Hernández et al. [189] scored the lowest (6).

3.4 Comparison between HIC European and LMICs studies

The CDC criteria were used for SSI diagnosis by most studies in both settings. The biggest methodological difference between the HIC and LMIC settings was the use of adjusted analyses for comparing SSI and no SSI patients. Most European studies used patient matching while the opposite was true for LMIC studies. Multicentre study settings were only present in the European studies. Slightly more European studies had follow-up beyond discharge, but the follow-up methods varied. Sample sizes of SSI patients tended to be higher in the European studies. On the other hand, LMIC studies had marginally better reporting of the average costs of the SSI and no SSI patient groups.

For the Cost of Illness reporting checklist, the European studies achieved a higher score on average compared with the LMIC studies. In both settings, studies tended to score highly in the discussion and conclusion checklist but poorly on the evaluation methods and result presentation sections.

3.5 Cost value robustness assessment

One of the goals of the review is to assess the robustness of the SSI cost value in the studies identified in the current review. Based on the desirable cost aspects discussed throughout the review, a quality checklist of the sourced cost values is presented in Table 3.7 to appraise the suitability of the values for use in the preliminary economic evaluation in Chapter 5. The

quality varied among the studies with one study achieving nearly all the applicable criteria [161].

Table 3.7 Quality assessment of cost studies for selection into preliminary model-based economic evaluation

Lead Author (Year)	21st century data collection	SSI Severity	Post-discharge Follow-up	CDC SSI definition	Patient covariate adjustment	SSI sample size >100	Multiple settings	Prospective data collection	Primary care costs	Abdominal surgery population*
HIC European studies										
Alfonso [27]	✓	×	✓	✓	✓	×	×	P	✓	P
Defez [171]	✓	×	×	✓	✓	×	×	✓	×	P
Edwards [166]	✓	×	×	×	×	×	×	×	×	×
Graf [175]	✓	×	×	✓	✓	×	×	×	×	×
Lynch [168]	×	×	✓	×	×	✓	×	✓	✓	P
Jenks [161]	✓	✓	✓	✓	✓	✓	×	✓	×	P
Hyldig [174]	✓	✓	✓	×	×	×	✓	✓	✓	✓
Parker [164]	✓	×	✓	✓	✓	×	✓	✓	✓	×
Pollard [162]	✓	×	×	×	✓	×	×	×	×	×
Reilly [169]	×	×	✓	×	×	✓	×	✓	✓	P
Tanner [163]	✓	×	✓	✓	×	×	×	✓	✓	×
Thakar [165]	✓	✓	×	×	×	×	×	✓	×	×
Turtiainen [170]	✓	×	✓	✓	×	×	✓	✓	×	✓
Vegas [167]	×	×	×	✓	✓	✓	×	✓	×	×
Vrijens [173]	✓	×	✓	✓	✓	×	✓	×	×	P
Weber [172]	✓	✓	✓	✓	✓	✓	×	×	×	P

Lead Author (Year)	21st century data collection	SSI Severity	Post-discharge Follow-up	CDC SSI definition	Patient covariate adjustment	SSI sample size >100	Multiple settings	Prospective data collection	Primary care costs	Abdominal surgery population*
LMIC studies										
Al-Zaru [182]	✓	×	✓	✓	×	✓	×	×	×	×
Coskun [177]	✓	✓	✓	✓	✓	×	×	✓	×	×
Dal-paz [186]	✓	×	×	✓	×	×	×	×	×	P
Dramowski [191]	✓	×	×	✓	✓	×	×	✓	×	✓
Galal [187]	✓	×	✓	✓	×	×	×	✓	×	P
Hweidi [183]	✓	×	×	×	✓	×	×	×	×	×
Köşüş [178]	✓	×	×	✓	×	×	×	✓	×	✓
Liu [180]	✓	×	×	✓	✓	×	×	×	×	×
Özmen [179]	✓	×	✓	✓	×	×	×	✓	×	×
Phothong [184]	✓	×	×	×	×	×	×	×	×	×
Porras-Hernández [189]	×	×	✓	✓	×	×	×	✓	×	P
Silverstein [190]	UC	×	×	×	UC	×	×	×	UC	✓
Siribumrungwong [185]	UC	×	×	×	UC	×	×	✓	×	×
Tiwari [188]	✓	×	×	✓	✓	×	×	×	×	P
Zhou [181]	✓	✓	×	✓	✓	×	×	✓	×	×

*Relevant for preliminary model-based economic evaluation in chapter 5
P: Partial; SSI: Surgical Site Infection; UC: Unclear

3.6 Discussion

3.6.1 Statement of principal findings

This review assessed the estimated the cost burden of SSIs in the reported literature for both LMICs and a selection of European High Income Countries. For medical costs, the additional cost of SSI was $21 to $34,000 in European studies while the additional cost attributed to SSI ranged from $174 to $29,610 in LMICs. The huge range of costs in both settings reflects the difficulty associated with accurately estimating the costs attributable to SSI and consequently limited cross-study comparability of findings. The higher variability in average costs in patients with SSI within studies signals that the healthcare resources consumed for each SSI patient can fluctuate markedly. Five main challenges to the estimation of the costs are summarised below:

1. ***Time horizon and follow-up:***

   Studies from both settings used the CDC criteria to define SSI, but the lack of follow-up in LMIC studies resulted in a failure to meet to meet the recommended time needed to detect an SSI. According to the CDC, the specified time horizon for an SSI to occur is up to 30 days post-surgery for non-implant operations and up to 12 months for implant operations. Where no follow-up exists, there is a risk of underestimating the true number of SSI patients and skewing the cost burden information to only patients with an inpatient SSI. The type of follow-up method will affect the detection rate but this was rarely mentioned in studies. Inadequate IT infrastructure in LMIC healthcare systems has been implicated as the cause of poor follow up through health care pathways [192].

2. ***The choice of comparator:***

   The selection of the counterfactual group of patients without SSI was important in the estimating the additional cost burden of SSI. Most LMIC studies did not use any

adjustments for potential confounders which risked producing a false estimation (overestimate or underestimate) of SSI costs due to an imbalance in the characteristics of the comparators. For example, some of the differences in costs between SSI patients and no SSI patients could be due to greater levels of comorbidity in one group, causing a higher estimated additional cost for SSI than may otherwise be true. In contrast, most European studies adjusted for potential confounders, but few gave justification for the included matching variables. Proper consideration of matching variables can help avoid the problem of undermatching or overmatching in case-control studies [152].

3. **Over reliance on single centre studies:**

Both settings had an overreliance on single centre studies and the lack of multi-centre settings affected the representativeness of the findings. Greater numbers of hospitals participating and more diversity in hospital settings for each study would help strengthen the applicability and robustness of any findings. Some studies with a patient population across multiple surgical categories indicated differential additional SSI costs by procedure. However, this was only reported in the European studies and there was no clear signal on which procedures would be the costliest across these studies. Some studies had low numbers of SSI patients; cost estimation with a small sample size are prone to unreliability and imprecision. This has an impact on the interpretation of the results given that the differences in costs between SSI patients and no SSI patients could be driven by chance or extreme values. In general, the European studies had more patients, but this could be as a result of better SSI surveillance.

4. **Lack of studies in Low Income and Lower Middle Income countries:**

The LMIC studies found in the review span across different continents, patient populations, surgical procedures, income levels, health systems and cultures. However,

there was an underrepresentation of studies in Low Income countries and Lower Middle Income countries making the generalisability of the overall findings to these settings more difficult.

5. **Inconsistency in consideration of costs and narrow cost perspective:**

   The type of costs included will have a direct impact on the estimation of SSI costs. The cross-country cost comparison of SSI was hindered by the absence of a standardized approach in the basket of cost items included. However, even when a standardized approach is adopted as in a multinational randomised control trial, costs and resource use will differ across countries [111]. Variations in clinical practice and relative prices across countries will affect the transferability of healthcare resource use and costs [141]. Despite an SSI has far-reaching resource use implications for the healthcare system, patient and community, costs from the patient's perspective were not considered in any LMIC study. The absence of patient and societal costs are concerning given the relatively high out of pocket expenditure faced by patients in LMICs. Lack of consideration of these costs is likely to underestimate the true cost burden of SSI, and one of the European studies found that the addition of informal care alone doubled the costs associated with SSI [27].

3.6.2 Strengths and weaknesses

The strength of this study is that it is the first systematic review to specifically investigate the economic impact of SSI in LMICs. By including a parallel review of SSI with HICs in Europe, the review offers new insight into the methodological considerations and the potential data gaps in SSI cost studies from the contrasting settings.

A limitation relates to the use of an *implied* PPP exchange rate for some of the LMIC settings and the English language restriction for the article inclusion criteria. A PPP exchange rate is used to adjust for the cost of living differences between countries. Relying on implied PPP

rates for adjusting the comparative cost results is likely to introduce measurement error in the study findings compared to those using official PPP rates [193]. A previous study looking at risk factors for child conduct problems and youth violence in LMICs reported that including only English language studies was likely to have reduced the number of potentially relevant articles by around 15% [194].

3.6.3 Comparison with other studies

Previous systematic reviews have looked at the costs of a SSI, mainly in high income countries [195–197]. Similar issues were encountered on the lack of standardized approach, insufficient detail on how costs were derived, and the failure to include societal costs. To better articulate the first two study issues, the present review added the use of a cost of illness reporting checklist to give an indication of the study transparency and comparability. In contrast to the previous systematic reviews, the search criteria of the present study were not limited by date to be as inclusive as possible. A previous systematic review established that many essential surgical interventions are cost-effective in resource poor countries [198]. However, complications such as SSI can impose unforeseen additional costs in these countries, which are overlooked by most of the studies included in the paper.

3.6.4 Implications for practice

An SSI is the most common hospital acquired infection in LMICs [199]. Preventing SSIs will decrease the financial burden of both the patient and health system. Hospital bed overcrowding is problematic in LMICs [200–202] and any reduction in SSIs would help to increase capacity in bed days.

There is need for multicentre studies with large number of SSI patients to capture relevant costs and consequences of the infection across settings. The use of a standardized data

collection pathway will help improve cross-study comparability. Future studies should include more detailed information on analytic approaches in the methods along with rationale and discussion of their likely impact on results. Ideally, reporting should include resource use, costs and cost categories of SSI and no SSI patients to give more context on the key influences for the cost difference between patient groups. The identification, measurement and collection of costs should as far as possible take a societal perspective to appropriately encompass all healthcare, patient and wider society costs that may be affected by an SSI. The costs of inpatient SSI and outpatient SSI need to be differentiated given that the former is plausibly more expensive from increased inpatient bed days. Subgroup analysis would allow the heterogeneity to be examined between these groups instead of being masked in overall figures.

Future studies should endeavour to achieve the most appropriate time horizon to include appropriate complications, focus on a comparator that has a degree of matching of patient characteristics, and researchers should limit their focus on single centre studies to increase generalisability. These three items are typically within the gift of researchers during the design stage. The impact of SSI in low-income countries is likely to be severe and more research in these setting is required with particular care on choosing the right perspective for the collection of cost data, which is key to ensuring the appropriate financial burden captured. Agreement on what would the composition of a standardised basket of items of costs to include would also be extremely helpful.

3.7 Conclusion

An SSI represents a financial burden in both high income and LMICs settings. The magnitude of the cost difference depends on the SSI definition used, severity of SSI, patient population, choice of comparator, hospital setting, and cost items included. Huge heterogeneity in design and lack of transparency has made it difficult to draw meaningful comparison across studies and countries. One study adhered to most of quality criteria for SSI [161]; this will now be taken forward for use as a model input for Chapter 5. Alternative values will be used in the deterministic sensitivity analysis of the model. With the systematic review on the additional costs of SSI complete, the next Chapter presents the systematic review on the health state valuations associated with SSI.

Chapter 4:

Systematic review on the health state valuations associated with SSI

When assessing the value for money of interventions to reduce Surgical Site Infection (SSI), both the costs and quality of life implications of SSI are of interest. Chapter 3 reviewed the literature on the costs associated with SSI. This Chapter aims to assess the literature on the utility values associated with SSI. The objective is to obtain an outcome value for use in the preliminary model-based economic evaluation in Chapter 5. A comprehensive assessment of the current literature will also inform the primary work of developing outcome measures associated with SSI (Chapter 9) and assess the rationale for undertaking the primary work given the existing evidence.

The Chapter is structured as follows: a brief background on the challenges associated with the measurement of utilities for SSI with the objectives of the systematic review are detailed; the methods of the systematic review are then listed, and the results of the search are presented, appraised, and critiqued. Lastly, the discussion will reiterate the main findings and the implications of the current state of the literature of SSI utility values.

4.1 Background

As mentioned in Chapter section 2.4.5, there are direct and indirect methods that can be used to obtain Health State Valuations associated with SSI to calculate Quality Adjusted Life Years (QALYs). Direct methods ask individuals to value hypothetical health states, presented in vignettes describing the severity of the complications. The direct health state valuation techniques include Standard Gamble (SG), Time Trade Off (TTO), Discrete Choice Experiments (DCE), and Visual Analogue Scale (VAS). Indirect methods include using a

preference health related quality of life measures such as the EQ-5D [94], SF-6D [203] and the Health Utility Index [204].

An SSI can have both significant physical and psychological impacts on a patient's quality of life [205,206]. However, quantifying these impacts when calculating utilities associated with Surgical Site Infection has many challenges. First, there are different definitions on what constitutes an SSI diagnosis which will affect the inclusion diagnostic criteria of those who are considered to have suffered an SSI in a study [207]. Second, the quality of life decrement associated with SSI is calculated as the difference between the quality of life of those with and without SSI, respectively. Thus, the selection of who is included as the patient without SSI for the quality of life comparison will impact the calculated decrement. As quality of life will vary due to factors other than the presence of an SSI, having similar patients for the SSI decrement calculation can help account for confounding [208]. Participants completing quality of life questionnaires may have different quality of life scores to non-responders and informative missingness can distort the true impact when evaluating the quality of life on the completed questionnaires alone [209].

The timing of when a Health Related Quality of Life (HRQOL) measure is implemented [210] in relation to the infection trajectory [22,211,212] will affect the utility value calculation. Since the impact of SSI on quality of life is not anticipated to be constant throughout the duration of the infection, the timepoint(s) that the quality of life is measured is of importance. A patient's preoperative HRQOL can be an important determinant of their postoperative HRQOL and it is recommended that their postoperative scores make adjustments for their baseline scores [213,214]. The quality of life impact of an SSI will be affected by the health state valuation method and mapping algorithm where applicable. The

person quantifying the impact of on quality of life –patient , medical professionals, general public –will affect the utility value calculation [215].

A previous systematic review [210] assessed the evidence base of SSI health utility values and concluded that these estimates were of questionable quality. The aim of this Chapter is to update the Gheorghe review [210] to include and assess the articles published since that review. This systematic review will specifically focus on utility values that can be used to calculate QALYs or Disability Adjusted Life Years (DALYs) in the anticipation that the data will be useful in a preliminary model-based evaluation, described in Chapter 5.

The objectives of the review are as follows:

1. To identify and critique the utility values on the impact of SSI that have either been used in published model-based economic evaluations or that have been developed in patient-level studies and assess the robustness of these values for use in an economic evaluation;
2. To critique the utility values identified in the previous review and assess the robustness of these values for use in an economic evaluation.

4.2 Methods

The systematic review adhered to the guidelines of the UK Centre for Review and Dissemination guidelines [154] and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [216].

4.2.1 Search strategy

The previous systematic review covered the literature from database inception until 2014. A search was undertaken on the 9th December 2022 across the five databases (Medline, Embase, Web of Science, NHS EED and Tuft CEA registry) from 2014 onwards. The search terms were adapted from the previous systematic review and are found in Appendix A4.1.

4.2.2 Eligibility criteria

Studies were included if they had developed and reported a utility value impact associated with a patient suffering an SSI (primary research) or had referenced and stated the utility value impact of suffering an SSI in a model-based economic evaluation (secondary research). To assess the SSI utility value impact, studies needed to report or provide information for the calculation of quality of life difference between the patients with an SSI and those in a no SSI control group (SSI utility decrement/increment).

Studies that used a different term for SSI were included, provided that the wound outcome was related to surgery. This covered labels such as periprosthetic joint infection, fracture-related infection and surgical wound infection. For an indirect valuation of SSI, the health-related quality of life instrument scores not mapped onto a utility scale were not included. There were no restrictions on country. Studies ineligible for the review were non-English language publications, conference abstracts, study protocols, commentaries, editorials, and studies covered in the original review.

4.2.2 Study selection

Study selection underwent a three-stage categorisation process to determine study eligibility using methods described elsewhere [157]. Two reviewers carried out the study screening and data extraction (MM, EW). One reviewer (MM) undertook all study screening and data extraction for the bibliographic search, and another reviewer (EW) screened a random subsample of the literature search (20%) to assess agreement. Disagreement on study screening were settled through discussion and a third independent reviewer (TR) advised where agreement could not initially be settled.

Stage 1 categorisation

A. The study mainly reports primary data on SSI utility or quality of life
B. The study contains useful primary or secondary SSI quality of life or utility data
C. The study may have useful economic information on aspects of SSI care, but does not fall into A or B
D. The study discusses aspects related to SSI care but neither A, B or C
E. The study has no relevance to SSI

Stage 2 categorisation

1. Cost-utility analysis reporting SSI utility decrement or DALY data
2. Cost-utility analysis not reporting SSI utility decrement or DALY data
3. Effectiveness study with SSI health utility decrement data
4. Effectiveness study where the SSI health utility decrement cannot be calculated
5. Methodological study on aspects of economic assessment of SSI
6. Review of medical or economic information
7. The study has no relevance to SSI

The study characteristics along with methods concerning the utility measurement of patients with and without SSI were extracted from each eligible study. This information was presented in tables and a narrative comparison of studies was undertaken. No studies were excluded on quality grounds. However, a quality assessment was undertaken on each study on the robustness of the utility estimates for selection of the most appropriate model inputs for the preliminary model-based economic evaluation.

To aid the selection of suitable SSI and no SSI utilities for the preliminary economic evaluation in Chapter 5, a de novo quality checklist was created to check the robustness of the utility values of the included studies in both the current and previous review and is presented in the last section of the results. At a minimum, only sourced utility values that contained SSI and no SSI values within the same reference were included for this section. The quality criteria was at follows: (1) Utility aspects evaluated included whether the health states descriptions matched those of postoperative patients with and without SSI; (2) whether the outcome measure is recommended for priority setting by NICE [72]; (3) whether patients have their HRQOL measured at same consistent timepoint; (4) whether multiple timepoints were used; (5) whether adjustment was made to the data in terms of preoperative utility scores; (6) whether adjustment was made to the data in the presence of patient confounding; and (7) whether severity levels of SSI were presented. As the preliminary economic evaluation will have an abdominal surgery patient population, an extra criterion (8) that the SSI and no SSI utility values were applicable to this population was also added.

4.3 Results

The bibliographic database search produced 6,034 citations. A PRISMA diagram of the selection process is shown in Figure 4.1. The search found 24 studies eligible for inclusion in the review, 19 model-based economic evaluations and 5 patient level studies. No studies used DALYs as an outcomes measure.

The country setting for studies included USA (n=16) [217–232], Canada (n=1) [233], Australia (n=1) [234], UK (n=5) [164,235–238], and Italy (n=1) [239]. The surgery categories included Cardiac (n=2) [222,223], Orthopaedic (n=9) [164,218,224,227,229,232,235–237], Colorectal (n=3) [220,233,239], Gastrointestinal (n=1) [226], General (n=2) [219,221], Multiple (n=1) [234], Obstetrics and Gynaecology (n=2) [230,231], Oncology (n=2) [225,228], and Vascular (n=2) [217,238].

4.3.1 Model-based economic evaluations

Table 4.1 describes the characteristics of the included model-based economic evaluations. The model types were either Markov models (n=5) [218,229,232,233,235] or decision trees (n=14) [217,219–223,225,226,228,230,231,234,237,239]. Few studies evaluated interventions where SSI was not a stated focus for prevention (n=4) [218,219,228,233]. The declared time horizon of the decision analytic models ranged from 47 days to a lifetime. Three studies did not state a time horizon [218,222,234].

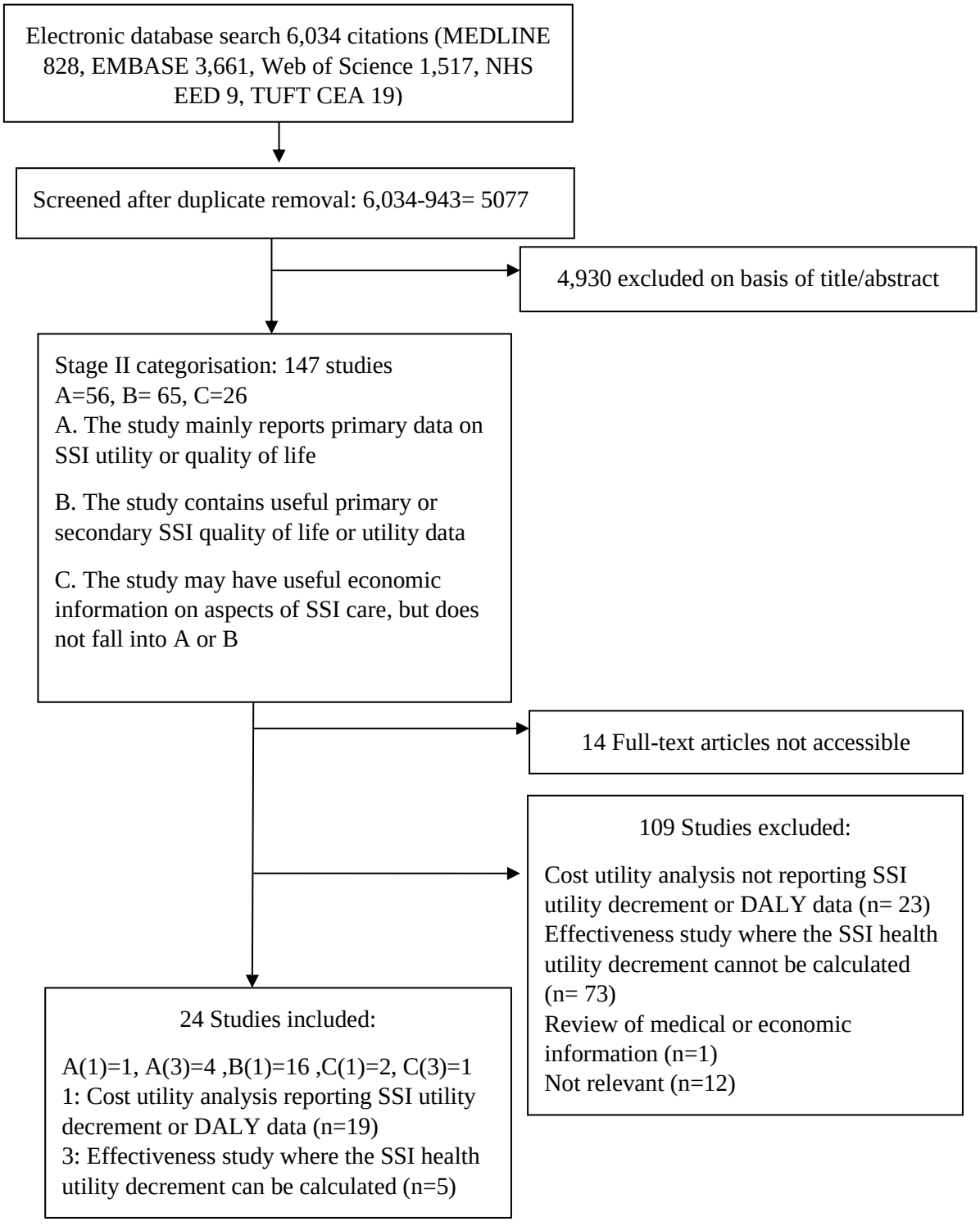


Figure 4.1 PRISMA diagram

Table 4.1 Characteristics of model-based economic evaluations

Lead Author (Year)	Country	Patient characteristics	Time horizon	Comparators	Model type
General surgery					
Chatterjee (2015) [219]	USA	Grades 1-2 ventral hernia patients	Lifetime	Sartorius flap versus the rectus femoris flap in the treatment of an infected vascular groin graft	Decision Tree
Chopra (2016) [221]	USA	Complex abdominal wall reconstruction procedure patients	Lifetime	Closed-incision negative-pressure therapy versus standard dressings	Decision Tree
Colorectal surgery					
Chomsky-Higgins (2019) [220]	USA	Colorectal surgery patients	Lifetime	Surgical wound protection devices versus generic SSI prevention bundle	Decision Tree
Lee (2014) [233]	Canada	Rectal cancer patients undergoing abdominoperineal resection	5 years	Mesh prophylaxis versus no mesh prophylaxis	Markov Model
Vicentini (2021) [239]	Italy	Elective colorectal surgery patients	47 days	Prophylactic use of ertapenem versus usual care	Decision Tree
Multiple surgical categories					
Conway (2019) [234]	Australia	Minor and major surgery patients at tertiary hospitals	Not stated	Perioperative thermal bundle versus no thermal bundle	Decision Tree
Cardiac surgery					
Hawkins (2019) [222]	USA	Cardiac surgery patients	Not stated	Negative pressure incision management systems versus no management system	Decision Tree
Hong (2018) [223]	USA	Coronary artery bypass graft surgery patients	1 year	Universal decolonization and only S aureus carriers treated versus no decolonization	Decision Tree
Gastrointestinal surgery					
Morrell (2022) [226]	USA	Percutaneous endoscopic gastrostomy patients	90 days	Sterile operative field versus no sterile operative field	Decision Tree
Oncology surgery					
Mericili (2019) [225]	USA	Oncologic spine surgery patients	Lifetime	Immediate reconstruction relative versus standard of care	Decision Tree

Lead Author (Year)	Country	Patient characteristics	Time horizon	Comparators	Model type
Sekigami (2020) [228]	USA	Breast Cancer-Related Lymphedema patients	Lifetime	Lymph node transfer versus Lymphovenous bypass	Decision Tree
Orthopaedic surgery					
Bydon (2015) [218]	USA	Spondylolisthesis patients	Unclear	Interbody fusion versus posterolateral fusions	Markov model
Graves (2016) [235]	UK	Total hip replacement patients	5 years	Strategies to reduce risk of infection following primary hip replacement	Markov model
Nherera (2017) [237]	UK	Primary hip and knee replacements surgery patients	6 weeks	Negative pressure wound therapy dressings versus standard care	Decision Tree
Shearer (2015) [229]	USA	Total hip arthroplasty patients	Lifetime	Hypothetical reduction in adverse outcomes versus standard care	Markov model
Zhuang (2020) [232]	USA	45 year old male smoker undergoing Posterior Lumbar Fusion	Lifetime	Smoking cessation interventions versus usual care	Markov model
Obstetrics and Gynaecology					
Siedhoff (2015) [230]	USA	Presumed fibroid tumours in premenopausal women	5 years	Laparoscopic hysterectomy versus abdominal hysterectomy	Decision Tree
Skeith (2017) [231]	USA	Nonelective caesarean patients	Lifetime	Azithromycin plus cephalosporin versus cephalosporin alone	Decision Tree
Vascular Surgery					
Bloom (2022) [217]	USA	Patients with lower extremity claudication and tissue loss	Lifetime	Femoral-popliteal bypass with closed-incision negative pressure therapy versus femoral-popliteal bypass alone	Decision Tree

Due to the inherent uncertainty on the true value of model inputs such as the utility of SSI, parameter uncertainty is recommended to be assessed in the economic evaluation through use of deterministic sensitivity analysis (DSA) and probabilistic sensitivity analysis (PSA) [121,137]. Half of the economic evaluations undertook DSA of the SSI utility values [217,220,223,225,226,229–234], with six of these studies presenting the impact of varying the SSI utility value on the cost-effectiveness results [220,223,225,230,232,234]. Nine studies assessed the joint parameter uncertainty of the SSI utility with the other model inputs in the PSA [217,220,223,229,232–235,237].

Source of utility values

The selection of model data sources are an important aspect for the face validity of the cost-effectiveness results [136]. Only three economic evaluations reported a systematic search of utility values model inputs [220,223,235]. Two studies [218,233] failed to state a source for the SSI and/or no SSI utility values (see Table 4.2). Other studies used SSI [223,230,234] and/or no SSI [220,223,230] utility values that were found to be incorrect when cross-checked with the stated sources. In addition, there were economic evaluations with the referenced SSI utility values [223,233] or no SSI utility values [229] that did not appear in the cited source.

Table 4.2 SSI values used in model-based economic evaluations

Lead Author (Year)	Mean Utility values (SE)	Mean SSI decrement	Duration of SSI	Utility elicitation method	Cited utility value sources
General Surgery					
Chatterjee (2015) [219]	SSI: 0.69 (not stated); No SSI: 0.81 (not stated);	-0.12*	1 month	SSI and No SSI: VAS	Primary data
Chopra (2016) [221]	SSI:0.49 (not stated); No SSI: 0.7 (not stated);	-0.31*	1 month, 10 days	SSI and No SSI: VAS	Primary data
Colorectal surgery					
Chomsky-Higgins (2019) [220]	SSI:0.705 (not stated); No SSI: 0.754 (not stated);	-0.049	1 month	SSI and No SSI: EQ-5D, incorrect values sourced	SSI and No SSI: [50,210,240]
Lee (2014) [233]	SSI and No SSI: Not stated	-0.05	1 year	SSI: Cited value absent; No SSI: Not stated	SSI:[241,242]; No SSI: Not stated
Vicentini (2021) [239]	SSI: 0.543* (not stated); No SSI: 0.6196* (not stated)	-0.076*	1 month	SSI and No SSI: EQ-5D	SSI and No SSI:[210]
Multiple surgical categories					
Conway (2019) [234]	SSI: Not stated; No SSI: 0.91 (SE: 0.02)	Superficial SSI: -0.2; deep SSI: -0.4	Superficial SSI: 2 weeks; deep SSI: 1 month	SSI: EQ-5D, incorrect values sourced; No SSI: EQ-5D	SSI:[243]; No SSI:[244]
Cardiac surgery					
Hawkins (2019) [222]	Superficial SSI: 0.9 (not stated); deep SSI: 0.5 (not stated); No SSI:1 (not stated)	Superficial SSI: -0.1*; deep SSI: -0.4*	Not stated	Assumption	SSI: Assumption [245]·[246]; No SSI: Assumption

Lead Author (Year)	Mean Utility values (SE)	Mean SSI decrement	Duration of SSI	Utility elicitation method	Cited utility value sources
Hong (2018) [223]	Superficial SSI: 0.787 (not stated); deep SSI: 0.700 (not stated); mediastinitis SSI: 0.53 (not stated); No SSI: 0.816 (not stated)	Superficial SSI:-0.029*; deep SSI: -0.116*; mediastinitis SSI: -0.286*	Superficial SSI: 2 months; deep SSI: 8 months; mediastinitis SSI:1 year	Superficial SSI, deep SSI, mediastinitis SSI: EQ-5D, Cited values absent; No SSI: EQ-5D, Incorrect value sourced	SSI and No SSI:[247]
Gastrointestinal surgery					
Morrell (2022) [226]	SSI: 0.69 (SD: 0.10); No SSI: 0.89 (not stated)	-0.20*	7 days	SSI: VAS; No SSI: Standard Gamble	SSI:[248]; No SSI:[249];
Oncology surgery					
Mericili (2019) [225]	SSI: 0.75 (not stated); No SSI: 0.92 (not stated)	-0.17*	Not stated	SSI and No SSI: VAS	Primary data
Sekigami (2021) [228]	SSI: 0.8 (not stated); No SSI: 0.953 (not stated)	-0.153*	8 weeks	SSI and No SSI: VAS	Primary data
Orthopaedic surgery					
Bydon (2015) [218]	SSI: 0.33 (not stated); No SSI: 0.97 (not stated)	-0.64*	2 weeks	SSI and No SSI: TTO	SSI:[250]; No SSI:[251]
Graves (2016) [235]	SSI: 0.4 (SD: 0.0514); No SSI: 0.86 (SD: 0.0117)	-0.46*	Not stated	SSI: aQoL; No SSI:15D	SSI:[252]; No SSI:[253]

Lead Author (Year)	Mean Utility values (SE)	Mean SSI decrement	Duration of SSI	Utility elicitation method	Cited utility value sources
Nherera (2017) [237]	SSI: 0.57 (SE: 0.034); No SSI:0.64 (SE: 0.036)	-0.07*	Not stated	SSI and No SSI: SF36	SSI and No SSI:[254–256]
Shearer (2015) [229]	SSI: 0.46 (not stated); No SSI:0.65 (not stated)	-0.19*	1 year	SSI: TTO; No SSI: Assumption	SSI:[257]; No SSI: Assumption
Obstetrics and Gynaecology surgery					
Siedhoff (2015) [230]	SSI: 0.607 (not stated); No SSI: 0.9 (not stated);	-0.293*	1 month	SSI: VAS, incorrect value sourced; No SSI: unclear, incorrect value sourced	SSI:[248]; No SSI:[258]
Skeith (2017) [231]	SSI: 0.52 (not stated); No SSI: 0.996 (not stated)	-0.476*	Not stated	SSI: QWB; No SSI: Assumption	SSI:[259]; No SSI: Assumption
Spinal surgery					
Zhuang (2020) [232]	SSI: 0.459 (not stated); No SSI: 0.692 (not stated);	-0.233*	1 month	SSI: ODI mapped to SF-6D [260]; No SSI: SF-6D	SSI:[261]; No SSI:[262]
Vascular surgery					
Bloom (2022) [217]	SSI:0.572 (not stated); No SSI: 0.706 (not stated)	-0.134*	Minor SSI: 4 weeks; Major SSI: 12 weeks	SSI and No SSI: VAS	SSI and No SSI:[219]

*Calculated from paper

aQOL: Assessment of Quality of Life; ODI: Oswestry Disability Index; QWB: Quality of Well-Being Scale; SSI: Surgical Site Infection; TTO: Time trade off; VAS: Visual Analogue Scale;

Methods of utility development

The approaches and instruments used to elicit the utility scores will affect the values derived [263]. There was a mix of direct and indirect approaches to the sourced SSI and no SSI utility values in the economic evaluations. Methods of utility development of sourced SSI and no SSI values comprised authors' assumptions (n=2) [222,231], aQoL (n=1) [235], SF-36 (n=1) [237], EQ-5D (n=4) [220,223,234,239], 15D (n=1) [235], Oswestry Disability Index (n=1) [232], SF-6D (n=1) [232], SG (n=1) [226], Quality of Well-being Scale (n=1) [231], TTO (n=2) [218,229] and the VAS (n=6) [217,221,225,226,228,230,248]. Individuals informing the SSI or no SSI health state utility scores were patients [220,223,229,232,234,235,237,239], clinicians [217,219,221,222,225,226,228–231], the general public [218,234] or was unclear [229,230,233]. Four economic evaluations created their own SSI and no SSI utility values [219,221,225,228], using surgical staff to rate health state descriptions using the VAS.

To convert the HRQOL responses onto a utility scale, mapping was used in two economic evaluations [232,237]. It is recommended the populations where the mapping was derived from have similar characteristics to the population whose utilities are being predicted by the mapping analysis [264]. This can be seen in one economic evaluation [232] where a comparable surgical patient population (Posterior Lumbar Fusion) was used for both the mapping study [260] and the target study population [261] whose utilities are being predicted. However, the other economic evaluation [237] utilised a mapping algorithm [255] that was based on an Israeli Arab general population to predict utilities from SF-36 responses of UK primary hip and knee replacements surgery patients [254].

SSI and no SSI utility values

Utility values should be representative of the health states and population under consideration for the economic evaluation [265]. The utility value associated with patients with an SSI would be expected to be typical of a postoperative patient who suffered the complication. Likewise, the expectation for the utility weight for the no SSI utility health state value would be that it closely aligned to the counterfactual of the SSI utility health state value, with the difference being the impact of the postoperative complication, that is, a patient undergoing the same procedure but did not suffer an SSI.

Most studies used utility values which matched descriptions of surgical patients with and without an SSI respectively (see Appendix Table A4.1). Exceptions to this were observed for both SSI and no SSI utility values. The description of the underlying utility value used for SSI included: (1) a hospital confinement for two weeks [218]; and (2) a composite postoperative complication health state which bundled sepsis, wound infection, pulmonary infection, uterine infection, and urinary infection together [231]. The description of the underlying utility value used for no SSI included: (1) person not affected by any of 28 health conditions in the past year [218]; and (2) the adult general population in Queensland [234]. Reported utility values for a surgical patient with an SSI ranged from 0.9 to 0.33. The no SSI utility values ranged from a perfect health score of 1 to 0.64. Four of the studies took their SSI and no SSI utility values from the same study reference [217,220,223,239].

The standard error or standard deviation associated with the utility values were rarely stated. Two model-based economic evaluation stated a standard error or standard deviation associated with the model input utility values of patients by SSI status [235,237] and both gave differing answers on which patient group had the higher variability associated with their utility value. The standard error associated with a No SSI utility was slightly higher than the

SSI utility value in the model-based economic evaluation that took the values from the same study reference [237], whereas SSI utility value had a much higher associated standard deviation compared to the No SSI utility model input in the model-based economic evaluation where the utilities were sourced using different studies using different quality of life instruments [235].

SSI duration

The duration of SSI will affect the QALYs gained along with the utility decrement used. Typically, duration should be based on the clinical scenarios likely to be observed and should thus be informed by clinical data. Five studies did not state the duration of SSI in their economic evaluation [222,225,231,235,237]. Thus, it was unclear in these studies what the assumed impact of SSI was. In the studies that did report duration, the stated duration of SSI varied from 1 week [226] to 1 year [229,233]. However, justification or clinical evidence supporting the stated duration of an SSI was provided in only three papers [217,221,223].

The SSI utility decrement used in the model-based economic evaluations varied from -0.049 to -0.64. Where different severity levels were included, the more severe SSIs all had a higher quality of life decrement [217,222,223,234]. Scaling the SSI utility decrement by taking duration of an SSI into account, the yearly impact of an SSI decrement ranged from -0.004 to -0.286.

4.3.2 Health state valuation studies

Methods of utility development

In the five health state valuation studies (Table 4.3), all but one applied indirect valuation methods to provide SSI and no SSI utility values. The health related quality of life instrument administered in all of the indirect valuation studies was the EQ-5D-3L. Alongside the EQ-5D-

3L, other instruments to calculate utilities included was the VAS [224,227] and the SF-6D [164]. The sole direct valuation study used a time-trade off approach to value SSI health state descriptions [236].

In contrast to some of the model-based economic evaluations, the source of the utilities for SSI and no SSI patients conformed to descriptions of postoperative surgical patients. Nearly all studies used the CDC definition of an SSI. The exception was the direct valuation study where SSI was defined using health state descriptions [236].

Sample size and quality of life measurement

As there will be variability in quality of life in each of the health states, consideration of sampling requirements to represent the diversity of quality of life experiences is recommended [265]. One factor that can affect quality of life estimation differences is the sample size in each health state [266,267]. The health state valuation studies had differences in number of patients with SSI (n=8 to 35) and no SSI patients (n=14 to 423).

Longitudinal data on quality of life where participants have their quality of life measured at multiple timepoints is preferable to cross sectional data alone as it can capture changes in health state utility values across timepoints and be used to calculate QALY differences. This was the case in all the indirect health state valuation studies; the direct valuation study used path dependence in the vignette to describe the changes in health symptoms throughout its 1-year duration [236]. The two follow-up lengths were 30 days and 1 year.

Table 4.3 Characteristics of health state valuation studies

Lead Author (Year)	Country	Study design	Population	HRQOL instrument(s)	SSI sample size across utility measurement timepoints	No SSI sample size across utility measurement timepoints
Orthopaedic						
Matza (2019) [236]	UK	Direct valuation	UK general population	TTO	n=201 (Vignette duration of 12 months)	n=201 (Vignette duration of 12 months)
Parker (2018) [164]	UK	RCT	Lower limb open fractures patients	EQ-5D-3L; SF-6D	n= 35 (missing cases imputed across baseline, 3 month, 6 month, 9 month, and 12 month timepoints for both EQ-5D & SF-6D)	n= 423 (missing cases imputed across baseline, 3 month, 6 month, 9 month, and 12 month timepoints for both EQ-5D & SF-6D)
Kuhns (2015) [224]	USA	Cohort study	Patients undergoing dorsal cervical fusions	EQ-5D-3L; VAS	EQ-5D Baseline: n=14; 6 months: n= 12; 12 months: n=12 VAS Baseline: n=17; 6 months: n=14; 12 months: n=15	EQ-5D Baseline: n=21; 6 months: n=14; 12 months: n=21; VAS Baseline: n=22; 6 months: n=16; 12 months: n=22
Pennington (2019) [227]	USA	Cohort study	Patients undergoing posterior lumbar decompression and fusion	EQ-5D-3L, VAS	EQ-5D Baseline: n=17; 6 months: n=18 VAS Baseline: n=17; 6 months: n=18	EQ-5D Baseline: n=17; 6 months: n=18 VAS Baseline: n=17; 6 months: n=16
Vascular						
Totty (2021) [238]	UK	Pilot RCT	Clean or Clean-Contaminated vascular surgery patients	EQ-5D-3L	Baseline: n=18;7 days: n=8; 30 days: n=9	Baseline: n=73;7 days: n=59; 30 days: n=52

HRQOL: Health related Quality of Life; RCT: Randomised Control Trial; SSI: Surgical Site Infection, TTO: Time trade off

Table 4.4 shows the utility values in each health state valuation study. Postoperative health state utility values associated with patients with SSI varied from 0.81 to 0.54. Postoperative utility values associated with patients without SSI varied from 0.86 to 0.57. The difference in utility values of SSI and no SSI patients in the patient-level studies varied from an SSI increment of 0.05 to an SSI decrement of -0.32. Severity levels were considered in the direct valuation study and the more severe SSI's had a greater utility decrement [236]. In contrast to the model-based economic evaluations, in the studies where standard error or standard deviation was reported, the dispersion was unequivocally higher for the patient group with SSI [164,236].

Where VAS or SF-6D was measured, mean utility values differed to the mean utility values measured by the EQ-5D with the direction of change inconsistent across timepoints. One study had a QALY SSI decrement difference of -0.031 or -0.102 depending on the whether the SF-6D or the EQ-5D is used [164].

Quality of life adjustment

The measurement of health state utility values before surgery provides the opportunity to adjust follow-up utility values for intergroup differences. All the indirect valuation studies reported the baseline/preoperative utility values of the SSI and no SSI patients. The starting preoperative utility values varied across studies from 0.89 to 0.36 (Table 4.4). However, postoperative utility values were not adjusted by the baseline utility score in two of the studies. Thus, the SSI decrements in these studies are cross-sectional changes in HRQOL values and these could differ with baseline utility adjustment.

In addition to preoperative quality of life values, other patient characteristics, such as comorbidities [268] influencing health-related quality of life is recommended to be adjusted

for analysis [265]. Approaches to covariate adjustment included a case-control study design matching patients with SSI and patients without SSI by patient characteristics [227] and a regression analysis accounting for the effects of patient factors [164,238].

Missing responses to HRQOL instruments could give misleading estimates for a complete-case analysis or available case analysis if the assumptions about the missing data do not hold [269]. In dealing with the missing data, multiple imputation [164] and available case analysis at the specific timepoint [224,227] were deployed.

Table 4.4 SSI values generated in health state valuation studies

Lead Author (Year)	**SSI mean utility values (SE)**	**No SSI utility mean utility values (SE)**	**Mean SSI decrement (95%CI)**
Orthopaedic			
Matza (2019) [236]	Joint Surgery Superficial wound infection: 0.76 (SD: 0.24); Deep infection (DAIR): 0.61 (SD: 0.32); Deep Infection: 0.47 (SD: 0.37) Spine Surgery Infection not requiring reoperation: 0.76 (SD: 0.24); Infection requiring reoperation: 0.62 (SD: 0.31)	Joint Surgery No SSI: 0.79 (SD: 0.23) Spine Surgery No SSI: 0.78 (SD:0.23)	Joint surgery Superficial wound infection: -0.03 (95% CI:-0.04 to -0.02); Deep infection (DAIR): -0.18 (95% CI:-0.21 to -0.15); Deep Infection: -0.32 (95% CI:-0.36 to -0.29); Spine Surgery Infection not requiring reoperation: -0.03 (95% CI:-0.04 to -0.02) Infection requiring reoperation: -0.16 (95% CI:-0.19 to -0.14)

Lead Author (Year)	SSI mean utility values (SE)	No SSI utility mean utility values (SE)	Mean SSI decrement (95%CI)
Parker (2018) [164]	EQ-5D Baseline: 0.88 (SE: 0.03); 3 months: 0.25 (SE: 0.06); 6 months: 0.34 (SE: 0.06); 9 months: 0.46 (SE: 0.07); 12 months: 0.41 (SE: 0.06) SF-6D Baseline: 0.87 (SE: 0.02); 3 months: 0.55 (SE: 0.02); 6 months: 0.57 (SE: 0.03); 9 months: 0.59 (SE: 0.04); 12 months: 0.62 (SE: 0.03)	EQ-5D Baseline: 0.89 (SE: 0.01); 3 months: 0.35 (SE: 0.02); 6 months: 0.48 (SE: 0.02); 9 months: 0.53 (SE: 0.02); 12 months: 0.57 (SE: 0.02); SF-6D Baseline: 0.86 (SE: 0.01); 3 months: 0.56 (SE: 0.01); 6 months: 0.61 (SE: 0.01); 9 months: 0.63 (SE: 0.01); 12 months: 0.65 (SE: 0.01)	EQ-5D 12 month adjusted QALY difference: -0.102 (95% CI: -0.202 to -0.001); SF-6D 12 month adjusted QALY difference: -0.031 (95% CI: -0.081 to 0.020);
Kuhns (2015) [224]	EQ-5D Baseline: 0.50 (not stated); 6 months: 0.54 (not stated); 12 months: 0.68 (not stated); VAS Baseline: 0.494 (not stated); 6 months: 0.443 (not stated); 12 months: 0.507 (not stated)	EQ-5D Baseline: 0.55 (not stated); 6 months: 0.69 (not stated); 12 months: 0.63 (not stated) VAS Baseline: 0.595 (not stated); 6 months: 0.419 (not stated); 12 months: 0.55 (not stated)	EQ-5D Unadjusted utility difference at 6 months: -0.15* (not stated); Unadjusted utility difference at 12 months: 0.05* (not stated); VAS Unadjusted utility difference at 6 months: 0.024* (not stated); Unadjusted utility difference at 12 months: 0.043* (not stated);

Lead Author (Year)	SSI mean utility values (SE)	No SSI utility mean utility values (SE)	Mean SSI decrement (95%CI)
Pennington (2019) [227]	EQ-5D Baseline: 0.36 (not stated); 6 months: 0.56 (not stated) VAS Baseline: 0.74 (not stated); 6 months: 0.36 (not stated);	EQ-5D Baseline: 0.38 (not stated); 6 months: 0.67 (not stated); VAS Baseline: 0.80 (not stated); 6 months: 0.36 (not stated);	EQ-5D Unadjusted utility difference at 6 months: -0.11* (not stated); VAS Unadjusted utility difference at 6 months: 0* (not stated)
Vascular			
Totty (2021) [238]	EQ-5D Baseline: 0.51 (not stated); 7 days: 0.47 (not stated); 30 days: 0.51 (not stated)	EQ-5D Baseline: 0.54 (not stated); 7 days: 0.56 (not stated); 30 days: 0.68 (not stated)	QALM mean difference of -0.156* (not stated);

DAIR: debridement and implant retention; SSI: Surgical Site Infection; VAS: Visual Analogue Scale; QALM: Quality Adjusted Life Month; QALY: Quality Adjusted Life Year

4.3.3 Comparison with previous review

The original review found the same amount of model-based economic evaluations (n=19) and more health state valuation studies (n=9). Similar themes persisted in the newer eligible articles. In common with the original review, the model-based economic evaluations had issues with transparency of reported utility values including the use of incorrect utility values. The lack of systematic reviewing of utility sources was another recurring theme. The range of SSI decrements was narrower (-0.04 to -0.48) with the ones found in this review (0.05 to -0.64). Two economic evaluations [220,239] in the updated review referenced the previous systematic review for the SSI and no SSI utility values [210]. Health state valuation studies and model-based economic evaluations covered in the previous review were referenced for utility values in six studies in the current review [220,222,223,234,237,239]. Lastly, in common with the previous review, orthopaedic studies were the most popular surgical category.

4.3.4 Utility value robustness assessment

One of the goals of the review is to assess the robustness of the SSI decrement utility values in the recent literature identified in the current review and the ones identified in the previous review. Based on the desirable utility aspects discussed throughout the review, a quality checklist of the sourced utility values is presented in Table 4.5 to appraise the suitability of the values for use in the preliminary economic evaluation in Chapter 5. For quality purposes, only sourced utility values that contained SSI and no SSI values within the same reference were included. Table 4.5 shows how each study has fulfilled desirable utility qualities. The quality varied among the studies with one study achieving nearly all the applicable criteria [236].

Table 4.5 Quality assessment of health state valuation studies associated with SSI

Lead Author (Year)	Descriptions match postoperative patients	NICE recommended outcome measure(s)	Consistent HRQOL timepoint(s) articulated	Multiple timepoints included	Mapping derived from comparable population	Adjustment by preoperative utility values	Patient covariate adjustment	Abdominal surgery population*	Severity of SSI
Cahill (2008) [252]	✓	×	×	×	×	×	×	×	×
Chatterjee (2015) [219]	✓	×	✓	×	NA	NA	NA	✓	×
Chatterjee (2014) [248]	✓	×	✓	×	NA	NA	NA	✓	×
Chopra (2016) [221]	✓	×	✓	×	NA	NA	NA	✓	×
Falavigna (2011) [270]	✓	✓	×	×	×	×	✓	×	×
Kuhns (2015) [224]	✓	✓	✓	✓	NA	×	×	×	×
Matza (2019) [236]	✓	✓	✓	✓	NA	NA	NA	×	✓
Mericili (2019) [225]	✓	×	✓	×	NA	NA	NA	×	×
Parker (2018) [164]	✓	✓	✓	✓	NA	✓	✓	×	×
Pennington (2019) [227]	✓	✓	✓	✓	NA	×	✓	×	×
Pinkney (2013) [50]	✓	✓	✓	×	NA	×	×	✓	×
Sekigami (2021) [228]	✓	×	✓	×	NA	NA	NA	×	×
Thoma (2003) [271]	✓	×	✓	×	NA	NA	NA	×	×
Totty (2021) [238]	✓	✓	✓	✓	NA	✓	✓	×	×
Whitehouse (2002) [254]	✓	✓	✓	×	×	×	✓	×	×
Yan Gu (2009) [272]	✓	✓	✓	✓	NA	NA	NA	×	×

*Relevant for preliminary model-based economic evaluation in chapter 5

4.4 Discussion

4.4.1 Statement of principal findings

SSI was found to have an adverse effect on quality of life across all studies in different surgical categories and countries in this updated systematic review. All included studies were from High Income countries. The absence of utility values of SSI and no SSI in Low- and Middle-Income countries may stem from a dearth of countries for which the popular preference measures are validated [273,274]. Country-specific valuation sets have the advantage of helping make resource allocation decisions reflective of the population's preferences with respect to the weighting of different health problems [273]. While the Gates foundation reference case recommend the use of DALYs for cost-utility analysis in LMICs, the absence of disability weights related to SSI and other complications prevents a cost per DALY averted analysis to be carried out in these clinical areas.

Most studies used preference-based outcome measures recommended by decision makers such as NICE for use in economic evaluations [72]. The instances of using alternative measures such as VAS could lead to erroneous resource allocation decisions where these calculated utility values differ from the values obtained by preference outcome measures.

Model-based economic evaluations with incorrect utility values may affect cost-effectiveness decisions. Where SSI and no SSI values are taken from different sources, this may increase or decrease the true SSI decrement due to different patient populations. With different indications for surgery, patient populations would be expected to have varying underlying health status depending on the intended surgical procedure. The appropriateness of the utility values for no SSI values including assuming perfect health or general population utility values for patients undergoing surgery is questionable, will inflate the SSI decrement and calls into question the model face validity of these economic evaluations. The lack of adjustment in a

comparison of patients with SSI and without SSI may be overstating or understating the actual quality of life decrement. Variables such as a patient's baseline utility score and characteristics such as comorbidities may confound the SSI utility decrement where these variables differ between groups. From the limited reporting of standard error or standard deviation associated with the utility values in patient-level studies, there was higher variability in the SSI utility estimates suggesting that there was a more heterogenous impact of SSI on quality of life of postoperative patients above what is the typical experience.

4.4.2 Strengths and weaknesses

The current review builds upon a previous published systematic review to assess the recent estimates of SSI and no SSI. The review provides up-to date insight on the current evidence on the methodological quality of utility values pertaining to SSI. Quality criteria on best practice for model input estimates was applied to studies [136,137,213,265] to evaluate the robustness of the estimates.

One limitation of the review was the broad definition of SSI included. This could affect the comparability of utility estimates as the categories of those with and without an SSI may differ. Another limitation of the review was that the specific focus on the utility values exploring the impact of SSI on quality of life. There may be other aspects of the economic evaluations and patient level studies that have methodological issues, but these are not covered here. This is because the objective of the review was to appraise and select the most appropriate SSI and non SSI utility values for a preliminary economic evaluation.

4.4.3 Implications for practice

The SSI impact varied considerably, making the careful selection of the utility values and assessment of parameter uncertainty an important part of the validation process of the

economic evaluation. The lack of systematic reviewing of utility values, coupled with the wide variability of estimates, can lead to using utilities that do not adequately reflect the consequences of the intervention under investigation. Poor reporting of utilities contribute to research waste [275] and call into question the robustness of estimates [136]. Compared to the original systematic review, little has changed in terms of methodological quality of studies.

This review has highlighted the many challenges in the measurement and valuation of SSI utilities and the approaches used by the recent literature in obtaining and generating the quality of life information. The review has several research recommendations for future studies. More transparency and better reporting of utility estimates together with justification on the analytic approaches and outcome measures used would improve the face validity of the economic evaluation. To address the research gap, future patient-level studies should include more subgroups on the severity levels of SSI to explore the quality of life impact from these complications. The outcome measures should be fit for purpose and be repeated across multiple timepoints to create the longitudinal profile of the complication rather than a cross-sectional estimate.

A recent meta-analysis quantified the EQ-5D utility decrement associated with SSI [276]. However, the lack of baseline adjustment of quality of life values for the cross-sectional decrement timepoints makes it difficult to know how much of decrement can be explained due to the presence of an SSI alone.

4.5 Conclusion

Quality of life is adversely affected by Surgical Site Infection. This review has identified the methodological approaches used in the recent evidence of SSI utilities and combed the previous systematic review for potential suitable estimates for the preliminary economic evaluation. The reduction of SSI will avert quality of life loss burden for many surgical patients. One study satisfied most of the most utility quality criteria for SSI [236]; this will now be taken forward for use as a model input for Chapter 5. Alternative values will be used in the deterministic sensitivity analysis of the model. The last two chapters systematically reviewed the literature for cost and utility estimates for SSI. The next chapter will incorporate the best available estimates to populate a preliminary model-based economic evaluation of interventions to reduce SSI.

Chapter 5:

A preliminary model-based economic evaluation of measures to reduce surgical site infection

5.1 Introduction

From the systematic reviews reported in the Chapters 3 and 4, it is clear that Surgical Site Infection (SSI) has both significant costs and quality of life implications. The findings demonstrate an additional cost burden of SSI, signalling the prevention of SSIs could save the consumption of additional scarce healthcare resources. Likewise, preventing SSI will avert its deleterious impact on a patient's postoperative health-related quality of life. In isolation, the costs and quality of life estimates separately underline the importance of SSI prevention to healthcare systems. Incorporating the best available cost and quality of life estimates within an economic evaluation modelling framework can inform resource allocation decisions for interventions focused on reducing SSI. As trials are an expensive and a time consuming approach to answer research questions, there is an ethical responsibility to maximise all available data to inform decision prioritization.

Building upon the quality of life and cost information of SSI systematically gathered in the previous chapters, the next step is to assess the cost-effectiveness of measures to reduce SSI. From the systematic reviews, no model-based economic evaluations of interventions to reduce SSI in a Low- and Middle- Income Country (LMIC) setting were identified.

This chapter presents a preliminary model-based economic evaluation of exemplar SSI-reducing interventions populated with cost and utility estimates from the systematic reviews reported in Chapters 3 and 4. The economic evaluation model considers the cost-effectiveness from a UK setting and selected LMIC settings (Ghana, Mexico, India). These LMIC settings

are used are examined in a later iterated model. Another iteration of the model will happen in the subsequent chapter with cost and QALY inputs from an RCT re-analysis. The model is revisited again later in the thesis after the primary research collection with a view of refining the model one final time with the model inputs more applicable to LMIC settings.

The methods section describes the process of modelling the patient pathways, their costs and utilities, and the inclusion of uncertainty. The results of the model are then presented with illustrations of the parameter uncertainty and the impact of univariate, multivariate and probabilistic sensitivity analysis with a Value of Information (VOI) analysis. Finally, the implications of the model results is discussed, taking into account the steps needed to assess cost-effectiveness and the drivers of uncertainty.

5.2 Methods

5.2.1 Model conceptualization

The starting point for model conceptualization was the representation of the decision problem [138]. The decision problem encountered here was to evaluate the cost-effectiveness of potential interventions that could reduce SSIs in an abdominal surgical population. Addressing the decision problem guides the development of the required type of model, model structure, model input needs, and analytic approaches [138].

A description of what is known about SSI was thus needed to understand the modelling requirements for the proposed preliminary analysis. Pertinent information on SSI presented so far in the doctoral thesis to inform the model is summarised next:

- SSI is an acute one off postoperative complication that does not reoccur after the wound has healed.

- Surgical procedure type [12] and degree of wound contamination [15,16] were found to affect the risk of SSI. Day of SSI onset varied [12] with occurrences of inpatient SSIs and outpatient SSIs possible.
- Severity of SSI was associated with differential onset and resolution of SSIs [22].
- More severe SSIs were associated with higher mortality and morbidity [7,19], costs [153,161,172], and lower utilities [217,222,223,234].
- Typical treatment of SSI included antibiotics [23] and possible reoperation of drainage and/or debridement [25] for more severe cases.

Another source of information on modelling SSI was by examination of the literature. Previous model-based economic evaluations with an SSI utility model input reported in Chapter 4 represented the decision problem with either decision trees [217,219–223,225,226,228,230,231,234,237,239] or Markov cohort models [218,229,232,233,235] (Table 4.1). All the Markov cohort models were within orthopaedic surgery populations with different detection windows and aetiology [277] for SSI. No model types with patient interactions or resource restrictions such as Discrete Event Simulation (DES), or system dynamics model were found in the review (see Chapter section 2.4 for explanation of model types).

5.2.2 Model structure

In consultation with the PhD supervisory team comprising of two health economists and a surgeon, and supported by information in the literature, a model structure and type to reflect the patient postoperative pathway for general surgery patients was constructed. A decision tree was built in TreeAge Pro 2023 [278] to represent the decision problem. TreeAge is a specialist decision analytic modelling software and is one of the software programmes that is accepted by NICE for its health technology appraisals [72]. A decision tree model type was

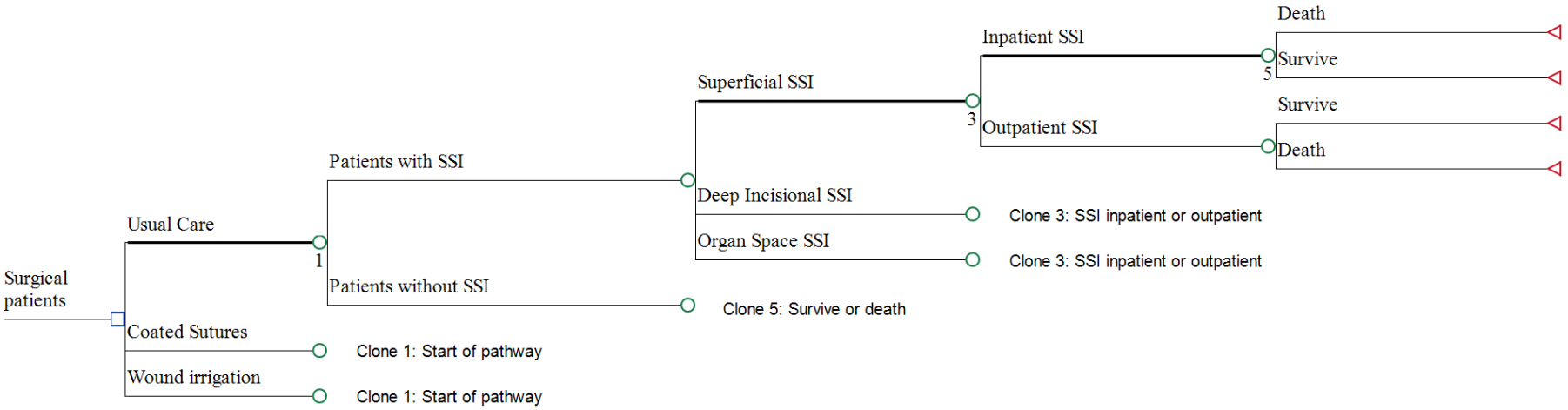
chosen for its suitability to represent the relevant costs and consequences of an acute decision problem for the patient population. Severity levels of SSI were incorporated into the model in recognition of their differential impact on costs and outcomes. A base case time horizon of 30 days after surgery was chosen which reflected data availability and usual RCT endpoint for SSI prevention [50,279,280].

Figure 5.1 presents the postoperative pathway of abdominal surgery patients undertaking abdominal surgery. After surgery, patients can either suffer an SSI or not suffer an SSI. For patients who do not suffer an SSI, these patients can survive or suffer a postoperative death. Postoperative death was assumed to occur at the half point of the time horizon (at 15 days) for utility calculation purposes. Patients can suffer one of three types of SSI:

1. Superficial SSI,
2. Deep Incisional SSI,
3. Organ Space SSI.

Patients are assumed not to be able to move between SSI severity types. Patients can suffer an SSI while they were still in hospital (inpatient SSI) or after they had been discharged (outpatient SSI). Patients with an SSI can survive or suffer a postoperative death. Patients with an SSI had a higher risk of a postoperative death. The severity of SSI was assumed to affect mortality in the model [7].

Figure 5.1 Patient pathways for the preliminary model



Where pathways were identical, a cloning feature was used where repeating pathways were copied and alterations to the "clone master" pathway would then be automatically reflected in the cloned pathways. Local variables specific to the pathway and strategy were also used to reflect the appropriate costs, outcomes, and probabilities. The combination of cloning and local variables was done to to make the decision tree more manageable and minimize the potential for data entry errors. Linked variables were used throughout so all values and equations representing the costs, outcomes, probabilities, and payoffs were displayed in the variable list. A model validation feature was run, which warns of potential errors including unused variables, tables and distributions, and calculation errors where probabilities were negative or the sum of probabilities across a particular set of branches does not sum to 1.

5.2.3 Model interventions

Potential interventions that could reduce SSIs can happen at the preoperative, perioperative, or postoperative stage. Two exemplar interventions were considered at the perioperative stage which were applied to all patients undergoing surgery. These were antiseptic Wound Irrigation, and Coated Sutures. Wound Irrigation involves cleansing the wound to reduce the level of microbial activity before wound closure [281]. Coated Sutures are treated with an antibacterial agent which reduce the chance of bacteria colonization on the suture material [282].

In the absence of data, the interventions were assumed to only have an impact on the risk of SSI. The interventions were assumed not to affect the SSI severity proportions nor timing of the SSI (inpatient SSI/ outpatient SSI). The Wound Irrigation strategy comprised Wound Irrigation and Uncoated Sutures. The Coated Sutures strategy comprised no Wound Irrigation and Coated sutures. A Usual Care arm of No Wound Irrigation and Uncoated Sutures was included as a model comparator.

5.2.4 Model input parameters

The model input parameters are displayed in Tables 5.1-5.3. The tables include information for the deterministic and probabilistic analyses, and their referenced sources. For the probabilistic sensitivity analysis, the choice of distribution and associated distribution parameters are detailed in the tables.

Costs

The cost parameters are listed in Table 5.1. For the UK setting, all costs were inflated to the 2021/2022 cost year using the NHS inflation index where applicable [283]. For international costs used in the UK setting sensitivity analyses, costs were inflated using their countries' consumer price inflation index [284] and then converted into UK costs using a Purchasing Power Parity (PPP) conversion factor [285]. For the LMIC setting, the UK costs are adjusted to improve transferability[142] with costs rebased using a PPP conversion factor [285] and are presented in international dollars. No cost study within the systematic review of costs reported in Chapter 3 had a sufficient level of detail to quantify the costs of SSI by severity status and timing of SSI alone. Instead, aspects from different studies were combined to quantify the SSI costs as detailed below.

For the base case analysis, the additional inpatient costs of an SSI were taken from Jenks et al. [161]. This was chosen on the basis of it the study scoring the highest quality criteria in Chapter 3 (see Table 3.7). Alternative literature values on additional inpatient costs of an SSI identifited from the systematic review in Chapter 3 were tested in a sensitivity analysis (see section subheading 5.2.6). The additional costs of SSI studies from Chapter 3 were not combined into a meta-analysis model input due to the challenges of synthesing studies with methological differences in cost items, time horizons, patient populations, study design, and healthcare systems.

The patients with SSI in the from Jenks et al. [161] were those with an inpatient SSI or those readmitted with an SSI. First, the mean cost attributable to SSI were calculated from the total cost attributable to SSIs divided by the number of SSI cases. Jenks et al. [161] only reported the additional median costs by SSI severity (superficial SSIs, and deep or organ space SSIs). For the model, the mean difference by SSI severity was assumed to follow the same ratio of SSI severity specific median costs to overall SSI median costs. This resulted in the additional superficial cost of SSI to be 0.888 of the overall mean costs attributable to SSI. Similarly, the additional deep or organ space related cost of SSI was assumed to be 1.27 times greater than the overall mean costs attributable to SSI. As the additional cost attributable to deep incisional SSI and organ space SSI were not reported separately, they were assumed to be the same cost in the base case analysis. As the study did not specify a cost year, the last year of data collection (2012) was used for inflation purposes.

To calculate the costs of an outpatient SSI, a ratio of inpatient SSI costs to outpatient SSI costs derived from Lynch et al. [168] was applied to the Jenks et al. [161] SSI costs (1: 0.26). The Lynch et al. [168] study calculated costs of patients from a preoperative whole body disinfection trial in Scotland. The cost components of outpatient SSI (n=312) and inpatient SSI (n=201) included GP visits, wound dressings, antibiotic costs and hospital stay. The study was chosen as it was the only identified study in the systematic review in Chapter 3 with the requisite information to calculate the ratio.

Table 5.1 Model cost parameters

Variable	Deterministic Value	PSA Distribution	PSA parameters	Source
Cost of Wound Irrigation Intervention	£5.83	Gamma	α=44.44 λ=7.623	Tables 2 & 3; NICE Guideline, No. 157. Evidence review H [286]
Cost of Antimicrobial-Coated Sutures Intervention	£4.37	Gamma	α= 44.44; λ = 10.17	Table 7 NICE medical technology consultation MT507 supporting documentation [287]
Outpatient SSI costs as a percentage of Inpatient SSI costs	26.12%	Beta	α= 13; β= 37	Lynch et al. [168], Table 3
SSI Primary care costs as a percentage of total costs	14.85%	Beta	α=15; β=86	Tanner et al. [163], Table 4
Additional SSI secondary costs	£10,128	Log-Normal	μ= 8.70; σ= 1.02	Jenks et al. [161], Table 3
Additional Inpatient Superficial SSI	£10,572	NA	NA	Jenks et al. [161],and Tanner et al. [163]
Additional Inpatient Deep Incisional SSI	£15,190	NA	NA	Jenks et al. [161],and Tanner et al. [163]
Additional Inpatient Organ Space SSI	£15,190	NA	NA	Jenks et al. [161] ,and Tanner et al. [163]
Additional Outpatient Superficial SSI	£2,762	NA	NA	Jenks et al. [161], Tanner et al. [163], and Lynch et al. [168]
Additional Outpatient Deep Incisional SSI	£3,968	NA	NA	Jenks et al. [161],Tanner et al. [163], and Lynch et al. [168]
Additional Outpatient Organ Space SSI	£3,968	NA	NA	Jenks et al. [161] ,Tanner et al. [163] and Lynch et al. [168]
UK 2021 Purchasing power parity to international dollars	0.644845	NA	NA	The Organisation for Economic Co-operation and Development [285]

As no primary care costs were included in Jenks et al. [161], the additional post-discharge costs for SSI patients were assumed to be the same ratio of secondary care costs to primary care costs of Tanner et al. [163]. Their study, included in the systematic review in Chapter 3, was a surveillance study of adult colorectal patients at a university hospital in England and they found the split of secondary care and primary care costs was 85.14:14.85. The secondary care costs to primary care costs ratio was similar to the other two studies that had reported the requisite information [27,169]. Primary care costs made up 14.32% and 10.83% of SSI costs of Alfonso et al. [27] and Reilly et al. [169] where, respectively. Although Tanner et al. [163] looked at both inpatient and outpatient SSIs (n=29), the information was not delineated by SSI timing. In the absence of any studies in Chapter 3 with a split of secondary care and primary care costs by SSI timing, the split was assumed to be the same for inpatient and outpatient SSIs. The costs of patients who died were assumed to be same as the surviving patients.

As no costs of Wound Irrigation intervention in abdominal surgery was found, it was assumed to be equivalent to the cost of Wound Irrigation for shoulder surgery and was taken from an evidence review for NICE guidelines [286]. The Wound Irrigation Intervention cost was calculated using an average of irrigation solution composition unit costs plus the delivery method [286]. The cost of the Antimicrobial-Coated Sutures Intervention was taken from a NICE medical technology consultation supporting documentation [45]. This was the additional cost of the Coated Sutures versus conventional sutures.

For the LMIC settings, the transferability of the additional cost of SSI pass the general knock-out criteria from using the study in Chapter 3 that highest cost quality assessment criteria fulfilled. No intervention costs could be uncovered for Coated Sutures and Wound Irrigation so the costs from the NICE guidelines and NICE medical technology consultation were used.

These costs also pass the general knock-out criteria as costs from NICE guidelines are subjected to methodological assessment [288] The relevance of the costs is improved by use of rebasing the costs using PPP.

Clinical parameters

Clinical parameters are listed in Table 5.2. The proportion of SSIs that happened before hospital discharge was taken from an international multicentre cohort study (GlobalSurg2 [289]) of patients undergoing a gastrointestinal resection surgery. the 30-day mortality by SSI status was also taken from GlobalSurg2 [289] and was calculated based on all the patients with non-missing mortality data at thirty days post-surgery. These model inputs were chosen from this study due to the large sample size of prospectively collected data with standardized SSI outcome assessment, and the procedure similarity to the model population. To incorporate the increased mortality by SSI severity in the model, mortality odds ratios of Deep Incisional SSI and Organ Space SSI versus Superficial SSI were calculated from a study of an SSI surveillance network of general surgery patients in northern France [7]. The Mortality Odds Ratio for Deep Incisional and the Deep Organ Space (both versus Superficial SSI) were 1.38 (95% CI 0.73 to 2.59) and 3.46 (95% CI 2.06 to 5.84), respectively.

As the GlobalSurg2 day mortality for patients with SSI was overall (4.83%) , a 30 day mortality for patients with an superficial SSI was required to use the odds ratios. Excel solver was used to calculate the 30 day mortality for patients with an superficial SSI. This was calculated given the expected severity proportions of SSI and the mortality odds ratios, and subject to the constraint that the expected overall SSI mortality matched as close as possible the GlobalSurg2 probability. This resulted in a 30 day mortality for patients with an superficial SSI of 2.86%.

Table 5.2 Model clinical parameters

Variable	Deterministic Value	PSA Distribution	PSA parameters	Source
Wound Irrigation Intervention Relative Risk	0.87	Log-Normal	μ= -0.1393 σ= 0.1250	Cochrane Review [290]
Antimicrobial-Coated Sutures Odds Ratio	0.72	Log-Normal	μ= -0.3285 σ= 0.1020	Meta Analysis [291]
Proportion of SSIs that were inpatient	54.7%	Beta	α=842; β=696	GlobalSurg2 [289] Table 5s
Superficial SSI proportion	42.12%	Dirichlet	α_1=8,560; $\alpha_1+\alpha_2+\alpha_3$= 20,322	SSI Surveillance Report [20]
Deep Incisional SSI proportion	29.73%	Dirichlet	α_2=6,042; $\alpha_1+\alpha_2+\alpha_3$=20,322	As above
Organ Space SSI proportion	28.15%	Dirichlet	α_3=5720; $\alpha_1+\alpha_2+\alpha_3$ =20,322	As above
30 day postoperative probability of SSI	12.27%	Beta	α=1,538; β=11,001	GlobalSurg2 [289] Table 2
30 day postoperative No SSI Death probability	1.50%	Beta	α=162; β=10,665	GlobalSurg2 [289] Table 2
30 day postoperative superfical SSI Death probability	2.86%	Beta	α=40; β=1,438	Derived from GlobalSurg2 [289], SSI Surveillance Report [20], and Astagneau [7]
Mortality Odds Ratio Deep Incisional versus Superficial SSI	1.38	Log-Normal	μ= 0.3207 σ= 0.3220	Astagneau[7]
Mortality Odds Ratio Organ Space versus Superficial SSI	3.46	Log-Normal	μ= 1.242 σ= 0.2647	Astagneau[7]
PSA: Probabilistic Sensitivity Analysis; SSI: Surgical Site Infection				

As no severity specific SSI proportions were detailed in GlobalSurg2 [289], severity proportions of SSI were instead taken from a European SSI surveillance report which had data on nine procedures across thirteen countries with data from 2018 to 2020 [20]. The model input was selected due to the large sample size of prospectively collected patient level data collected by hospitals participating in SSI surveillance. The proportions were calculated from all non-missing SSI severity data. This was the overall SSI severity proportions as procedure specific values were not reported. As no breakdown of severity by SSI on an inpatient/outpatient basis was provided in the report, inpatient and outpatient SSIs were assumed to have the same severity proportions in the model.

For treatment effectiveness parameters, evidence synthesis of SSI prevention RCTs in the form of summary estimates from meta-analyses [292] were sought. Treatment effectiveness for the Wound Irrigation strategy was taken from a Cochrane review which undertook a random-effects meta-analysis of RCTs comparing Wound Irrigation versus no Wound Irrigation, and reported a relative risk of 0.87 (95% Confidence Interval: 0.68 to 1.11) [290]. The certainty of evidence, based on the Cochrane Grading of Recommendations Assessment, Development and Evaluation (GRADE) Approach [117], was judged to be low due to high risk bias of studies (design and reporting) and imprecision (95% Confidence Interval crosses 1) [290]. A low quality level on the certainty of evidence corresponds to a limited confidence in the accuracy of the effect estimate, as the true effect could vary significantly from the estimated value [117].

Treatment effectiveness for the Coated Suture strategy was taken from a random-effects meta-analysis of RCTs comparing Antimicrobial-Coated Sutures versus non-Coated Sutures and reported an odds ratio of 0.72 (95 % Confidence Interval: 0.59 to 0.88) [291]. Using the

GRADE approach [117], the quality of included RCTs was judged to be moderate to low with potential risk of study design bias including industry sponsorship of studies [291].

Utility parameters

Utility parameters are listed in Table 5.3. For the base case analysis, the health state utility value for a patient without an SSI was taken from Gheorghe et al. [293]. These were adult surgical patients who were enrolled in the Reduction Of Surgical Site Infection using a Novel Intervention (ROSSINI) trial and were undergoing a laparotomy with a major incision [50]. The utility value was chosen from the others in Chapter 4 utility robustness section as it closely matched the model patient population and used a NICE recommended outcome measure. This was calculated as the average monthly utility of a patient without SSI across three timepoints (baseline, 7 days, and 30 days post surgery) of EQ-5D-3L scores using the area under the curve method. The SSI decrement studies from Chapter 3 were not combined into a meta-analysis model input due to the study differences in outcome measures, measurement timepoints, surgical patient populations and underreporting of uncertainty estimates. A meta-analysis summary estimate of an SSI decrement [276] was not selected for the model due to lack of baseline adjustment between patient groups in all the included studies which can be an important determinant of utility scores [213], and methodological issues of pooling within study estimates (across timepoints) without accounting for their inherent correlation [294,295].

Table 5.3 Model utility parameters

Variable	Deterministic Value	PSA Distribution	PSA parameters	Source
No SSI health state	0.543	Beta	α= 221.07; β= 185.71	Gheorghe [293] Table 5.19
For calculation of SSI decrement: Spine surgery patient with No SSI health state	0.79	Beta	α= 497.19; β= 132.17	Matza et al. [236]
For calculation of SSI decrement: Spine surgery patient with superficial wound infection	0.76	Beta	α= 525.96; β= 166.09	Matza et al. [236]
For calculation of SSI decrement: Spine surgery patient with Deep Infection (Two-Stage Revision Arthroplasty)	0.61	Beta	α= 284.24; β= 181.72	Matza et al. [236]
For Calculation of SSI decrement: Spine surgery patient with Deep Infection with a debridement and implant retention	0.47	Beta	α= 171.42; β= 193.30	Matza et al. [236]
Superficial SSI health state	$\frac{0.76}{0.79} \times 0.543 = 0.522$	N/A	N/A	Matza et al. [236], Gheorghe [293]
Deep Incisional SSI health state	$\frac{0.61}{0.79} \times 0.543 = 0.419$	N/A	N/A	Matza et al. [236], Gheorghe [293]
Deep Organ SSI health state	$\frac{0.47}{0.79} \times 0.543 = 0.323$	N/A	N/A	Matza et al. [236], Gheorghe [293]
PSA: Probabilistic Sensitivity Analysis; SSI: Surgical Site Infection				

The SSI utility decrements were taken from the post-spine surgery health states from Matza et al. [236]. These utility decrements were chosen as it was the study which scored the highest in the Chapter 4 utility robustness assessment section. Their health state valuation study elicited utility values of orthopaedic health state vignettes a using time-trade off [236]. The SSI utility decrements were assumed to be relative decrements and applied using a multiplicative method with the utility of patients without an SSI [296]. A superficial SSI was assumed to be equivalent to the "superficial wound infection" health state. A Deep Incisional SSI was assumed to be equivalent to the post-spine surgery "Deep Infection with a debridement and implant retention" health state. A Deep Organ Space SSI was assumed to be equivalent to the "Deep Infection (Two-Stage Revision Arthroplasty)" health state. In the absence of studies reporting utilities by SSI timing, the utilities of inpatient and outpatient SSIs were assumed not to differ. Due to no studies found in Chapter 4, the utilities were assumed to be the same in the LMIC settings.

5.2.5 Analysis

A cost-utility analysis was adopted with outcomes measured in Quality Adjusted Life Years (QALYs). For the UK setting, a healthcare perspective was taken for the analysis [72]. Discounting was not undertaken due to the thirty day postoperative time horizon. A UK cost-effectiveness threshold of £20,000 per QALY was considered for the analysis [297].

For the LMIC settings, a healthcare perspective was also used in relation to cost effectiveness an a country specific cost-effectiveness threshold for QALYs were used [298]. These thresholds were estimated based on the marginal productivity of health expenditure. The reported values were adjusted by a Purchasing Power Parity (PPP) conversion factor into international dollars and are shown in Table 5.4. As these were presented as a range, the upper bound was used for the base case analysis with the lower bound used for a deterministic

sensitivity analysis. As the cost per QALY thresholds were based on health expenditure, only healthcare costs were considered for costs in the cost-effectiveness assessment.

Table 5.4 Cost-effectiveness thresholds

Country	**Base Case threshold**	**Sensitivity Analysis threshold**	**Source**
Ghana	$2,043	$224	Woods et al. [298]
India	$2,781	$416	Woods et al. [298]
Mexico	$10,780	$3,850	Woods et al. [298]

An incremental approach was taken with strategies ordered by increasing costs. More costly and less effective strategies were considered dominated by the comparator strategy. A strategy was considered extended dominated if the current strategy would be dominated on costs and effects by a mixture of two other strategies [299]. Base case results were displayed with total costs and QALYs along with incremental costs and incremental QALYs. Interventions were considered cost-effective if their incremental cost-effectiveness ratio was less than or equal to the country specific QALY threshold. A summary of the model assumptions is given in Table 5.5.

Table 5.5 Model assumption list

Model Assumption	Model assumption section
Postoperative death was assumed to occur at the half point of the time horizon.	5.2.2 Model Structure
Patients are assumed not to be able to move between SSI severity types.	5.2.2 Model Structure
Interventions were assumed to only have an impact on the risk of SSI.	5.2.3 Model Interventions
Mean difference in additional cost by SSI severity was assumed to follow the same ratio of SSI severity specific median costs to overall SSI median costs in the Jenks et al. [161] study.	5.2.4 Model input parameters
Additional cost attributable to deep incisional SSI and organ space SSI assumed to be the same.	5.2.4 Model input parameters
Additional post-discharge costs for SSI patients were assumed to be the same ratio of secondary care costs to primary care costs as in Tanner et al. [47] study.	5.2.4 Model input parameters
The costs of patients who died were assumed to be same as the surviving patients.	5.2.4 Model input parameters
Wound Irrigation intervention cost was assumed to be equivalent to the cost of Wound Irrigation for shoulder surgery.	5.2.4 Model input parameters
Inpatient and outpatient SSIs were assumed to have the same severity proportions.	5.2.4 Model input parameters
SSI decrements were assumed to relative decrements equivalent to those in post-spine surgery health states.	5.2.4 Model input parameters
The utilities of inpatient and outpatient SSIs were assumed not to differ.	5.2.4 Model input parameters

5.2.6 Sensitivity analyses

Deterministic and probabilistic sensitivity analysis was also undertaken to quantify the model parameter uncertainty.

Deterministic sensitivity analysis

The deterministic sensitivity analyses (DSA) included univariate sensitivity analysis, multivariate sensitivity analysis, and threshold analysis. Where possible, values from studies reported in the systematic reviews and the literature were used. Threshold analyses was undertaken to assess the magnitude of difference required from one variable to change the decision recommendation. A description of the planned deterministic sensitivity analyses is listed in Table 5.6.

Probabilistic Sensitivity Analysis

10,000 iterations were run for the Probabilistic Sensitivity Analysis (PSA) to assess the joint parameter uncertainty of the model inputs. To ensure the reproducibility of the PSA output, seeded runs were undertaken. Probabilities with two possible outcomes were assigned beta distributions which were bounded between 0 and 1. Beta distribution parameters for probabilities were derived from count data or assumed count data where the sample size for the events was not specified or the probabilities source was an assumption. Probabilities with more than two possible outcomes were assigned a Dirichlet distribution. The Dirichlet distribution used count data for parameters. The treatment effectiveness odds ratio parameter for Coated Sutures and treatment effectiveness relative risk parameter for Wound Irrigation were both assigned log-normal distributions.

Table 5.6 Deterministic sensitivity analysis scenarios

Scenario number	Description
	Clinical Parameters
DSA1	The Proportion of SSIs that occurred before hospital discharge was altered from 54.7% to 37.5%. This value was taken from an SSI surveillance report spanning 9 procedures in 13 European Countries [20] excluding those with missing discharge dates.
DSA2	The 30 day postoperative probability of SSI was varied from 12.27% to 11%. The revised value was taken from a meta-analysis on the 30 day cumulative incidence of SSI in an adult general surgery patient population [300]
DSA3	The SSI primary care costs as a percentage of total costs parameter (14.85%) was changed to 10.83% which was taken from Reilly et al. [169]
DSA4	The Outpatient SSI costs as a percentage of Inpatient SSI costs parameter (26%) was doubled (52%)
DSA5	The Outpatient SSI costs as a percentage of Inpatient SSI costs parameter (26%) was halved (13%)
	Cost Parameters
DSA6	As the costs from Jenk et al. [161] assessed costs across 12 months, the overall additional cost of SSI was revised down by 50% of the original value (from £11,895 to £5,948). It was not reduced by 1/12 as most costs attributable to SSI would be skewed to the short-term postoperative time period. As the primary costs and outpatient SSI costs was proportional, this effectively reduces the overall additional total cost of SSI for all modelled SSI severities by 50%.

Scenario number	Description
DSA7	From the European search of SSI cost studies, the additional cost of an SSI was taken from Parker et al. [164] and applied to all health states. The cost value used was the mean cost difference of Deep SSI versus No Deep SSI 0-3 months post randomisation (£163). The cost value included both primary and secondary costs.
DSA8	From the LMIC search of SSI cost studies, the additional cost of an SSI by severity was taken from Liu et al. [180]. Keeping the model primary care cost percentage and outpatient SSI cost multiplier fixed, the total additional cost of a superficial inpatient SSI was changed to £371, the total additional cost of a Deep Incisional inpatient SSI was changed to £2,753, and the total additional cost of a Deep Organ Space inpatient SSI was changed to £19,725.
DSA9	The overall additional cost of SSI was taken Dramowski et al. [191]. Again, as these did not include primary care costs nor outpatient SSIs, it was assumed that the multiplier in the models were applicable to an LMIC setting. The overall additional cost of SSI was applied to all SSI severity health states and an inpatient SSI was changed to £1,048.
	Utilities
DSA10	As the severity of SSI utility values were taken from a study that had used a 1 year path state approach at odds with the model time horizon, the SSI utility decrements were arbitrarily reduced by 25%. This is in recognition that the path state included part valuation of a no SSI health state.
DSA11	To test the robustness in the other direction, the SSI utility decrements were arbitrarily increased by 25%
DSA12	A 30 day SSI decrement (0.156) from Totty et al. [238] which included adjustment for EQ-5D baseline imbalances was applied across all the SSI health severity states

Scenario number	Description
DSA13	The time horizon was extended to 2 months with utility decrements assumed to last an additional month
	Threshold Analysis
DSA14	The effectiveness of the Wound Irrigation intervention was varied to assess the minimum level of effectiveness required for it to be the most cost effective option
DSA15	The effectiveness of the Coated Sutures intervention was varied to assess the minimum level of effectiveness required for it to be the most cost effective option
DSA16	The baseline SSI risk was varied to assess the minimum level of SSI risk required for any of the SSI reducing interventions to remain cost-effective versus Usual Care.
DSA17	The overall cost of SSI was varied to assess the minimum level of costs associated with SSI required for any of the interventions to remain cost-effective versus Usual Care.
DSA18	An overall quality of life decrement associated with SSI was varied to assess the minimum level of disutility associated with SSI required for any of the interventions to remain cost-effective versus Usual Care.

The intervention costs were assigned Gamma distributions with an assumed standard error of 15% of the mean cost as no standard error had been reported. For the overall costs of SSI, no standard error had been reported. However, as the study reported mean and median values, the overall costs of SSI parameter was assigned a log-normal distribution as information on the mean and median values can be used to approximate the log-normal distribution parameters. Both Gamma and Log-Normal distributions are commonly used for cost parameters [137].

Utilities were assigned beta distributions with the information on the mean and standard deviation translated into beta distribution parameters using method of moments method [124] . Post-spine surgery health states used for calculation of the relative SSI decrement were assigned their own separate beta distributions to derive relative SSI decrements across the PSA iterations.

The average PSA iterations were summarised in a Table with the mean costs, QALYs and Net Monetary Benefit (NMB) for each strategy. The NMB valued total QALYs by strategy valued at £20,000 per QALY. 95% Prediction Intervals (PI) are displayed for the costs, QALYs and NMB. 95% PIs display the variability around the model mean output predictions.

The PSA output was illustrated using a incremental cost-effectiveness plane and a cost-effectiveness acceptability curve (CEAC). A Confidence ellipse conveyed the region in the incremental cost-effectiveness plane where 95% of the incremental iterations resided [301].

As the treatment effectiveness may not be generalisable to an LMIC setting, a PSA scenario explored the situation of the treatment effectiveness confidence intervals arbitrarily widened by 20%. This was done for both the Wound Irrigation relative risk [μ= -0.1393;σ= 0.2284] and the coated suture odds ratio [μ= -0.3285;σ= 0.2054].

5.2.7 Value of information

A Value of Information analysis was undertaken to assess the EVPI and EVPPI using the model's PSA output. The EVPI was first calculated on a per patient basis across a range of willingness to pay (WTP) thresholds. The VOI analysis was undertaken with the assumption that it would be of use to LMIC decision makers or a UK decision maker with an interest in improving health outcomes in overseas patients in LMIC settings. The latter was inferred from the multimillion pound global health funding by the UK government allocated to address the unmet need for research in global surgery [302]. To calculate the population EVPI, the number of general surgery patients per year in Ghana, India, and Mexico was estimated.

For Ghana, the number of general surgery procedures (n=42,850) was taken from a surgery enumeration study [303] which included a breakdown by surgical category. For India, a general surgery procedure per 100,000 population estimate [304] was combined with a United Nations population estimate for India [305] to quantify the number of general surgery patients per year (n=13,357,781). For Mexico, only surgical volume could be found (726.9 procedures per 100,000 inhabitants [306]) without breakdown by surgical category. For the purpose of the population EVPI in Mexico, a simple average of the General Surgery proportions from Ghana and Mexico was used (22.2%). Combined with a United Nations population estimate for Mexico [63], this results in a general surgery population of 205,926 in Mexico every year.

EVPPI was calculated using a double loop Monte Carlo simulation [134]. Selected parameters of interest were grouped in the outer loop and the rest of the parameters averaged within the inner loop. The inner loop was run for 10,000 samples and the outer loop were run with 1,000 samples. The results were presented on a per patient basis. The EVPPI of following groups of parameters were assessed:

1. Wound Irrigation and Coated Sutures effectiveness (Wound Irrigation Intervention Relative Risk; Antimicrobial-Coated Sutures Odds Ratio)
2. SSI quality of life decrements (Spine Surgery Patient with No SSI health state; Spine Surgery Patient with superficial wound infection; Spine Surgery Patient with Deep Infection [Two-Stage Revision Arthroplasty]; Spine Surgery Patient with Deep Infection with a debridement and implant retention)
3. Additional Cost of SSI (additional SSI secondary care costs, cost proportion of outpatient SSIs to inpatient SSIs, and percentage of primary care costs of an SSI).

5.3 Results

5.3.1 Deterministic results

The base case results with the total costs and QALYs by strategy are shown in Table 5.7 for the UK setting and the LMIC setting. Both SSI reducing interventions were cheaper and more effective than Usual Care. However, Wound Irrigation was dominated by the Coated Sutures intervention with higher incremental costs (£136) and lower QALYs (-0.0001). The Coated Sutures Intervention would be considered the most cost effective option due to its dominance over the other strategies.

Table 5.7 Base case results

Strategy	**Cost**	**Incremental Costs**	**QALY**	**Incremental QALY**	**ICER**
UK setting (£)					
Coated Sutures	£810		0.04409		Dominant
Wound Irrigation	£946	£136	0.04395	-0.000144	Dominated
Usual Care	£1,080	£270	0.0438	-0.000294	Dominated
LMIC settings (Int$)					
Coated Sutures	$1,256		0.04409		Dominant
Wound irrigation	$1,467	$211	0.04395	-0.000144	Dominated
Usual Care	$1,676	$419	0.0438	-0.000294	Dominated
Total QALYs rounded to five decimal places, and incremental QALYs rounded to six decimal places;ICER: Incremental cost effectiveness ratio; QALY: Quality Adjusted Life Year					

The deterministic sensitivity analysis results are shown in Appendix Tables A5.1-2 for UK and LMIC settings. Coated Sutures remained the dominant option in all univariate and multivariate scenarios except for when the additional cost of SSI was changed to £163. Under this scenario, Coated Sutures would be considered cost effective compared to the thresholds

in the UK, and Mexico. Usual Care would be considered the most cost-effective option under this scenario in India and Ghana.

The threshold analysis results are shown in Table 5.8. These varied by setting due to country-specific cost effectiveness thresholds with some of variation hidden due to rounding. For Usual Care to be cost effective, the additional SSI cost would have to lower than $227.61, $133.08, and $219.63 in Ghana, India, and Mexico, respectively. For the UK setting, SSI would have to reduce costs by more than £55.34 for Usual Care to be cost effective. Based on the impossible utility decrements, variables in addition to a SSI utility decrement would have change for Usual Care to be cost effective. To remain the most cost-effective option, the odds ratio for Coated Sutures would have to be just lower than 0.856 (Base case value: 0.72). Similarly, the Wound Irrigation relative risk would need to decrease to 0.744 (Base case value: 0.87) to overtake Coated Sutures as the most cost-effective option. The 30 day postoperative baseline risk of SSI would have to drop to below 0.17% or 0.18% for any of the interventions to not be cost-effective versus Usual Care.

Table 5.8 Threshold analysis

	Target value by country cost-effectiveness threshold			
Scenario	**UK**	**Ghana**	**India**	**Mexico**
DSA14: Minimum level of effectiveness required for Wound Irrigation intervention to the most cost effective option				
Threshold value	0.744	0.744	0.744	0.744
DSA15: Minimum level of effectiveness required for Coated Sutures intervention to the most cost effective option				
Threshold value	0.856	0.856	0.856	0.856
DSA 16: Minimum level of baseline SSI risk required for any of the SSI reducing interventions to remain cost-effective versus Usual Care				
Threshold value	0.17%	0.18%	0.18%	0.18%
DSA17: Minimum level of costs associated with SSI required for any of the interventions to remain cost-effective versus Usual Care				
Threshold value	-£55.37	$227.61	$219.63	$133.08
DSA 18: Minimum level of disutility associated with SSI required for any of the interventions to remain cost-effective versus Usual Care.				
Threshold value	-5.34	-80.93	-59.45	-15.34
SSI: Surgical Site Infection				

5.3.2 Probabilistic results

The mean PSA iterations are shown in Table 5.9 for the UK setting and Table 5.10 for LMIC settings. Coated Sutures had the lowest costs, highest QALYs and highest Net Monetary Benefit (NMB) on average based on the mean output of the 10,000 iterations.

Table 5.9 Probabilistic sensitivity analysis results averaged across iterations

Strategy	**Cost (95% PI)**	**QALY (95% PI)**	**NMB (95% PI)**
Coated Sutures	£795 (£774 to £815)	0.04474 (0.04418 to 0.0453)	£100 (£76 to £124)
Wound Irrigation	£929 (£905 to £953)	0.04476 (0.04419 to 0.04532)	-£34 (-£60 to -£8)
Usual Care	£1057 (£1,029 to £1,084)	0.04476 (0.04419 to 0.04533)	-£161 (-£191 to -£132)
PI: Prediction Interval; NMB: Net Monetary Benefit; QALY: Quality Adjusted Life Year			

Incremental Cost-effectiveness Scatterplots are shown in Figures 5.2-5.4 with 95% Confidence Ecilpse for the UK setting. As the costs rebasing is the only difference between the model settings, the patterns (with costs multiplied by a constant) would be the same. An incremental cost-effectiveness report for all settings is reported in Appendix Table A5.3. As most of the iterations ended up in the Southeast or Northwest quadrant, the proportions of cost-effective iterations was similar across settings even with different willingness to pay thresholds.

Table 5.10 Probabilistic sensitivity analysis results averaged across iterations (international dollars)

Strategy	Cost (95% PI)	QALY (95% PI)	Ghana NMB (95% PI)	India NMB (95% PI)	Mexico NMB (95% PI)
Coated Sutures	$1232 ($1200 to $1,265)	0.04474 (0.04418 to 0.0453)	-$1,141 (-$1,110 to -$1,172)	-$1,108 (-$1,077 to -$1,139)	-$750 (-$724 to -$776)
Wound Irrigation	$1441 ($1,404 to $1,477)	0.04476 (0.04419 to 0.04532)	-$1,349 (-$1,314 to -$1,385)	-$1,316 (-$1,281 to -$1,351)	-$958 (-$928 to -$989)
Usual Care	$1639 ($1,596 to $1,681)	0.04476 (0.04419 to 0.04533)	-$1,547 (-$1,506 to -$1,589)	-$1,514 (-$1,473 to -$1,555)	-$1,156 (-$1,120 to -$1,193)
PI: Prediction Interval; NMB: Net Monetary Benefit; QALY: Quality Adjusted Life Year					

Figure 5.2 Coated Sutures versus Usual Care incremental cost-effectiveness scatterplot

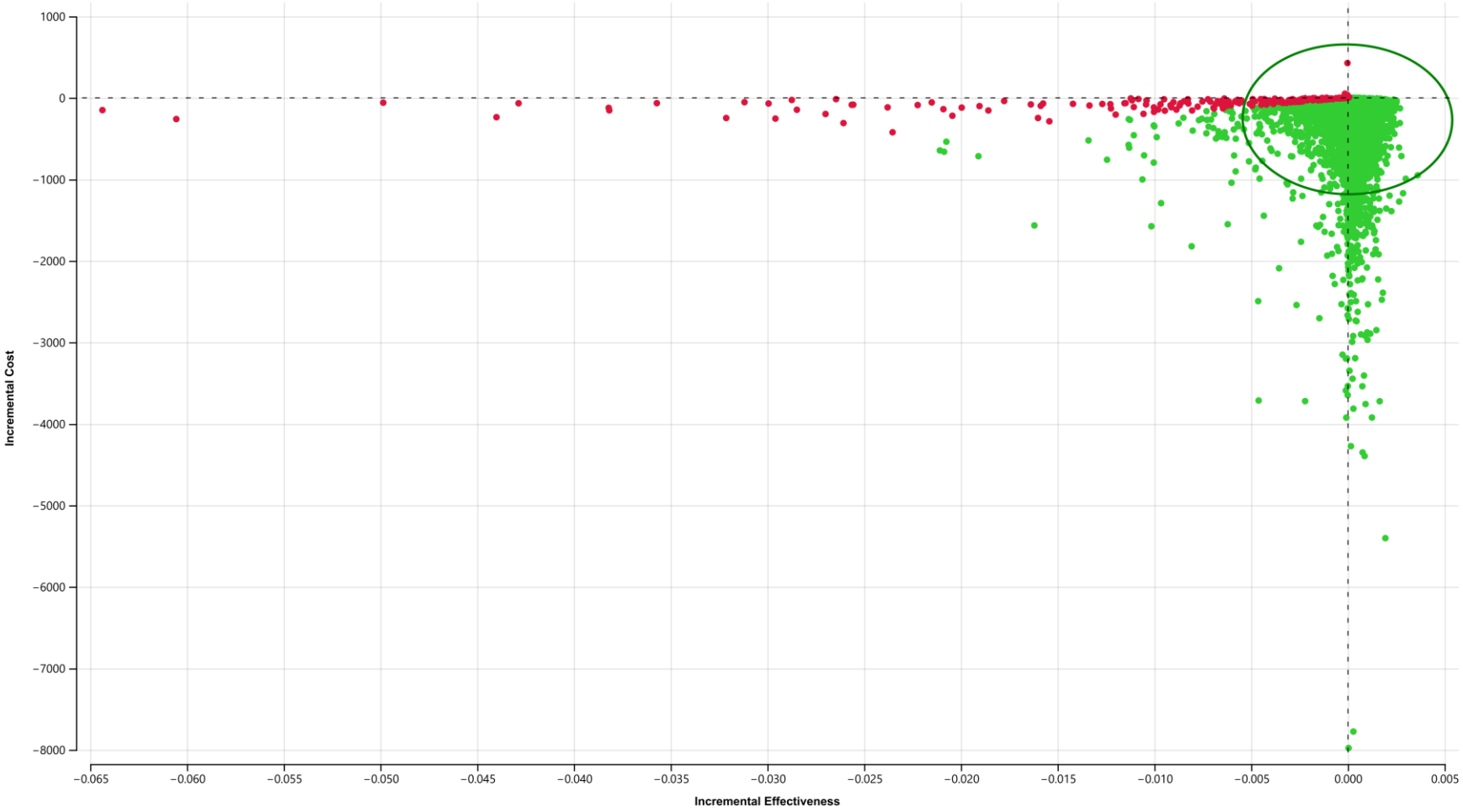


Figure 5.3 Wound Irrigation versus Usual Care incremental cost-effectiveness scatterplot

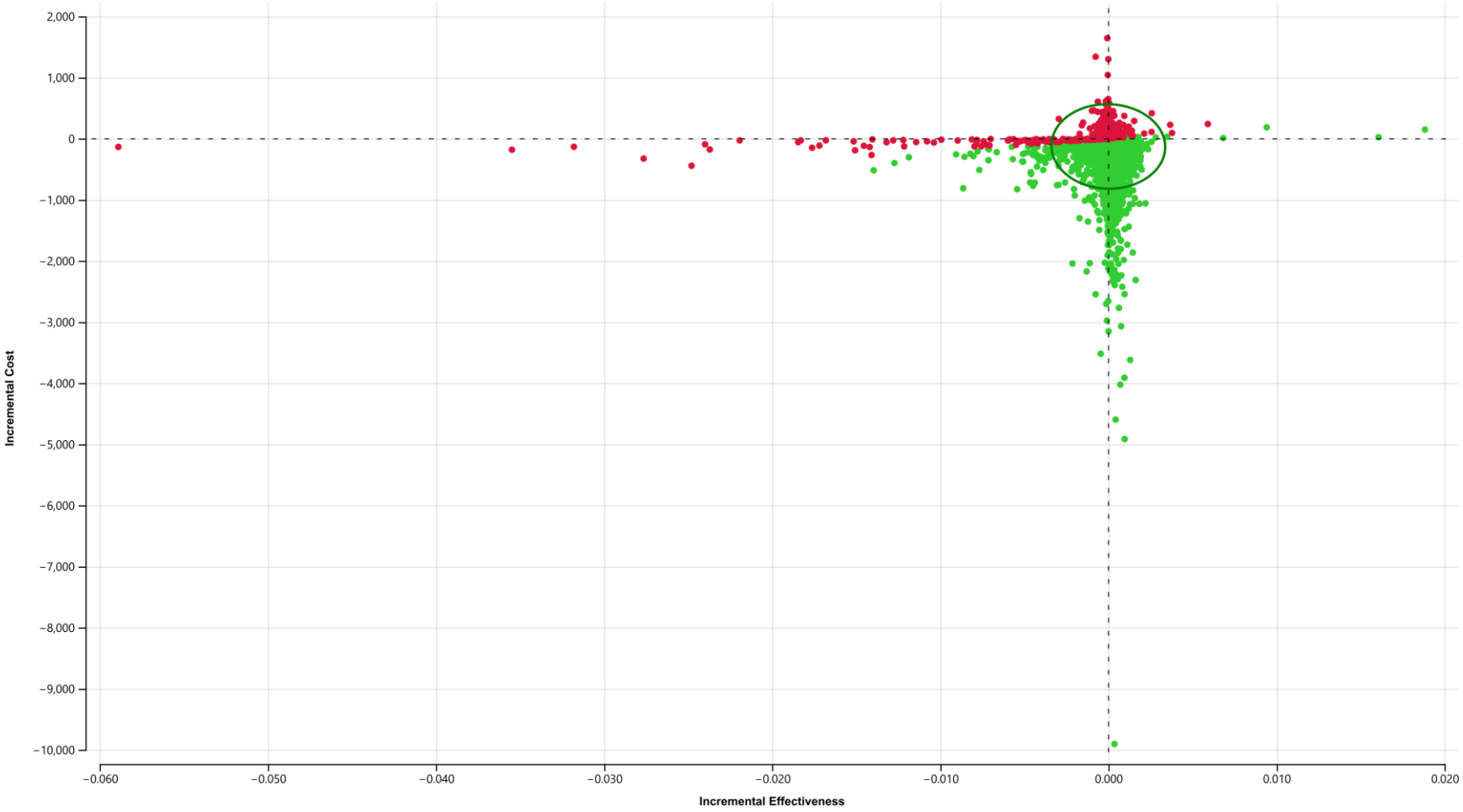
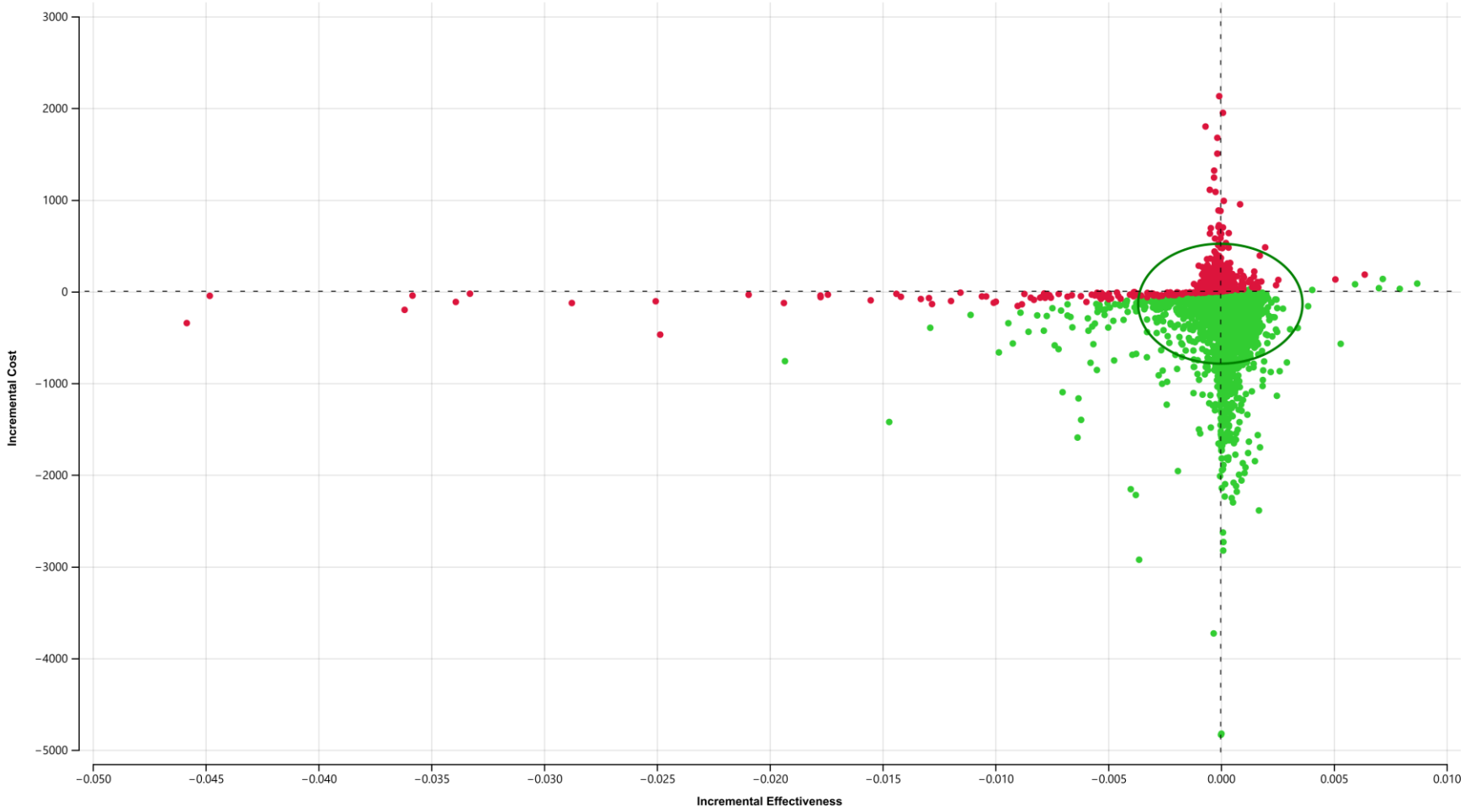


Figure 5.4 Coated Sutures versus Wound Irrigation incremental cost-effectiveness scatterplot



For Coated Sutures versus Usual Care (Figure 5.2), 99.72% of the PSA iterations resided in the Southeast Quadrant indicating that Coated Sutures was cheaper and more effective than Usual Care. The Incremental cost-effectiveness scatterplot of Wound Irrigation versus Usual Care is shown in Figure 5.3. 83.21% of the PSA iterations resided in the Southeast Quadrant suggesting that Wound Irrigation dominated Usual Care while 13.57% of the PSA iterations resided in the Northwest Quadrant suggesting that Wound Irrigation was dominated by Usual Care.

For the 3.22% of the PSA iterations that resided in the Northeast Quadrant, only 15.53% of these iterations would be considered cost-effective. For Coated Sutures versus Wound Irrigation (Figure 5.4), 84.44% of PSA iterations reside in the Southeast quadrant, indicating that Coated Sutures was cheaper and more effective compared to Wound Irrigation. 14.84% of the PSA iterations were in the northwest quadrant indicating that Coated Sutures was more expensive and less effective compared to Wound Irrigation.

The PSA iterations were quantified into a CEAC in Figure 5.5 for the UK setting. At a WTP threshold of £20,000 per QALY, 85% of the PSA iterations that were the most cost-effective option belonged to the Coated Sutures strategy. The Wound Irrigation strategy was a distant second with it being the most cost effective option in 14.9% of all the PSA iterations. Lastly, the Usual Care strategy had only 0.1% of the PSA iterations that had the strategy as the most cost-effective option. The curves were flat across a range of WTP thresholds which suggests that the most cost-effective option within each PSA iteration most likely dominated the other strategies. At a zero WTP threshold for an additional QALY, the proportion of PSA iterations that indicated Coated Sutures was the most cost-effective option was still 85%.

For the LMIC settings, the CEAC is shown in Figure 5.6. At the LMIC country specific cost-effectiveness thresholds, Coated Sutures remained the most cost-effective option with the same rankings of Wound Irrigation and Usual Care being the second and third most cost-effective options.

Figure 5.5 UK Cost-effectiveness acceptability curve

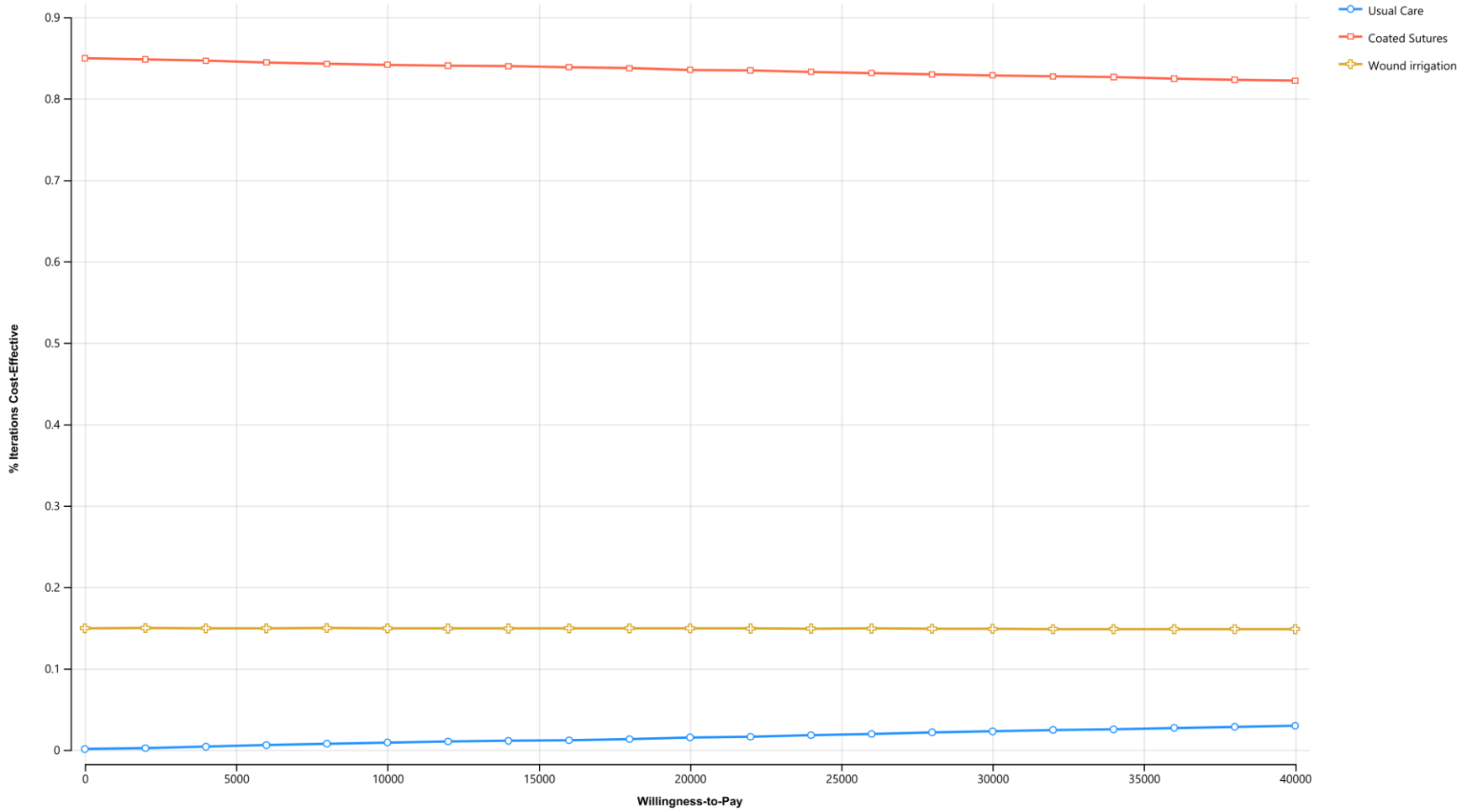
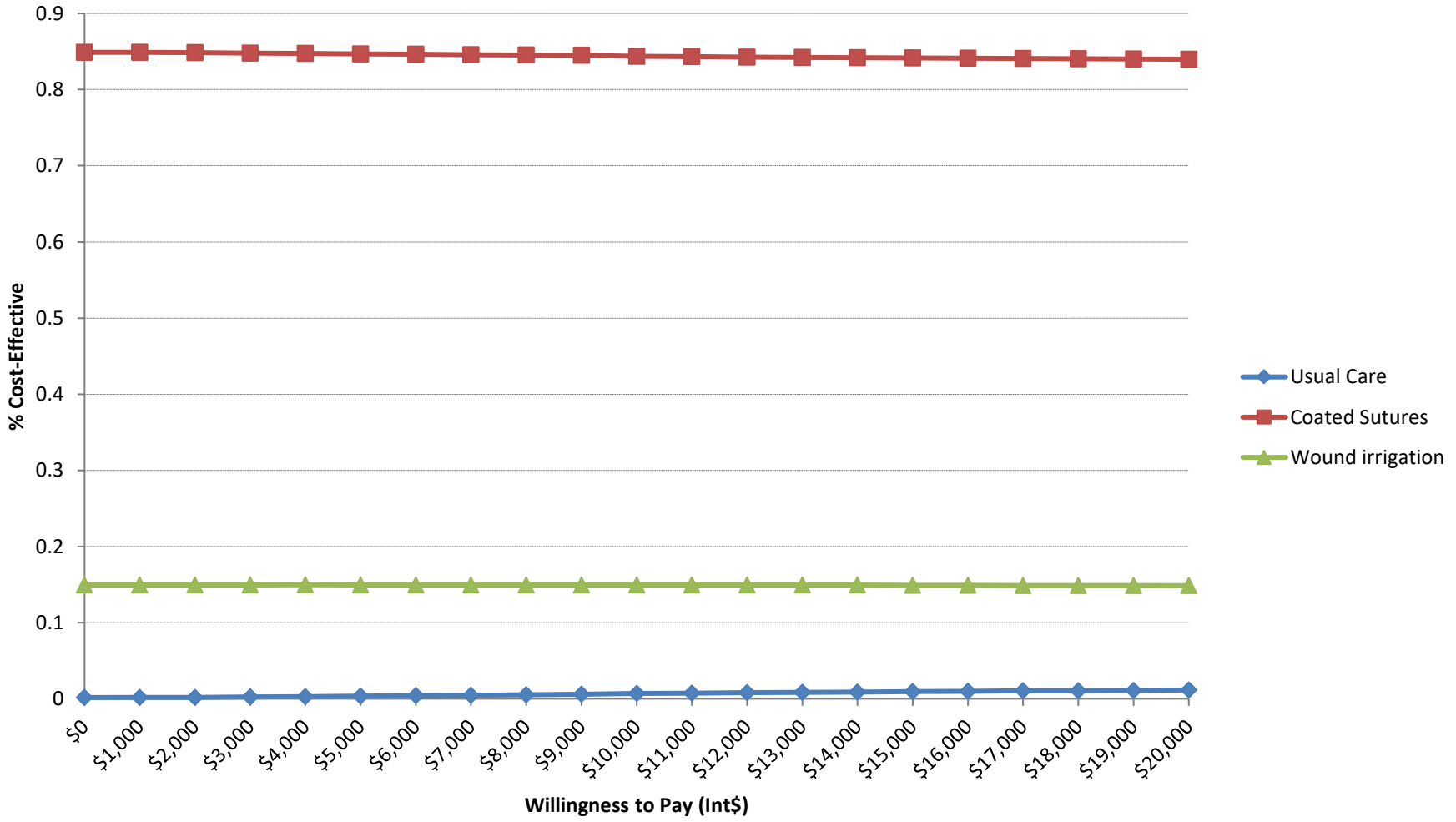


Figure 5.6 Cost-effectiveness acceptability curve (International dollars)



Increased treatment effectiveness confidence interval PSA Scenario

The mean PSA results for the increased treatment effectiveness confidence interval scenario is shown in Tables 5.10-5.11. On average, Coated Sutures remained cheaper and more effective than the other scenarios. Furthermore, Coated Sutures had the highest NMB on average. A CEAC under the PSA scenario is shown in Figures 5.7-5.8. Coated Sutures remains the most cost-effective option across all the country setting cost-effectiveness thresholds although this proportion has decreased. Like the previous CEACs, the proportion of PSA iterations by strategy that were most cost-effective option varied little across the range of WTP thresholds.

Table 5.10 PSA Scenario Mean results (UK setting)

Strategy	**Cost (95% PI)**	**QALY (95% PI)**	**NMB (95% PI)**
Coated Sutures	£804 (£782 to £825)	0.04474 (0.04418 to 0.0453)	£91 (£67 to £115)
Wound Irrigation	£943 (£919 to £968)	0.04477 (0.0442 to 0.04534)	-£48 (-£75 to -£21)
Usual Care	£1057 (£1029 to £1084)	0.04476 (0.04419 to 0.04533)	-£161 (-£191 to -£132)
PI: Prediction Interval; NMB: Net Monetary Benefit; QALY: Quality Adjusted Life Year			

Table 5.11 Probabilistic sensitivity analysis results averaged across iterations (international dollars)

Strategy	Cost (95% PI)	QALY (95% PI)	Ghana NMB (95% PI)	India NMB (95% PI)	Mexico NMB (95% PI)
Coated Sutures	$1,232 ($1,200 to $1,265)	0.04474 (0.04418 to 0.0453)	-$1,141 (-$1,110 to -$1,172)	-$1108 (-$1,077 to -$1,139)	-$750 (-$724 to -$776)
Wound Irrigation	$1,441 ($1,404 to $1,477)	0.04476 (0.04419 to 0.04532)	-$1,349 (-$1,314 to -$1,385)	-$1,316 (-$1,281 to -$1,351)	-$958 (-$928 to -$989)
Usual Care	$1,639 ($1,596 to $1,681)	0.04476 (0.04419 to 0.04533)	-$1547 (-$1,506 to -$1,589)	-$1,514 (-$1,473 to -$1,555)	-$1,156 (-$1,120 to -$1,193)

PI: Prediction Interval; NMB: Net Monetary Benefit; QALY: Quality Adjusted Life Year

Figure 5.7 Cost-effectiveness acceptability curve PSA scenario (UK setting)

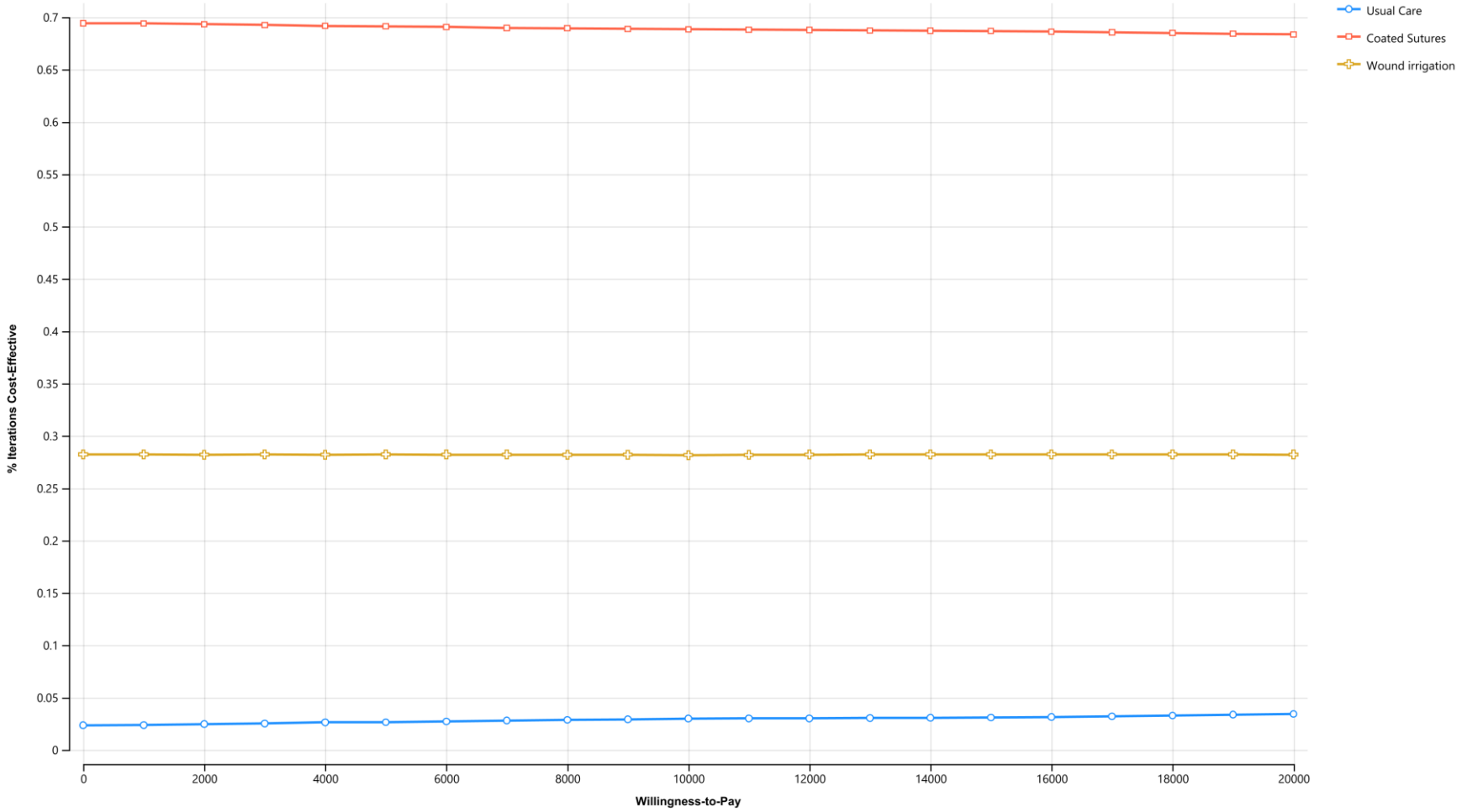
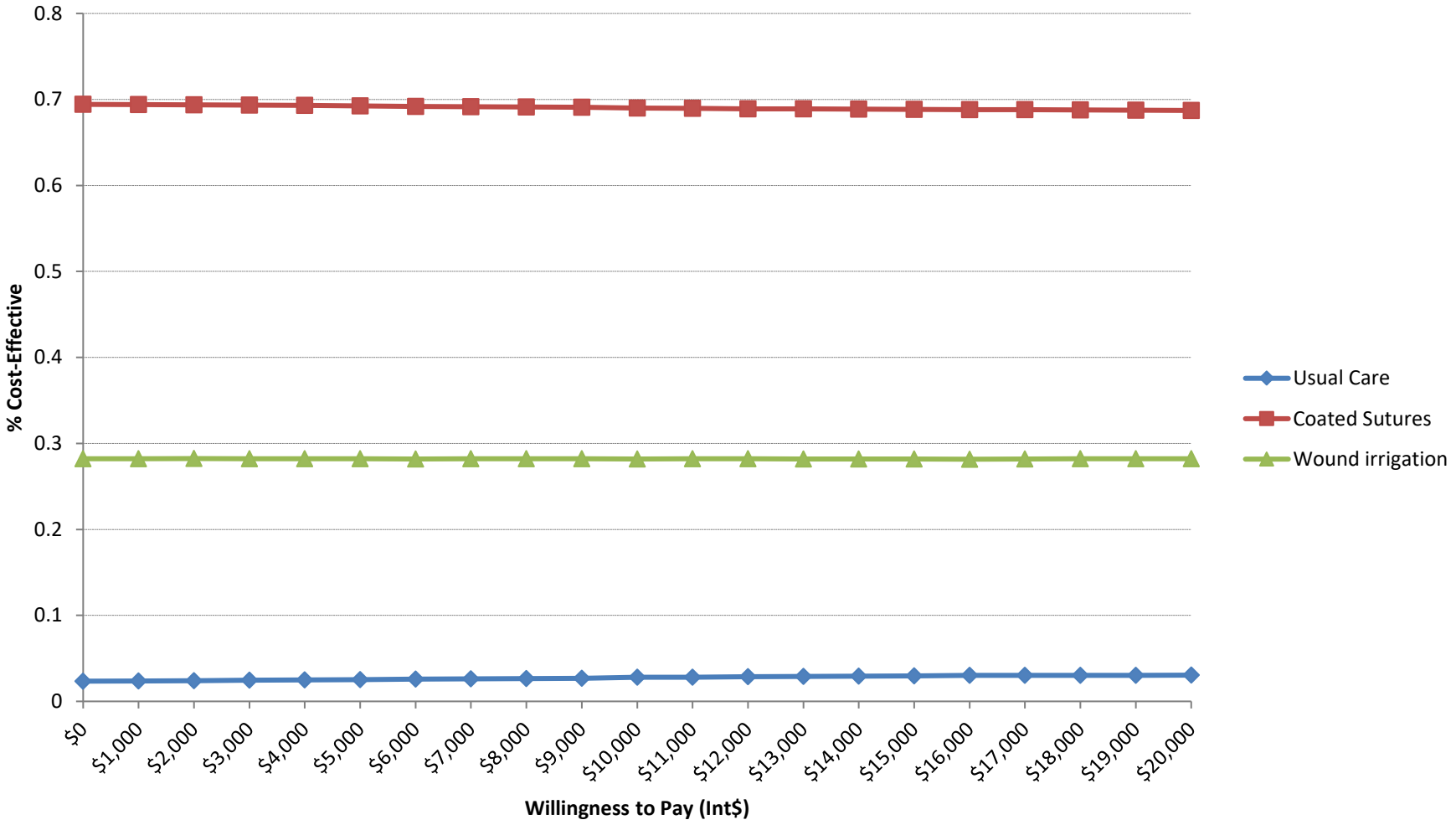


Figure 5.8 Cost-effectiveness acceptability curve (LMIC setting and International dollars)



5.3.3 Value of information results

The EVPI across WTP thresholds and population is shown in Table 5.12. At a $10,000/QALY WTP threshold, the per-patient EVPI is $16.93. Even with a WTP threshold of zero per QALY, the population EVPIs for India, Mexico, and Ghana were $219,698,201, $3,386,908, and $704,763, respectively. The EVPPI results for selected groups of parameters is shown in Table 5.13. The results indicate there was value primarily in reducing uncertainty associated with treatment effectiveness but no value in reducing uncertainty associated with SSI utilities. For the SSI cost parameters, there was a small per patient EVPPI above the willingness to pay thresholds specified for Ghana, India and Mexico.

Table 5.12 Population expected value of perfect information

Willingness to pay threshold (Int $)	Per patient EVPI (Int $)	India population EVPI (Int $)	Mexico population EVPI (Int $)	Ghana population EVPI (Int $)
$0	$16.45	$219,698,201	$3,386,908	$704,763
$1,000	$16.45	$219,700,600	$3,386,945	$704,771
$2,000	$16.45	$219,786,368	$3,388,267	$705,046
$3,000	$16.47	$220,052,608	$3,392,371	$705,900
$4,000	$16.51	$220,500,281	$3,399,273	$707,336
$5,000	$16.55	$221,093,394	$3,408,416	$709,238
$6,000	$16.61	$221,847,084	$3,420,035	$711,656
$7,000	$16.67	$222,715,268	$3,433,419	$714,441
$8,000	$16.75	$223,705,774	$3,448,689	$717,619
$9,000	$16.83	$224,866,627	$3,466,585	$721,342
$10,000	$16.93	$226,166,541	$3,486,625	$725,512
$11,000	$17.04	$227,558,121	$3,508,078	$729,976
$12,000	$17.14	$229,018,844	$3,530,596	$734,662
$13,000	$17.26	$230,605,931	$3,555,063	$739,753
$14,000	$17.39	$232,274,378	$3,580,784	$745,106
$15,000	$17.52	$233,974,375	$3,606,992	$750,559
$16,000	$17.65	$235,729,840	$3,634,054	$756,190
$17,000	$17.78	$237,535,884	$3,661,897	$761,984
$18,000	$17.92	$239,383,082	$3,690,373	$767,909
$19,000	$18.06	$241,273,389	$3,719,515	$773,973
$20,000	$18.21	$243,204,610	$3,749,287	$780,168

Table 5.13 Expected value of perfect parameter information (per patient)

Willingness to pay threshold (Int $)	Treatment effectiveness parameters (Int $)	SSI decrements parameters (Int $)	SSI cost parameters (Int $)
$0	$6.36	$0.00	$0.00
$1,000	$6.36	$0.00	$0.00
$2,000	$6.36	$0.00	$0.00
$3,000	$6.36	$0.00	$0.00
$4,000	$6.36	$0.00	$0.00
$5,000	$6.36	$0.00	$0.00
$6,000	$6.36	$0.00	$0.00
$7,000	$6.36	$0.00	$0.00
$8,000	$6.36	$0.00	$0.00
$9,000	$6.36	$0.00	$0.00
$10,000	$6.36	$0.00	$0.00
$11,000	$6.36	$0.00	$0.00
$12,000	$6.36	$0.00	$0.00
$13,000	$6.36	$0.01	$0.00
$14,000	$6.35	$0.03	$0.00
$15,000	$6.35	$0.04	$0.00
$16,000	$6.35	$0.06	$0.00
$17,000	$6.35	$0.07	$0.00
$18,000	$6.35	$0.08	$0.00
$19,000	$6.35	$0.10	$0.00
$20,000	$6.35	$0.11	$0.00

5.4 Discussion

5.4.1 Statement of principal findings

A preliminary economic evaluation was undertaken to assess the cost-effectiveness of interventions to reduce SSI. Based on the model structure, assumptions, and model inputs, Coated Sutures were cheaper and more effective than a Wound Irrigation or Usual Care strategy. The results were robust to both deterministic and probabilistic sensitivity analysis. Given the low cost of the SSI reducing interventions, it makes intuitive sense that the intervention cost would be offset by the considerable economic consequences associated with SSI. Ignoring the cost impact of SSI or the utility impact of SSI still resulted in the Coated Sutures strategy being the most cost-effective option.

The VOI analysis indicated that there was value associated with the elimination of parameter uncertainty. This was higher in more populated countries given the larger general surgery patient population. However, the EVPPI indicated that the value of future research was focused on reducing the parameter uncertainty treatment effectiveness between Wound Irrigation and Coated Suture. This relies on the assumption that only one SSI reducing intervention can be recommended for resource allocation decisions. As both Wound Irrigation and Coated Sutures could be used concurrently in the same surgery, a combined Wound Irrigation and Coated Sutures strategy versus Usual Care could be even more cost-effective but the bundle treatment effectiveness is unknown.

5.4.2 Strengths and weaknesses

There are several strengths associated with the preliminary economic model. It benefitted from separate systematic reviews on the cost and utility estimates associated with SSI. The model recognised that SSI could occur before or after hospital discharge and that SSI can differ by severity. The model underwent extensive deterministic and probabilistic sensitivity analysis to assess the model parameter uncertainty. A VOI analysis to assess the benefit of future research on eliminating or reducing parameter uncertainty of all or some of the model inputs was also undertaken to inform the importance for further evidence generation.

There are several limitations associated with the preliminary economic model. Owing to data availability, simplifying assumptions were needed on the impact of different types of SSI. The base case SSI disutility estimates were taken from a different surgical patient population. Further, the disutilities and costs of SSI were taken from sources with a different time horizon (1 year) that did not correspond with the model time horizon (1 month). DSA varying these estimates did not change the decision recommendation. The aforementioned transferability of treatment effectiveness was also tested in a PSA scenario which marginally increased the iterations where Usual Care was the most cost-effective option but the SSI reducing interventions still had the vast majority of cost effective iterations. The severity of SSI was not assumed to affect mortality in the model. As the interventions did not affect the severity of SSI, the cost-effectiveness results would be affected by the assumption if the severity distribution from Globalsurg2 was different from the European SSI surveillance report. As severity distribution from Globalsurg2 was not reported, it is unclear whether the overall mortality risk used in the model by SSI status is reflective of the severity distribution used.

For the LMIC settings, the transferability of the cost and utility model inputs is unknown. While the costs were adjusted using PPP, the relevance of these costs even after adjustment to different income settings is unclear. Preferences with respect to health attributes differ by setting[273] which may affect the generalisability of the utility valuations. If the costs and utility valuations are similar to the transferred setting, the EVPPI does not suggest there is much value to reduce decision uncertainty for these model inputs. Societal costs can be an important consideration in LMIC settings but this was examined here due to a cost-effectiveness threshold only including healthcare costs. SSI is associated with productivity loss costs [27] and its inclusion would have likely have made the interventions that reduced SSI even more appealing in terms of societal costs avoided.

The cost of increased antibiotic resistance due to prescribing of antibiotics to treat SSI was not accounted for within the model. However, accounting for the externality would have increased the costs of treating an SSI and penalise strategies with higher SSI even more.

The short time horizon of 30 days postoperatively is another limitation of the study. A retrospective cohort analysis of routine data found that while by 6 months healed wounds were similar for patients by SSI status (95% of SSI cases and 98% of non-SSI cases), the mean wound healing time was time to heal was 49.4 days and 64.3 days for patients with SSI and patients without SSI, respectively [307]. The longer wound healing times for SSI patients beyond the model time limits the additional economic impact associated with SSI and the benefits associated with interventions to prevent SSI. A sensitivity analysis extending the time horizon to 2 months after surgery served to increase the cost-effectiveness of the interventions to prevent SSI.

The transferability of the treatment effectiveness of the SSI reducing interventions to LMIC settings is unknown. Extrapolating RCT evidence generated from High Income Country surgical settings to LMIC surgical settings may be problematic. As noted in Chapter 1, LMICs face shortfalls in surgical labour [35–38] and surgical infrastructure [39–42] which limits the number of operations that can be performed; threatens the effectiveness of surgery, and can lead to adverse patient outcomes [43]. The effectiveness of the intervention in a different surgical environment along with a different patient profile [44,308] is unknown and caution is required for any interpretation of the model results for LMIC decision recommendations. The value of information analysis relies on the assumption that the model inputs transferred from a UK setting are applicable to LMIC settings. It is likely that the population EVPI and EVPPI would differ if country specific data in the LMIC specific data on costs, utilities and clinical data settings was available and could be used in the model.

5.4.3 Implications for practice

For the UK jurisdiction where the model has followed the NICE reference case [72], the evidence suggests that Coated Sutures would decrease costs and increase utility compared to Usual Care. Indeed, this was the case for the manufacturer economic model submitted to NICE [287]. Wound Irrigation was considered cost-effective versus the no Wound Irrigation in Usual Care strategy in the current economic evaluation, but no identified economic evaluations were found in the literature assessing the cost-effectiveness of Wound Irrigation. The cost-effectiveness of the Wound Irrigation strategy versus Usual Care was apparent even with the imprecision of the 95% confidence interval of the Relative Risk containing values equal to and greater than 1. This highlights the argument that statistical inference may not be entirely informative to decision making and that non-statistically different treatment strategies can still have different decision recommendations on cost-effectiveness [309].

The limitations of cost and quality of life estimates sourced from the systematic reviews were reported in Chapter 3 and Chapter 4. The lack of reporting on clinical parameters relevant to the SSI cost and quality of life estimation within the model has meant the use of assumptions and reliance on other studies to populate the model. Future research should report the costs and consequences of SSI by severity and timing to capture the diversity of experiences by patients. As the costs and outcomes of SSI differ by severity, RCTs measuring treatment effectiveness should consider a secondary analysis looking at the impact of reducing SSI by severity as reducing more severe SSIs are more worthwhile than reducing superficial SSIs in an economic evaluation.

5.4.4 Conclusion

Interventions that reduced SSI were found to reduce overall costs and increase utilities in a decision analytic model assessing the cost-effectiveness of exemplar interventions to prevent SSI in a general surgery population for a UK and LMIC setting. With the limitations relating to the SSI cost and quality of life estimation currently used in the model, the next Chapter will attempt to overcome some of these limitations with a re-analysis of trial data to provide robust estimates to further refine the model-based economic evaluation. The model is revisited again later in the thesis after the primary research collection with a view of refining the model one final time with the model inputs more applicable to LMIC settings.

Chapter 6:

ROSSINI trial re-analysis

6.1 Introduction

The aim of this chapter is to develop more robust estimates of the costs and quality of life consequences from suffering an SSI. These estimates will be then used for further refinement of the preliminary model-based economic evaluation built in the preceding chapter. Chapter 3 presented a systematic review of the costs associated in SSI across income groups. The review concluded that the available cost estimates associated with SSI were derived from heterogenous methods, making the true magnitude of cost difference across studies and countries challenging. Likewise, SSI had an adverse effect on quality of life across all studies in the systematic review reported in Chapter 4, but the estimation of the SSI utility decrement was beset with methodological challenges, making accurate quantification difficult to ascertain. These cost and quality of life estimates were brought together to assess the preliminary cost-effectiveness of an intervention to reduce SSI in the last Chapter. Given the limitations of the estimates used to populate the model, the next steps are to refine the preliminary economic model with more robust estimates. The development of the estimates is performed by a re-analysis of a large SSI Randomised Control Trial (RCT) in the UK, the Reduction Of Surgical Site Infection using a Novel Intervention (ROSSINI) trial [50], the original economic analysis by SSI status was included in a doctoral thesis [293].

This chapter is divided into three sections.

(i) Section A is a representation of the original ROSSINI analysis on the cost and quality of life implications of SSI. A summary of the economic evaluation of ROSSINI is introduced first [48] before describing the analyses specific to SSI reported in the doctoral thesis [293]. The original analysis assessed unadjusted differences in costs and utilities by SSI status. The original analysis methods are detailed including aspects inferred from the analysis code where the detail has been omitted in the doctoral thesis. The results are also rereported for comparison against the re-analysis estimates.

(ii) The ROSSINI re-analysis forms the second section of the chapter (Section B). The re-analysis employed three separate approaches to develop the SSI cost and quality of life consequences from the patient level data. One approach was modification of the original analysis' Cross-Comparison approach whilst the other two represented new approaches (Generalised Linear Model, and Case Control). The results of the re-analysis from each estimation approach along with the sensitivity analyses was presented and the section concluded with a discussion of the results, including a comparison with the original analysis.

(iii) Section C includes the refinement of the model-based economic evaluation using the ROSSINI re-analysis estimates for the cost and quality of life consequences of SSI. The preliminary model is updated with the new estimates with deterministic and probabilistic analyses undertaken. The Value of Information analysis is undertaken again to assess the value of reducing decision uncertainty in one or more of the parameters. The section ends with a discussion of the findings and comparison with the preliminary model results in Chapter 5

6.2 ROSSINI economic evaluation summary (completed and published in 2014)

The ROSSINI trial assessed the clinical effectiveness of wound edge protection devices versus standard care on reducing SSI in patients undergoing laparotomy in the UK [50]. From February 2010 to January 2012, 760 patients were enrolled in the multicentre RCT which found that the wound edge protection device intervention was not associated with a reduction in SSIs compared to standard care [50]. The accompanying trial-based economic evaluation collected postoperative resource use information on inpatient and outpatient healthcare service utilisation up to 30 to 33 days after surgery. The EQ-5D-3L was also collected as part of the trial and was administered to patients at three time points: at baseline prior to surgery, at 5 to 7 days post-operatively and at 30 to 33 days post-operatively. The trial-based economic evaluation found wound edge protection devices were not cost-effective compared to standard care [48]. Wound edge protection devices were more costly and less effective on average than standard care with a low probability of cost-effectiveness (<20%) based on the cost-effectiveness acceptability curve [48].

The total costs by trial arm in the economic evaluation were calculated using a Generalised Linear Model with a gamma distribution and log link identify function. The covariates in the cost were treatment allocation, age, current smoking status, Body Mass Index (BMI), diabetes status, stoma creation plans, emergency/elective surgery, plan to create a viscus, and SSI. The utilities were calculated using a Generalised Linear Model with a normal distribution and log link identify function. The covariates in the utility shared same covariates as the cost with the addition of baseline utility to adjust for quality of life imbalances for participants at the start of the trial.

However, results regarding the additional cost of an SSI and utility decrement associated with SSI were only reported in the linked doctoral dissertation [293] and were not included in the economic evaluation publication [48].

6.3 Representation of the ROSSINI trial information

For context for the original and re-analysis, the ROSSINI trial information on the patient population, assessment of SSI, resource use and quality of life measurements was detailed first. Next, the additional cost and/or decrement associated with SSI from the original analysis was then reproduced for comparison with the subsequent re-analysis results.

6.3.1 ROSSINI patient population

The inclusion criteria for enrolling in the ROSSINI trial were adult surgical patients having either an elective or emergency laparotomy with a major incision. The exclusion criteria were laparotomies with a laparoscopic approach or a recent laparotomy in the previous three months. Baseline demographic details were collected on each patient along with operative information on the procedure [50]. To provide context on the setting, Appendix Table A6.1 displays information on the type of hospitals who participated in the ROSSINI trial.

6.3.2 ROSSINI surgical site infection assessment

In the original trial, the wounds were assessed for SSI at 5 to 7 days post operation, or at discharge if the patient had been discharged earlier than the 5 to 7 postoperative day, and additionally at 30 to 33 days post operation at a face to face wound review at the hospital. Trained trial research staff undertook the 30 to 33 days post operation wound review as a home visit for patients unable to attend the wound review at the hospital. The wound assessment questionnaire was derived from the Health Protection Agency SSI surveillance system (HPA SSISS) which itself was based on the CDC SSI definition criteria [50].

6.3.3 ROSSINI resource use

Resource use collected prospectively in the ROSSINI trial included both primary care and secondary care resource use. For primary care, resource use on the number of General Practitioner (GP) visits, practice nurse visits, district nurse visits, and medication (antibiotics and pain relief) was collected. The primary care resource use was asked in a wound healing post-discharge questionnaire Case Report Form (CRF) completed at 30 to 33 days after the surgery by the patient. For medication, the name of drug and dose was collected, and antibiotic use was requested only in relation to any infection in the wound.

Secondary care resource use consisted of number of days in intensive therapy unit (ITU), number of days in high dependency unit (HDU), number of days on ventilation, readmission length of stay, and outpatient clinic visits. The number of days in ITU, HDU, and on ventilation, were asked within the 30-day period post operation and could include both the index postoperative length of stay days and any hospital readmission length of stay. All the secondary care resource use was collected at 30 to 33 days post-surgery in the resource utilisation CRF, except for the outpatient clinic visits which were collected in the wound healing post-discharge questionnaire CRF. The resource utilisation CRF was completed by research trial staff at the hospital.

6.4 Reproduction of the original analysis results

In the original analysis, a cross comparison of costs by SSI status approach was taken. The mean costs of inpatient care, costs of outpatient care and total costs by SSI status was presented. A mean difference between the groups were calculated along with a 95% Confidence Interval with an assumed Gamma distribution.

For EQ-5D-3L utility scores, the scores by timepoint and SSI status was presented. A mean difference between the groups by timepoint were calculated along with a 95% Confidence Interval with an assumed Normal distribution. The mean differences were not adjusted by baseline utility scores.

The results from the original analysis are reproduced in Table 6.1. The additional cost of an SSI was £1,067 [95% Confidence Interval: £237 to £1,901]. Patients with SSI had lower EQ-5D-3L scores across all timepoints relative to patients without SSI. The utility decrement at 30 days post-surgery (-0.119) was statistically significant.

Table 6.1 Original analysis cross comparison results by SSI status

Variable	SSI (n=184)	No SSI (n=551)	Difference (SSI – no SSI)
	Mean (SE)	Mean (SE)	Mean (95% Confidence Interval)
Costs			
Inpatient Care	£5,506.01 (£371.06)	£4,766.21 (£185.71)	£739.79 (-£75.77 to £1,555.35)
Outpatient Care	£564.01 (38.56)	£234.35 (£22.36)	£329.65 (£241.97 to £417.34)
Total Costs	£6,077.49 (£381.86)	£5,008.19 (£182.09)	£1,069.29 (£237.71 to £1,900.87)
EQ-5D-3L Utilities			
Score at baseline	0.718 (0.023)	0.762 (0.013)	-0.044 (-0.096 to 0.008)
Score at 7 days	0.464 (0.028)	0.514 (0.015)	-0.049 (-0.011 to 0.110)
Score at 30 days	0.594 (0.023)	0.714 (0.013)	-0.119 (-0.067 to -0.172)
Adapted from Table 5.21 in Gheorghe doctoral dissertation [293]			

Section B ROSSINI re-analysis

6.5 Re-analysis methods

The methods of the re-analysis used to develop the new estimates are detailed below with any assumptions or techniques that differ from the original analysis highlighted. Data cleaning for the re-analysis is shown in Appendix A6.2.

6.5.1 Re-analysis resource use and costing methods

As per the original analysis, hospital length of stay was calculated as the difference between the surgery date and the discharge date. Similarly, hospital readmission length of stay was calculated as the difference between the readmission date and the readmission discharge date.

As per the original analysis, a bottom-up costing approach was taken. For the re-analysis reported here, more recent unit costs were used to value the ROSSINI resource use unless stated otherwise. The unit costs used for the re-analysis are listed in Table 6.2. All the unit costs for the re-analysis were inflated to cost year 2021/2022 using the NHS cost inflation index where applicable [283]. For the re-analysis, the cost of a bed day in a hospital ward was weighted by the average excess bed day across general, abdominal, and colorectal procedures from NHS 2017/2018 reference costs [310] using equivalent currency codes of the original analysis. The NHS 2017/2018 reference costs was the last available year that disaggregated costs per hospital ward day were provided and has now been superseded by patient episode costs which does not break down the cost components between procedure and length of stay.

The original analysis used ITU and HDU bed day costs from the last available NHS reference costs (2007/2008) which had provided these costs. As these historical costs arguably may not be reflective of current costs even after accounting for NHS inflation, different data sources were sought in more recent NHS reference cost publications. In the re-analysis, an ITU bed day cost was assumed to be the weighted average of the cost per day of critical care surgical

adult patients [311]. A HDU bed day cost was assumed to be the weighted average of the cost per day of critical care patients in nonstandard locations using a ward area and using the operating department [311]. An outpatient clinic visit was assumed to be the weighted average cost of a follow-up consultant led non-admitted face-to-face attendance in the NHS reference costs [311].

The unit costs of primary care visits were taken from PSSRU costs for the re-analysis. The cost of GP visit was assumed to be a clinic consultation and included direct care staff costs and a contribution to GP training qualification costs [283]. The cost of a practice nurse visit was assumed to be equivalent to 20 minutes of Band 7 Nurse's time and included a contribution to training qualification costs [283].

The original analysis assumed that the district nurse visit took 1 hour and the cost of the visit was taken from the PSSRU Unit costs 2011 [312]. As the cost of district nurse visits are no longer published in PSSRU, for the re-analysis a district nurse home visit was assumed to be 1 hour of a Band 6 Nurse [283] with an associated travel costs taken from a derived District nurse home visit cost ratio (1: 1.46) from PSSRU Unit costs 2011 [312]. The original analysis medication costs valued from the BNF 2011 [313] were inflated to the 2021/2022 cost for the re-analysis. In both analyses, the time horizon for the analysis was thirty days after surgery and no discounting of costs or utilities were performed.

Table 6.2 Unit costs for re-analysis

Item	Cost	Source
Hospital day on ward	£412	National Schedule of NHS Costs Year 2017/18; (Currency codes: FD02A-D, FD03A-E, FE02A-C, FF02A-C, FF04A-C, FF21A-D, FF22A-D, FF31A-D, FF32A-C, FF33A-B, FF34A-C, FF37B-D, FF40A-B, FF41A-C, FF51A-E, FF52A-C, FF61A-C, FF63A) [310]
Hospital day on Intensive Therapy Unit	£2,025	National Schedule of NHS Costs Year 2021/22; Weighted average of surgical adult patients (Service code CCU02) [311]
Hospital day in High Dependency Unit	£1,230	National Schedule of NHS Costs - Year 2021/22; Weighted average of nonstandard locations using a ward area and using the operating department (Service codes CCU90-CCU91) [311]
Cost per GP visit (Including direct care staff)	£41	Unit Costs of Health and Social Care 2022 [283]
Practice nurse visit	£17	Unit Costs of Health and Social Care 2022 (Band 7 nurse) [283]; Average length 20 minutes
District nurse visit	£92	Unit Costs of Health and Social Care 2022 band 6 Nurse [283] with calculated District nurse home visit multiplier from Unit costs 2011 [312]
Outpatient clinic visit	£157	National Schedule of NHS Costs - Year 2021/22; Weighted mean of Consultant Led Non-Admitted Face-to-Face Attendance, Follow-up [Service codes 100;104;105; 106] [311]
Medication (antibiotics, painkillers)	as appropriate	Gheorge et al. [48] and British National Formulary 2011 [313]

6.5.2 Re-analysis quality of life

As per the original analysis, cross-sectional utilities by SSI status were presented across the three timepoints (baseline, 5-7 days post-surgery, and 30 days post-surgery). For the re-analysis, QALYs and Quality Adjusted Life Months (QALMs) were calculated using the area under the curve method across the three EQ-5D-3L time points. A QALM gives the quality adjusted life score across the thirty days while the QALY scales the 30-day quality of life score to an annual equivalent by dividing the QALM by 12. The EQ-5D-3L data was converted to utility data using UK population norms [314] and the 30 to 33 days post-operative EQ-5D-3L measurements were assumed to occur at 30 days to fit a 1 month time horizon. For the QALY re-analysis calculations, the 5-7 postoperative EQ-5D-3L timepoint was assumed to occur on the 5th postoperative day.

6.5.3 Re-analysis imputation

As per the original analysis, multiple imputation was undertaken to account for missing cost data and quality of life data. This was done using the MICE technique [315]. Both analyses undertook item level imputation for missing values relating to the baseline demographics, surgical procedure, and cost items. The items were imputed using predictive mean matching [315] to the nearest observation. The original analysis used age and SSI status variables to predict the missing values. The re-analysis used the complete patient data of age, sex, and SSI status to predict the values.

Partial completion of EQ-5D-3L was considered fully missing and index score level imputation was undertaken. The original analysis imputed utility scores using MICE and predictive mean matching the nearest observation with age, and SSI status variables used to predict the EQ-5D-3L scores at baseline. For the 30 to 33 days postoperative EQ-5D-3L timepoint, the utility value was imputed using MICE and predictive mean matching the

nearest observation with age, SSI status, and the 5 to 7 days postoperative EQ-5D-3L scores. For the re-analysis, the utility scores were imputed using age, sex, and SSI status to predict the values at each EQ-5D-3L timepoint (baseline, 5 to 7 days postoperative, and 30 to 33 days postoperative). In both analyses, twenty imputation datasets were generated for each missing item with the mean values and their standard errors were pooled across the imputed datasets using Rubin's Rule [316].

6.5.4 Re-analysis approaches

For the re-analysis, three methods were used to assess the cost and quality of life implications of SSI: (1) Simple Cross-Comparison analysis, (2) Generalised Linear Model approach, and (3) Case Control design. The Cross-Comparison and Case Control approaches used the bootstrapping technique to deal with data skewness [317].

1. **Re-analysis Cross-Comparison analysis**

A Cross-Comparison approach was used to assess the mean additional cost and quality of life decrement associated with SSI. Total healthcare costs were compared in patients by SSI status. Likewise, for the utility difference of SSI, the Cross-Comparison analysis looked at the differences in utilities between the group of patients with SSI and the group of patients without SSI. The difference in quality of life by SSI status was adjusted for baseline utilities [213]. The Cross-Comparison approach used the bootstrapping technique to deal with data skewness [317].

Multiple imputation was performed first on the dataset and then bootstrapping was undertaken 1,000 times for each of the 20 imputed datasets. Then the 20,000 bootstrapped replications were pooled together where the mean difference and the 95% percentile Confidence Interval were calculated (pooled multiple imputation bootstrapping method [318]).

2. Re-analysis Generalised Linear Model

A Generalised Linear Model approach was used the model the costs and quality of life estimates for SSI. This approach was taken because of the flexibility in selecting different distribution types and link functions to best match the cost or QALY data distribution [319] being modelled with the added advantage of the interpretability of coefficients [320]. Models were fitted using maximum likelihood estimation. The covariates to predict total healthcare costs were age, sex, planned stoma, diabetic status, BMI, surgery group (Clean-Contaminated, Contaminated-Dirty), current smoking status, elective or emergency surgery, and SSI. The covariates of age [321], elective or emergency surgery [321], sex [322], smoking status [323], diabetic status [324], planned stoma [325], surgical contamination [326] and increased BMI [327] have all been previously shown to be associated with higher postoperative healthcare costs.

To predict utilities, the same covariates were used for consistency with baseline utility also included to adjust any quality of life imbalances at the start of the trial. The covariates age and sex [328,329], smoking status [330], stoma [331], diabetic status [332], elective or non-elective surgery [333], and BMI [334] have all been previously shown to affect EQ-5D scores.

The best fitting link function and family distribution were used for the base case with the second best family distribution with their best fitting link function used for the sensitivity analysis. Selection of the family distribution was made using the modified Park test [122,335]. The coefficient from modified Parks test indicates the distribution (Gamma, Gaussian, Poisson, Inverse Gaussian) that best reflects the mean and variance relationship. Where the modified Parks test resulted in a negative coefficient greater than -0.5 for the QALY data, making the potential distribution choices unsuitable, the QALY data was

transformed into QALY decrements and retested [122,335]. To convert the QALY data into decrements, the scores were subtracted from the best possible observed health score over the month.

Once the preferred family distribution was selected, link power functions from the range of -2 to 2 were tested in 0.1 increments using the Pearson's correlation test, the Pregibon link test and the modified Hosmer and Lemeshow test [122,336]. These tests assessed the goodness of fit of a given link function based on the predicted response values versus the observed dependant variable values. For a given link function, statistical significance on the Pearson's correlation test indicates a lack of fit from the correlation between the fitted response values and the residuals[337]. For a given link function, statistical significance on the Pregibon link test signifies a lack of fit from a non-linearity of the response [122]. For a given link function, statistical significance on the modified Hosmer and Lemeshow test signals a lack of fit due to systematic bias in the fit on a raw scale [122].

For all link functions that had non-significant p-values (greater than 0.05) from the goodness of fit tests, the best fitting link function was chosen on the basis of the lowest Akaike information criterion (AIC) score. AIC is a measure of a model's prediction error and a lower score is preferred [338]. Huber-White sandwich estimators were used to generate robust standard errors to account for variance heterogeneity [339].

For the multiple imputation, twenty separate models were run, and the results are pooled using the "mi estimate" Stata command. The predicted marginal effect of SSI along with the 95% Confidence Intervals across the imputation datasets were estimated using Rubin's Rule [316]. The results were presented by SSI status and the predicted marginal effect of SSI was adjusted for the other covariates.

3. Re-analysis Case Control approach

A Case Control design approach was used to assess the average additional cost and quality of life decrement associated with SSI. A Case Control study design compares the outcome of interest (i.e., cost or quality of life score difference) of patients by SSI status with similar characteristics [340]. Matching cases and controls can be balanced (i.e., 1 patient with SSI [case] compared to 1 patient without SSI [control]) or imbalanced (1 patient with SSI [case] compared to 2 or more patients without SSI [control]). Matching characteristics were selected by factors that could confound the cost and quality of life differences by SSI status. A Case Control on a 1:2 matching basis was undertaken without replacement using the "calipmatch" Stata module [341] where 1 patient with SSI matched to 2 patients without SSI. The Stata module works on a greedy algorithm basis by incrementally selecting the best control matches for a given case without consideration that the selected controls could be better matches for a different case [342].

There were several studies identified in Chapter 3's systematic review that utilised the Case Control design approach for estimating the additional cost associated with SSI. Tables 3.2 and Table 3.5 provided detail on the included studies' adjustments to the SSI and no SSI group comparisons in Europe and LMICs, respectively. The cost studies employed different sets of matching variables relating to the patient (e.g., age, sex, comorbidities, infection risk) and surgery (e.g., National Nosocomial Infections Surveillance risk index, operation type, and operation date). The most popular number of selected controls per case in the systematic review was 1:1 balanced matching [167,171,172,177,180,183,188] and 1:2 matching [162,165,175,181].

For the Case Control cost analysis undertaken in the re-analysis, patients with SSI were matched to two patients without SSI based on the following characteristics: Age (within 5

years), Sex, Elective or Non-Elective, Surgery Group (Clean-Contaminated, Contaminated-Dirty), Planned Stoma, Diabetic, and Current Smoker. The cost difference was calculated by the paired differences within the costs of the matched case and control groups.

For the Case Control quality of life analysis, patients with SSI were matched to two patients without SSI with the above covariates plus the same starting quality of life score. The starting quality of life score was used in the selection of controls to circumvent the issue of paired QALY and QALM differences having non-similar baseline utility scores. The QALY and QALM differences was calculated by the paired differences within the matched case and control groups. There were one study in Chapter 4 which assessed the utility decrement associated with SSI via a Case Control study design [227]. No rationale was provided for their covariate inclusion of gender, age , surgery date, and operating surgeon [227]. To increase the number of paired differences matches, a 1:1 matching explored in a sensitivity analysis.

Like the Cross-Comparison approach, a pooled multiple imputation bootstrapping method [318] was also used and the bootstrapped mean differences were shown with 95% percentile Confidence Intervals.

6.5.5 Re-analysis sensitivity analysis

To assess the impact on the additional economic burden of SSI, the following sensitivity analyses was undertaken:

1. Complete Case analysis was undertaken where the cost and quality of life estimation approaches were rerun with observations with imputed cost or quality of life information excluded from the analysis. Patients with complete cost information and incomplete quality of life information were included in the complete case cost analysis

and patients with incomplete cost information and complete quality of life information were included in the complete case quality of life analysis.

2. Generalised Linear Model approach: The second best family was used for the costs and quality of life estimates, respectively. The best link function for the second best family was selected for the sensitivity analysis.
3. Case Control: A 1:1 matching selection was undertaken for the cost and quality of life estimates.

6.6 Re-analysis results

6.6.1 Patient characteristics

There were 732 patients from the ROSSINI trial available for the re-analysis. Complete quality of life and cost information was available for 571 and 670 patients, respectively (see Tables 6.3-4 for demographic details prior to imputation). For the quality of life utility values, there were more missing values at the postoperative time points compared to baseline measurement. For the costs, there was more missing values for the primary care costs compared to the secondary care costs. There was generally good completion of demographics, and the highest level of missing values was observed for BMI where 6% of values missing. Information on the number of imputations for missing observations provided in Table 6.5.

The demographic details by SSI status with imputation is shown in Table 6.6. All patients were used in the Cross-Comparison and Generalised Linear Model approaches. For the 184 patients with SSI and 548 patients without SSI, there were differences in baseline and operative characteristics. Patients with SSI were typically younger, less likely to be female, more likely to have a planned stoma, had a higher mean BMI, and a longer duration of surgery compared with patients without an SSI.

Table 6.3 Demographic details for SSI cost analysis prior to imputation

Variable	Estimation approach					
	Cross-Comparison Approach		Generalised Linear Model Approach		Case Control Approach 1:2	
	SSI (n= 164)	No SSI (n=506)	SSI (n=153)	No SSI (n=453)	SSI (n= 95)	No SSI (n=190)
Mean Age in years (SE)	58.6 (1.1)	63.7 (0.6)	59 (1.1)	63.7 (0.7)	62.9 (1.2)	62.9 (0.8)
Females	41.46%	48.62%	40.40%	48.40%	36.84%	36.84%
Current Smokers	19.02%	15.31%	20.53%	15.35%	10.53%	10.53%
Mean Body Mass Index (SE)	28 (0.5)	26.6 (0.3)	27.9 (0.6)	26.5 (0.2)	27.62 (0.48)	26.56 (0.37)
Diabetics	16.46%	14.29%	17.22%	14.71%	11.58%	11.58%
Planned Stoma	24.39%	16.8%	23.84%	16.63%	9.47%	9.47%
Clean-Contaminated Surgeries	76.69%	80.43%	75.50%	80.60%	91.58%	91.58%
Mean Surgery duration in minutes (SE)	201 (8.9)	177.7 (4)	197.6 (8.7)	176.1 (4.1)	208.8 (13.33)	178.89 (6.58)
Elective Surgeries	53.66%	48.22%	52.98%	49.47%	50.53%	50.53%

Table 6.4 Demographic details for SSI quality of life analysis prior to imputation

Variable	Complete Case Estimation approach					
	Bootstrapped mean difference		Generalised Linear Model		Case Control approach 1:2	
	SSI (n=139)	No SSI (n=432)	SSI (n=127)	No SSI (n=402)	SSI (n= 36)	No SSI (n=72)
Mean Age in years (SE)	59.4 (1.2)	64.4 (0.7)	59.4 (1.3)	64.5 (0.7)	63.69 (1.59)	63.96 (1.14)
Females	47.92%	46.04%	44.88%	48.01%	33.33%	33.33%
Current Smokers	18.84%	15.19%	19.69%	15.42%	11.11%	11.11%
Mean Body Mass Index (SE)	28.2 (0.6)	26.6 (0.3)	28.2 (0.6)	26.5 (0.3)	26.77 (0.68)	25.99 (0.63)
Diabetics	17.27%	15.12%	17.32%	15.42%	2.78%	2.78%
Planned Stoma	21.58%	16.67%	20.47%	16.67%	5.56%	5.56%
Clean-Contaminated Surgeries	81.16%	80.79%	80.31%	80.85%	100%	100%
Mean Surgery duration in minutes (SE)	203.4 (9.9)	181.3 (4.5)	198 (9.5)	179.7 (4.6)	208.69 (12.3)	210.68 (13.16)
Elective Surgeries	51.80%	48.15%	51.97%	49.25%	50.00%	50.00%

Table 6.5 Observations imputed per variable across 20 datasets

Variable	Complete	Imputed	Total
Surgery Group (Clean-Contaminated or Contaminated-Dirty)	731	1	732
Surgery Duration	719	13	732
Diabetic Status	730	2	732
Smoking Status	727	5	732
Body Mass Index	688	44	732
Hospital ward Length of Stay Costs	704	28	732
Cost of Intensive Therapy Unit stay	728	4	732
Cost of High Dependency Unit stay	728	4	732
General Practitioner Visit Costs	694	38	732
Practice Nurse Visit Costs	694	38	732
District Nurse Visit Costs	694	38	732
Outpatient Clinic Visit costs	694	38	732
Antibiotics Medication costs	694	38	732
Painkiller Medication costs	694	38	732
Baseline EQ-5D-3L score	694	38	732
Postoperative 5-7 day EQ-5D-3L score	650	82	732
Postoperative 30 day EQ-5D-3L score	655	77	732

Table 6.6 Demographic details with imputation

Variable	Estimation approach	
	Cross comparison and Generalised Linear Model Approaches	
	SSI (n=184)	**No SSI (n=548)**
Mean Age in years (Pooled SE)	59.4(1)	64.1(0.6)
Proportion of Females	44.02%	48.18%
Proportion of Current Smokers	18.51%	15.29%
Mean Body Mass Index (Pooled SE)	28.2 (0.53)	26.5 (0.24)
Proportion of Diabetics	10.19%	10.21%
Planned Stoma proportion	23.91%	16.97%
Proportion of Clean-Contaminated Surgeries	89.55%	88.89%
Mean Surgery duration in minutes (Pooled SE)	201.4 (8.18)	178.0 (3.99)
Proportion of Elective Surgeries	50%	48.18%

With the 1:2 case matching approach, there were varying number of patients with SSI matched to two controls (see Appendix Tables A5.2-3 for the Case Control demographic details across the 20 imputation datasets for the cost and quality of life analysis, respectively). Across the 20 imputations for the cost analysis, the Case Control without replacement found 108-113 SSI case matches to two controls per case. As expected, the exact matching characteristics for the Case Control approach gave identical proportions for patients with and

without SSI. With the flexible matching characteristic of age being within 5 years, patients without an SSI were broadly older than patients with an SSI. For the non-matched characteristics, patients with SSI had a higher mean BMI, and a longer duration of surgery compared with patients without an SSI.

Across the 20 imputations for the quality of life analysis, the Case Control without replacement found less matches than the cost Case Control analysis with 45-49 SSI case matches to two controls per case. The quality of life Case Control approach had the added prerequisite of matched cases and controls having the same starting quality of life scores which reduced the number of potential matches. None of the ~10% of the entire sample of patients with a Contaminated-Dirty surgery type were matched for the quality of life Case Control approach with all selected patients having underwent a Clean-Contaminated surgery. There was a noticeably lower proportion of matched diabetic patients (~4%) for the quality of life Case Control relative to the cost analysis Case Control (~11%). Cases and controls were more similar in age for the quality of life Case Control approach relative to the cost Case Control approach, with the mean age being within a year for the majority of the twenty imputation datasets.

6.6.2 Resource use information

The complete case primary care and secondary care resource use information is shown in Table 6.7 with the number of missing observations per item. Resource use was consistently higher in patients with SSI compared to patients without SSI.

Table 6.7 Resource use by SSI status

Variable	Non- SSI			SSI		
	Mean (SE)	**n**	**Missing (%)**	**Mean (SE)**	**n**	**Missing (%)**
General Practitioner Visits	0.39 (0.03)	518	30 (5.5%)	0.78 (0.09)	176	8 (4.3%)
Practice Nurse Visits	0.21 (0.04)	518	30 (5.5%)	0.35 (0.09)	176	8 (4.3%)
District Nurse Visits	2.56 (0.27)	518	30 (5.5%)	6.68 (0.65)	176	8 (4.3%)
Outpatient clinic visits	0.34 (0.03)	518	30 (5.5%)	0.55 (0.1)	176	8 (4.3%)
Hospital days on ward	9.3 (6.78)	532	16 (2.9%)	11.74 (7.86)	172	12 (6.5%)
Hospital days in Intensive Therapy Unit	0.82 (2.64)	548	0 (0%)	1 (3.4)	184	0 (0%)
Hospital days in High Dependency Unit	0.57 (1.57)	548	0 (0%)	0.59 (1.69)	184	0 (0%)

6.6.3 Costs

Cross-Comparison approach

The per-patient costs associated with SSI with the Cross-Comparison approach is shown in Table 6.8. The mean difference in total costs was £1,785 (£620 to £3,114) higher for patients with SSI versus patients without SSI. Most (78%) of the additional costs associated with SSI were borne at the secondary care level. The bootstrapped mean difference in costs was higher across all cost items although the 95% Confidence Interval mean difference crossed zero for practice nurse visits, ITU hospital days in, HDU hospital days, and painkiller medication cost items. The standard error associated with total health care cost was more than for patients with SSI compared to those without SSI.

Table 6.8 Cross-Comparison of healthcare costs by SSI status

	No SSI	SSI	Bootstrapped Mean difference (95% Confidence Interval)
Cost Variable	Mean (Pooled SE)	Mean cost (Pooled SE)	
General Practitioner visits	£16.21 (£1.34)	£31.80 (£3.67)	£15.57 (£8.34 to £23.45)
Practice Nurse Visits	£3.62 (£0.66)	£5.79 (£1.44)	£2.15 (-£0.83 to £5.37)
District Nurse Visits	£236.91 (£25.00)	£613.55 (£60.17)	£376.27 (£249.02 to £505.24)
Outpatient clinic visits	£52.59 (£4.90)	£85.84 (£17.04)	£33.03 (£3.08 to £72.27)
Hospital day on ward	£3849.46 (£122.26)	£4803.16 (£241.24)	£956.67 (£433.63 to £1486.1)
Hospital day in Intensive Therapy Unit	£1671.73 (£233.42)	£2041.51 (£510.59)	£377.39 (-£629.06 to £1572.95)
Hospital day in High Dependency Unit	£715 (£82.36)	£734 (£153.50)	£23.29 (-£303.99 to £377.52)
Antibiotics	£0.13 (£0.04)	£2.08 (£0.90)	£1.95 (£0.74 to £4.18)
Painkiller medication	£0.51 (£0.10)	£0.82 (£0.16)	£0.31 (-£0.04 to £0.71)
Total Health Care Cost	£6,547 (£261)	£8,319 (£576)	£1,785 (£620 to £3,114)

Generalised Linear Model

Based on the goodness of fit tests (see Appendix Tables A6.4-5), the Poisson distribution and link power function of -0.5 were selected for the Generalised Linear Model for total healthcare costs. The selection of the Poisson distribution indicates that the variance is proportional to the mean[335]. The link function had the lowest AIC score and had non-statistically significant p-values from the Pearson's correlation test, the Pregibon link test and the modified Hosmer and Lemeshow test. Table 6.9 displays the Generalised Linear Model predictions for patients with and without SSI, respectively. Adjusted for the covariates, the marginal effect of SSI was predicted to increase costs by £2,107 (95% Confidence Interval: £712 to £3,502).

Table 6.9 Generalised Linear Model SSI cost predictions

	SSI	No SSI	
Variable	Mean (Pooled SE)	Mean (Pooled SE)	Marginal effect (95% Confidence Interval)
Total Health Care Cost	£8,592 (£646)	£6,485 (£256)	£2,107 (£712 to £3,502)

The results of the Generalised Linear Model for total health care costs are reported in Table 6.10 including model coefficients, pooled standard errors, and associated p-values. SSI, planned stoma, age, and elective status of surgery were all statistically significant predictors of total costs at the 5% level. The presence of an SSI (versus no SSI), and a planned stoma (versus no planned stoma) were associated with higher total health care costs. Undergoing elective surgery compared to an emergency surgery was associated with lower total health care costs.

Table 6.10 Generalised Linear Model for total costs

Variables	**Coefficient**	**Pooled Standard Error**	**P-value**
Age	-0.0000605	0.0000147	0
Female Sex	0.0006683	0.0004073	0.101
Male Sex (reference category)	-	-	-
Planned Stoma	-0.0011813	0.0005504	0.032
No Planned Stoma (reference category)	-	-	-
Current Smoker	0.0000623	0.0006156	0.919
Not current smoker (reference category)	-	-	-
Diabetic	-0.0002782	0.000466	0.551
Not Diabetic (reference category)	-	-	-
Elective Surgery	0.0016429	0.0004396	0
Emergency Surgery (reference category)	-	-	-
Body Mass Index	0.0000115	0.0000367	0.754
Surgical Site Infection	-0.0015983	0.0004769	0.001
No Surgical Site Infection (reference category)	-	-	-
Contaminated-Dirty Surgery	-0.0004116	0.0005397	0.446
Clean-Contaminated Surgery (reference category)	-	-	-
Intercept	0.0153541	0.001775	0

Case Control Approach

The results of the Case Control approach are shown in Table 6.11. Patients with SSI matched to two patients without SSI had higher per patient average costs, with a bootstrapped mean difference of £1,555. The 95% Confidence Interval ranged from £0.08 to £3,100.

Table 6.11 Case Control Approach Costs by SSI status

	SSI	No SSI	
Variable	Mean (Pooled SE)	Mean (Pooled SE)	Bootstrapped mean difference (95% Confidence Interval)
Total Health Care Cost	£8,086 (£749)	£6,520 (£509)	£1,555 (£0.08 to £3099.93)

6.6.4 Quality of life decrement associated with SSI

Cross-Comparison approach

For the quality of life decrement associated with SSI, the EQ-5D-3L scores across time points are shown along with the bootstrapped mean difference in QALYs by SSI status in Table 6.12. Patients with SSI had lower EQ-5D-3L values and higher standard errors across the time points compared to patients without SSI. Adjusting for the lower baseline quality of life measurement, patients with SSI still retained a lower overall quality of life compared to patients without SSI, with a mean QALY difference of -0.0062 (95% Confidence Interval: -0.012 to -0.0043). In terms of quality of life difference across the month, the QALM difference associated with patients with SSI versus patients without SSI was -0.0749 (95% Confidence Interval: -0.1434 to -0.0516). These differences were statistically significant at the 5% level.

Table 6.12 EQ-5D-3L scores across time points for patients by SSI status

Variables	No SSI (n=548) Mean (Pooled SE)	SSI (n=184) Mean (Pooled SE)	Bootstrapped mean difference (95% Confidence Interval)
EQ-5D-3L baseline	0.7636 (0.0122)	0.6966 (0.0266)	-0.0675 (-0.1256 to -0.0118)
EQ-5D-3L 5 days	0.5174 (0.0151)	0.4421 (0.0266)	-0.0752 (-0.1335 to -0.0167)
EQ-5D-3L 30 days	0.7199 (0.0124)	0.5904 (0.0251)	-0.1295 (-0.1845 to -0.0755)
Quality Adjusted Life Year	0.0519 (0.0009)	0.0438 (0.0018)	-0.0062 (-0.0120 to -0.0043)
Quality Adjusted Life Month	0.6223 (0.0109)	0.5251 (0.0213)	-0.0749 (-0.1434 to -0.0516)

Generalised Linear Model

Based on the modified Park test results, the QALY data was transformed into QALY decrements and upon retesting, the Poisson distribution was judged to be the best fitting family distribution (see Appendix Table A6.4). The selection of the Poisson distribution indicates that the variance is proportional to the mean [335]. The link function of 1.4 was chosen for the QALY decrement model. This link function had the lowest AIC score and had non-statistically significant p-values from the Pearson's correlation test, the Pregibon link test and the modified Hosmer and Lemeshow test (see Appendix Table A6.5). Table 6.13 displays

the QALY decrement Generalised Linear Model predictions with a Poisson distribution and a 1.4 power link function for patients with and without SSI, respectively. The model predicted that the marginal effect of an SSI QALY decrement was 0.0047 (95% Confidence Interval: 0.0012 to 0.0082), holding other covariates fixed. The marginal effect of an SSI QALM decrement was 0.0560 (95% Confidence Interval: 0.014 to 0.0981). The quality of life decrements were statistically significant at the 5% level.

Table 6.13 Generalised Linear Model SSI decrement predictions

	No SSI	SSI	Mean Decrement
Variable	Mean (Pooled SE)	Mean (Pooled SE)	(95% Confidence Interval)
Quality Adjusted Life Year	0.0513 (0.0009)	0.0466 (0.0016)	0.0047 (0.0012 to 0.0082)
Quality Adjusted Life Month	0.6156 (0.0104)	0.5595 (0.019)	0.056 (0.014 to 0.0981)

The results of the Generalised Linear Model for QALY decrements are reported in Table 6.14 including model coefficients, pooled standard errors, and associated p-values. SSI, BMI, Contaminated-Dirty surgery, and baseline quality of life variables were all statistically significant predictors of QALY decrements at the 5% level. Having an SSI, undergoing a Contaminated-Dirty surgery, being diabetic and increased BMI were all associated with a higher QALY decrement.

Table 6.14 Generalised Linear Model for QALYs Decrements

Variables	**Coefficient**	**Pooled Standard Error**	**P-value**
Age	0.00000465	0.0000197	0.813
Female Sex	0.0007737	0.0005328	0.147
Male Sex (reference category)	-	-	-
Planned Stoma	0.0010391	0.0006564	0.113
No Planned Stoma (reference category)	-	-	-
Current Smoker	0.0004897	0.0007262	0.5
Not current smoker (reference category)	-	-	-
Diabetic	0.001218	0.0007475	0.103
Not Diabetic (reference category)	-	-	-
Elective Surgery	-0.0002212	0.0005465	0.686
Emergency Surgery (reference category)	-	-	-
Body Mass Index	-0.0000803	0.0000398	0.044
Surgical Site Infection	0.0020404	0.0006444	0.002
No Surgical Site Infection (reference category)	-	-	-
Contaminated-Dirty Surgery	0.0015186	0.0007095	0.032
Clean-Contaminated Surgery (reference category)	-	-	-
Baseline EQ-5D-3L score	-0.0101346	0.0012624	0
Intercept	0.0167013	0.0022045	0

Case Control Approach

For the Case Control approach, the QALY and QALM results by SSI status are shown in Table 6.15. The bootstrapped mean difference in QALYs between matched patients with SSI and control patients without SSI was -0.0035 (95% Confidence Interval: -0.0095 to 0.0025). In terms of quality of life decrement across the month, the QALM decrement associated with SSI was -0.0421 (95% Confidence Interval: -0.1138 to 0.0306). The quality of life difference by SSI status was not statistically significant at the 5% level.

Table 6.15 Case Control Approach QALY by SSI status

	No SSI	SSI	Bootstrapped mean
	Mean	Mean	difference
Variable	(Pooled SE)	(Pooled SE)	(95% Confidence Interval)
Quality Adjusted Life Year	0.0586	0.0551	-0.0035
	(0.0023)	(0.0028)	(-0.0095 to 0.0025)
Quality Adjusted Life Month	0.703	0.6607	-0.0421
	(0.0278)	(0.0335)	(-0.1138 to 0.0306)

6.6.5 Sensitivity analysis

Costs complete case sensitivity analysis

Results for the complete case Cross-Comparison mean difference costs in total health care costs by SSI status is shown in Appendix Table A6.6. For demographic details on the complete cost analyses, see Table 6.3. For all cost items, patients with an SSI had a higher bootstrapped mean difference in costs with the 95% Confidence Interval crossing zero for Practice Nurse Visits, Hospital days in ITU, Hospital days in HDU and painkiller medications. Other cost items were statistically significant at the 5% level. For total

healthcare costs, SSI was associated with an additional average cost of £1,208 with a 95% Confidence Interval ranging from £299 to £2093.

The complete case Generalised Linear Model predictions of total healthcare costs for patients with and without SSI, respectively are displayed in Appendix Table A6.7. The Generalised Linear Model with a Poisson distribution and a link power function of -0.5 predicted that the marginal effect of SSI increased costs by £1,360 (95% Confidence Interval: £429 to £2291).

The results of the complete case Generalised Linear Model for total healthcare costs are reported in Appendix Table A6.8 including model coefficients, pooled standard errors, and associated p-values. An SSI, planned stoma, age, and elective status of surgery were all statistically significant predictors of total costs at the 5% level. An SSI, a planned stoma (versus no stoma) and a higher age were associated with higher total costs while undergoing elective surgery compared to an emergency surgery was associated with lower total health care costs.

The results of the Case Control approach with complete case cost data are shown in Appendix Table A6.9. 95 patients with SSI were matched to 190 patients without SSI. Patients with SSI matched to two patients without SSI had higher per patient average costs with a bootstrapped mean difference of £1,009. The 95% Confidence Interval ranged from £162 to £1,831.

Quality of life complete case sensitivity analysis

For the quality of life decrement associated with SSI, the complete case EQ-5D-3L scores across time points are shown along with the bootstrapped mean difference in QALYs by SSI status in Appendix Table A6.10. Patients with SSI had lower EQ-5D-3L values across the time points compared to patients without SSI. Adjusting for the lower baseline quality of life measurement, patients with SSI still had a lower overall quality of life compared to patients

without SSI, with a QALY decrement of -0.0052 (95% Confidence Interval -0.0089 to -0.0013). The mean thirty day quality of life difference for patients with an SSI versus patients without an SSI was -0.062 (95% Confidence Interval: -0.108 to -0.018). The quality of life differences by SSI status were statistically significant at the 5% level.

Appendix Table A6.11 displays the Complete Case QALY decrement Generalised Linear Model predictions with a Poisson distribution and a link power function of 1.4 by SSI status. The model predicted that the marginal effect of a patient with SSI compared to a patient without SSI increased the QALY decrement by 0.0045 (95% Confidence Interval: 0.0007 to 0.0083), adjusting for the other covariates. The model predicted that the average QALM decrement of a patient with SSI compared to a patient without SSI was 0.0539 (95% Confidence Interval: 0.0079 to 0.0999), adjusting for the other covariates. The decrements were statistically significant at the 5% level.

The results of the Generalised Linear Model for QALY decrements are reported in Appendix Table A6.12 including model coefficients, standard errors, and associated p-values. SSI, BMI, and baseline quality of life variables were all statistically significant predictors of QALY decrements at the 5% level. Having an SSI was associated with a higher QALY decrement whilst an increase in BMI was associated with a lower QALY decrement.

For the quality of life Case Control approach, 35 Patients with SSI were matched to 70 patients without SSI (1:2) on the complete case data. The mean QALY difference is shown in Appendix Table 6.11. The mean difference in QALYs by SSI status was -0.006 (95% Confidence Interval: -0.0115 to -0.0002). The mean difference in QALMs by SSI status was -0.0724 (95% Confidence Interval: -0.1376 to -0.0028). The quality of life differences were statistically significant at the 5% level.

Generalised Linear Model different distribution specification sensitivity analysis

The second best fitting Generalised Linear Model in terms of distribution for total healthcare costs was a Gamma family distribution (see Appendix Tables A6.4). The selection of the Gamma distribution indicates that the variance is proportional to the square of the mean [335] . The link function of -0.4 was selected as it had the lowest AIC score and had non-statistically significant p-values from the Pearson's correlation test, the Pregibon link test and the modified Hosmer and Lemeshow test (see Appendix Table A6.5). Appendix Table A6.14 displays the Generalised Linear Model predictions of total costs for patients with and without SSI, respectively. Adjusted for the covariates, the marginal effect of SSI was predicted to increase costs by £2,071 (95% Confidence Interval: £861 to £3,280).

The results of the Generalised Linear Model for costs are reported in Appendix Table A6.15 including model coefficients, pooled standard errors, and associated p-values. Age, SSI, planned stoma, age, and elective status of surgery were all statistically significant predictors of total costs at the 5% level. A planned stoma (versus no stoma), an SSI, and an increased age were associated with higher total costs while undergoing elective surgery compared to an elective was associated were lower total costs.

Appendix Table A6.15 displays the Generalised Linear Model predictions in QALY and QALM decrements. The second best fitting Generalised Linear Model in terms of distribution for QALY decrements was a Gaussian distribution (see Appendix Tables A6.4). The selection of the Gaussian distribution indicates that the variance-mean relationship is constant [335]. The link function of -0.7was selected as it had the lowest AIC score and had non-statistically significant p-values from the Pearson's correlation test, the Pregibon link test and the modified Hosmer and Lemeshow test (see Appendix Table A6.5). The model predicted that the average QALY decrement of a patient with SSI compared to a patient without SSI was

0.0048 (95% Confidence Interval: 0.0013 to 0.0083). The model predicted that the average QALM decrement of a patient with SSI compared to a patient without SSI was 0.0578 (95% Confidence Interval: 0.0158 to 0.0997). The marginal effects for SSI were statistically significant at the 5% level.

The results of the Generalised Linear Model for QALY decrements are reported in Appendix Table A6.17 including model coefficients, standard errors, and associated p-values. SSI, diabetic status, undergoing a Contaminated-Dirty surgery, and baseline quality of life variables were all statistically significant predictors of the QALY decrements at the 5% level. An SSI, undergoing a Contaminated-Dirty surgery and being diabetic were all associated with a higher QALY decrement.

Case Control 1:1 approach sensitivity analysis

The results of the Case Control 1:1 approach is shown in Appendix Table A6.18. For the cost analysis, 146 to 148 SSI cases were matched to 292 to 296 non SSI controls across the twenty imputation datasets. Patients with SSI matched to two patients without SSI had higher per patient average costs with a bootstrapped mean difference of £2,121 and was statistically significant at the 5% level. The 95% Confidence Interval ranged from £345 to £3,935. For the quality of life analysis, 60 to 65 SSI cases were matched to 120 to 130 non SSI controls across the twenty imputation datasets. The bootstrapped QALY mean difference amongst the matched patients with and without SSI was -0.0029 and it was statistically insignificant at the 5% level. The 95% Confidence Interval ranged from -0.0127 to 0.0025. The bootstrapped QALM mean difference amongst the matched patients with and without SSI was -0.0349 with a 95% Confidence interval ranging from -0.152 to 0.0295.

6.6.6 Summary of the results comparison across approaches

Costs

The mean difference of healthcare costs by SSI status is summarised in Table 6.16. All the costing approaches found an additional mean difference of healthcare costs for patients with SSI compared to patients without SSI. These additional mean differences were all statistically significant at 5% level. For the base case approaches, the Generalised Linear Model predicted the highest cost difference of patients with SSI while the Case Control 1:2 had the lowest cost difference. The Case Control 1:2 in the base had the highest confidence interval relative to the mean difference, with the 95% lower confidence interval close to zero (£0.08). The approaches with imputation were all higher than the complete case equivalent approaches.

Table 6.16 Summary of mean difference in cost of SSI by costing approach

Costing Approach	**Base Case or Sensitivity Analysis**	**Mean difference (95% Confidence Interval)**
Cross-Comparison	Base Case	£1,785 (£620 to £3,114)
Generalised Linear Model (Poisson, Power link -0.5)	Base Case	£2,107 (£712 to £3,502)
Case Control 1:2	Base Case	£1,555 (£0.08 to £3,099.93)
Complete Case Cross Comparison	Sensitivity Analysis	£1,208 (£299 to £2,093)
Complete Case Generalised Linear Model (Poisson, Power link -0.5)	Sensitivity Analysis	£1,360 (£429 to £2,291)

Case Control 1:2 Complete Case	Sensitivity Analysis	£1,009 (£162 to £1,831)
Generalised Linear Model (Gamma, Power link -0.4)	Sensitivity Analysis	£2,071 (£861 to £3,280)
Case Control 1:1	Sensitivity Analysis	£2,121 (£345 to £3,935)

Quality of life

The mean difference of QALYs by SSI status is summarised in Table 6.17. All the quality of life approaches except for the Case Control approaches found a lower mean QALY difference for patients with SSI, compared to patients without SSI that was statistically significant at 5% level. For the base case approaches, the Cross-Comparison approach had the highest SSI QALY decrement, and the Case Control approach had the lowest SSI QALY decrement. The generalised linear model predicted the highest cost difference of patients with SSI, while the Case Control 1:2 had the lowest. The Case Control 1:2 (Base Case) had the highest confidence interval relative to the mean difference with the 95% lower confidence interval close to zero (£0.08). The Case Control approach used less patients than the other approaches due to the matching criteria requirements. The approaches with imputation were mixed in terms of QALY differences relative to the complete case equivalent approaches.

6.7 Re-analysis estimates comparison with the original analysis estimates

Using the same dataset, the original analysis and current re-analysis found markedly different cost and quality of life estimates. Table 6.18 contains a comparison of the re-analysis and original analysis with the costs displayed in 2020/2021 cost year.

The original analysis was that the additional cost of an SSI gave an estimate of £1,270 (95% Confidence Interval: £282 to £2,262). This contrasted with the present analysis estimate of an additional cost of SSI of £1,785 (95% Confidence Interval: £620 to £3,114). Possible reasons for the difference between the analyses include the data cleaning processes, the use of an inflation index that may not reflect the current cost of healthcare items, different sources for some of the unit costs, random draws from multiple imputation, and the addition of bootstrapping for the mean difference in costs calculation.

Table 6.17 Summary of mean QALY difference in by SSI status by approach

Quality of Life Approach	Base Case or Sensitivity Analysis	QALY mean difference (95% Confidence Interval)
Cross-Comparison	Base Case	-0.0062 (-0.0120 to -0.0043)
Generalised Linear Model (Poisson distribution, Power link 1.4)	Base Case	-0.0047 (-0.0012 to -0.0082)
Case Control 1:2	Base Case	-0.0035 (-0.0095 to 0.0025)
Complete Case Cross Comparison	Sensitivity Analysis	-0.0052 (-0.0089 to -0.0013)
Complete Case Generalised Linear Model (Gaussian distribution, Power link -0.7)	Sensitivity Analysis	-0.0045 (-0.0007 to -0.0083)
Case Control 1:2 Complete Case	Sensitivity Analysis	-0.006 (-0.0115 to -0.0002)
Generalised Linear Model (Gamma distribution, Power link -0.4)	Sensitivity Analysis	-0.0048 (-0.0013 to -0.0083)
Case Control 1:1	Sensitivity Analysis	-0.0029 (-0.0127 to 0.0025)

Table 6.18 Original Analysis and re-analysis comparison

Variable	SSI	No SSI	Difference
	Mean (SE)	Mean (SE)	Mean (95% CI)
Costs (£)			
Original analysis Total Costs*	£7,234 (£445)	£5,962 (£217)	£1,273 (£283 to £2,263)
Re-analysis Total Costs	£8,319 (£576)	£6,547 (£261)	£1,785 (£620 to £3,114)
EQ-5D-3L Utilities			
Original Analysis Score at baseline	0.718 (0.023)	0.762 (0.013)	-0.044 (-0.096 to 0.008)
Original Analysis Score at 7 days	0.464 (0.028)	0.514 (0.015)	-0.049 (-0.011 to 0.110)
Original Analysis Score at 30 days	0.594 (0.023)	0.714 (0.013)	-0.119 (-0.067 to -0.172)
Re-analysis Score at baseline	0.6966 (0.0266)	0.7636 (0.0122)	-0.0675 (-0.1256 to -0.0118)
Re-analysis Score at 7 days	0.4421 (0.0266)	0.5174 (0.0151)	-0.0752 (-0.1335 to -0.0167)
Re-analysis Score at 30 days	0.5904 (0.0251)	0.7199 (0.0124)	-0.1295 (-0.1845 to -0.0755)
*Inflated to 2021/2022 cost year			

The EQ-5D-3L scores also differed by analysis. Again, possible reasons for the difference between the analyses include the data cleaning processes, slightly more patients in the No SSI cases in the original analysis (n=551 versus n=548 in re-analysis) random draws from multiple imputation, and the addition of bootstrapping for the mean utility decrement calculation. Upon further investigation of the original analysis code, an error in the conversion of EQ-5D-3L responses into utilities was found which explains some of the observed differences across the timepoints.

6.8 Re-analysis Discussion

6.8.1 Statement of principal findings

Using information from the ROSSINI trial, this chapter quantified the economic burden associated with SSI using several approaches to develop robust cost and quality and life estimates.

Costs

The cost estimates differed by approach. The total health care cost of patients without SSI was either £6,547 (cross-comparison), £6,485 (generalised linear model), or £6,520 (Case Control). The total health care cost of patients with SSI was estimated to be either £8,319 (cross-comparison), £8,592 (Generalised Linear Model), or £8,086 (Case Control). The average mean differences were all considered statistically significant at the 5% level, although the magnitude of difference varied by approach. The average mean difference by SSI status was estimated to be either £1,784 (cross-comparison), £2,107 (Generalised Linear Model), or £1,555 (Case Control). The relatively wide confidence interval in the Case Control approach is partly down to the lower sample size utilised compared to the other approaches.

The addition of adjusting for covariates in the Generalised Linear Model (approach 2) increased the size of the cost difference relative to the unadjusted cross comparison approach. The statistically significant covariates in the Generalised Linear Model had the coefficient direction of movement as expected. Imputation had a large effect on the estimates relative to complete case. Upon investigation, it appears that relatively more patients with SSI had high secondary healthcare utilisation but were missing the post-discharge case report forms which had excluded them from the complete case analysis.

Quality of life

The quality of life estimates varied by approach. The QALY score of patients without SSI was either 0.0519 (cross-comparison), 0.0513 (generalised linear model), or 0.0586 (Case Control). The QALY score of patients with SSI was estimated to be either 0.0438 (cross-comparison), 0.0466 (generalised linear model), or 0.0551 (Case Control). The average mean QALY decrement were considered statistically significant at the 5% level for the Cross-Comparison and Generalised Linear Model approaches. The average mean QALY decrement was as estimated to be either 0.0062 (cross-comparison), 0.0047 (generalised linear model), or 0.0035 (Case Control). The addition of adjusting for covariates in the Generalised Linear Model decreased the size of the QALY decrement relative to the unadjusted cross comparison approach. Imputation did not have a consistent effect on increasing or decreasing the estimates.

The Case Control approach (approach no 3) is the first known study to examine QALY differences with adjustment for baseline imbalances in quality of life by this design. The Case Control approach matched patients based on their starting quality of life scores to avoid the need for baseline adjustment but at the expense of further restricting the number of possible matches. The alternative to the same baseline quality of life criteria would be to adjust the baseline differences across all the matched groups to give a QALY difference with baseline adjustment. However, this would be contrary to the Case Control approach of examining differences within the matched groups. Both the Case Control approaches for costs and quality of life did not use all the available observations for the analysis compared to the other approaches and thus its results are based on smaller sample sizes.

6.8.2 Strengths and weaknesses

There are several strengths of the analysis. Estimates were taken from a prospective multicentre Randomised Control Trial which had standardized multiple data collection forms, blinding of wound assessors and patients to the treatment allocation, and post-discharge follow up data for a month post-surgery. The ROSSINI trial had a high SSI rate (~25%) which provided data on the ranges of costs and quality of life burden faced by patients with SSI. A further strength of the analysis is the variety of different approaches used, which allowed for comparison of estimates including extensive sensitivity analysis. The selection of family distributions and link functions for the Generalised Linear Model approaches was made on the basis of goodness of fit tests to ensure that the model was not misspecified. All the link functions used in the Generalised Linear Model approach base case and sensitivity analysis passed the Pearson's correlation test, the Pregibon link test and the modified Hosmer and Lemeshow test, indicating there was not a lack of fit issue with the link function.

A limitation of the analysis was that information on wound dressings was not collected, which would likely be higher in patients with an SSI. However, primary care visits including district nurse home visit were collected, which would have captured some of the additional health care utilisation of patients requiring wound dressings. Ethnicity was not collected in the ROSSINI trial, so it is difficult to know whether or not SSI disproportionately affected certain ethnic groups. The trial is more than a decade old at time of writing and the resource use may differ to current practice. Likewise, the results of ROSSINI may generalise only to the type of participating hospitals which were limited to general hospitals and teaching hospitals.

6.8.3 Comparison with other studies

As mentioned previously, cross study comparison of costs and quality of life consequences of SSI is hampered by methodological challenges. For the ROSSINI re-analysis, other studies

were compared to the estimate of the closest matching approach. The additional costs of SSI from the Cross-Comparison approaches were lower than the deep SSI and higher than the superficial SSI for the only RCT designed study [174] included in the High Income Country European group in the cost burden of SSI systematic review (Chapter 3). No weighted average was provided on the overall costs of SSI for their patient population of obese women who underwent caesarean section. Their unreported overall costs of SSI may have been comparable to the ROSSINI re-analysis cost results although other study aspects hinder comparability included different definitions of an SSI methodological divergence and their time horizon being three times longer than ROSSINI. The highest scoring European study on the Cost of illness checklist (Alfonso et al. [27]) within the cost burden systematic review had a higher additional healthcare cost of SSI compared to the ROSSINI re-analysis Case Control approach. Their prospective study was a nested case–control design with an undeclared time horizon from a single centre setting.

The additional cost of an SSI from the European study [161] used in the preliminary model-based economic evaluation was higher than the equivalent estimate from the Case Control approach in the ROSSINI analysis. The comparison warrants caution as the SSIs in the Jenks et al. study [161] was skewed towards more severe SSIs, no primary care costs were included, and the 1 year time horizon in the single centre study was much longer than the 1 month ROSSINI time horizon. The higher standard error associated with the SSI costs agrees with most of the cost studies results reporting dispersion statistics in Chapter 3.

For the utility estimates developed from the ROSSINI re-analysis, the SSI QALY decrement estimates with adjusted baseline results are compared to the two equivalent studies included in the Health State Valuation systematic review. Parker et al. [164] had a higher QALY decrement of 0.102 for deep SSI patients with an open lower limb fracture compared to the

Generalised Linear Model estimate of 0.0047 from the ROSSINI re-analysis. However, the time horizon for the Parker et al. [164] study was over a longer time period of 1 year; assuming that the difference in quality of life scores by SSI status remained constant in ROSSINI from 1 month to 1 year (0.056) would still make the ROSSINI estimate much lower. Possible reasons for the difference could be the manifestation of an orthopaedic SSI and the exclusion of Superficial SSIs in the Parker et al. [164] study.

With the same ROSSINI time horizon, Totty et al. [238] had a higher SSI QALM decrement (0.156) in its pilot study of Clean-Contaminated vascular surgery patients. One possible reason that could be driving the difference is the low number of patients with SSI (n=9) used in their QALM calculation and the omission of the 7 day EQ-5D-3L timepoint. The higher standard error associated with the SSI utility scores is in agreement with the findings of the patient-level utility studies in Chapter 4.

6.8.4 Implications for practice

An SSI is associated with additional costs and a quality of life decrement. The magnitude varies by estimation approach. This is to be expected given the observations used and underlying assumptions of each approach. The adjustment of potential cofounders increased the cost difference and decreased the QALY decrement associated with SSI compared with the unadjusted Cross-Comparison analysis. As the QALY data had to be converted into decrements for the generalised linear model, it is important to undertake goodness of fit tests in the selection of family distribution to avoid an inappropriate error distribution affecting the efficiency of the parameter estimates [343]. The difference in baseline differences of EQ-5D-3L scores by SSI status underlines the importance of longitudinal follow up and how cross-sectional utility decrements can be misleading. The 30 day SSI utility decrement for the

Cross-Comparison approach (-0.1295) overstated the 1 month decrement by 72.89% based on the was QALM calculation that adjusted for baseline imbalances (-0.0749).

Section C Refinement of the preliminary model from ROSSINI re-analysis

The aim of this section is to incorporate the ROSSINI re-analysis estimates into the preliminary model-based economic evaluation from Chapter 5 and assess the impact on the cost-effectiveness results in comparison with the results from Chapter 5.

6.9 Updated methods for the preliminary model

All methods of the updated model were the same as those in Chapter 5 unless otherwise indicated. The input parameters for the updated preliminary model are presented in Appendix Table A6.17.

The ROSSINI re-analysis cost and utility estimates of SSI were for overall SSI with no breakdown on the different severities and timings (inpatient SSI; outpatient SSI). The same costs and utility estimates were applied to each SSI. As the ROSSINI re-analysis cost included both primary and secondary care costs on both inpatient and outpatient SSIs, no assumptions were required from the literature on their proportions in contrast to the preliminary model-based economic evaluation in Chapter 5.

The cost and quality of life estimates from the Generalised Linear Model was used in the base case analysis. These estimates were selected as they were adjusted for potential confounders that may otherwise bias the estimates. The other approaches (Cross-Comparison, Case Control) were assessed in a deterministic sensitivity analysis (see Appendix Table A6.18). For the LMIC setting, the UK costs are adjusted to improve transferability[142] with costs rebased using a PPP conversion factor [285] and are presented in international dollars. The Generalised Linear Model estimates pass the general knock-out criteria on quality grounds.

For these deterministic sensitivity analyses, the corresponding utility estimate of a patient without an SSI of the ROSSINI re-analysis approach was also used.

6.10 Model results comparison

Detailed information on the results are provided in Appendix 6.1. A comparison of the base case deterministic results for the current Chapter and the model-based economic evaluation in Chapter 5 is shown in Table 6.19. With the lower costs associated with SSI from the ROSSINI re-analysis, the total costs for each strategy have decreased compared to the model results in Chapter 5. Likewise, the lower SSI decrement and higher No SSI health utility value have resulted in relatively higher QALYs for each strategy. Coated Sutures remained the dominant strategy and was cheaper and more effective than the Wound Irrigation and Usual Care strategies. As per the original preliminary economic evaluation results, the Wound Irrigation strategy was still cheaper and more effective versus Usual Care alone.

Table 6.19 Base case deterministic results comparison

Strategy	**Cost**	**Incremental Costs**	**QALY**	**Incremental QALY**	**ICER**
Chapter 5 UK setting (£)					
Coated Sutures	£810		0.04409		
Wound Irrigation	£946	£136	0.04395	-0.000144	Dominated
Usual Care	£1,080	£270	0.0438	-0.000294	Dominated
Chapter 6 UK setting (£)					
Coated Sutures	£197		0.05044		Dominant
Wound Irrigation	£231	£34	0.05036	-0.000083	Dominated
Usual Care	£258	£61	0.05027	-0.000169	Dominated
Chapter 5 LMIC setting (Int $)					
Coated Sutures	$1256		0.04409		Dominant
Wound Irrigation	$1467	$211	0.04395	-0.000144	Dominated
Usual Care	$1676	$419	0.0438	-0.000294	Dominated
Chapter 6 LMIC setting (Int $)					
Coated Sutures	$306		0.05044		Dominant
Wound Irrigation	$358	$52	0.05036	-0.000083	Dominated
Usual Care	$401	$95	0.05027	-0.000169	Dominated

A comparison of the base case probabilistic results for the current Chapter and the model-based economic evaluation in Chapter 5 is shown in Tables 6.20-6.21. Like the deterministic results, the total costs for each strategy have decreased and the total QALYs have increased in the present chapter compared to the model results in chapter 5. The ranking order of costs, QALYs and NMB have remained the same between the two models.

Table 6.20 PSA results comparison

Strategy	**Cost (95% PI)**	**QALY (95% PI)**	**NMB (95% PI)**
Chapter 5			
Coated Sutures	£794 (£774 to £815)	0.04411 (0.04407 to 0.04415)	£88 (£67 to £108)
Wound Irrigation	£929 (£906 to £953)	0.04396 (0.04392 to 0.044)	-£50 (-£74 to -£26)
Usual Care	£1,057 (£1,029 to £1,084)	0.04381 (0.04377 to 0.04385)	-£180 (-£208 to -£153)
Chapter 6			
Coated Sutures	£197 (195 to 198)	0.05045 (0.05044 to 0.05047)	£812 (811 to 814)
Wound Irrigation	£231 (229 to 233)	0.05037 (0.05035 to 0.05039)	£776 (775 to 778)
Usual Care	£257 (255 to 259)	0.05029 (0.05027 to 0.0503)	£749 (747 to 751)

Table 5.9 Probabilistic sensitivity analysis results averaged across iterations (international dollars)

Strategy	Cost (95% PI)	QALY (95% PI)	Ghana NMB (95% PI)	India NMB (95% PI)	Mexico NMB (95% PI)
Chapter 5					
Coated Sutures	$1232 (1200 to 1265)	0.04474 (0.04418 to 0.0453)	-$1141 (-1110 to -1172)	-$1108 (-1077 to -1139)	-$750 (-724 to -776)
Wound Irrigation	$1441 (1404 to 1477)	0.04476 (0.04419 to 0.04532)	-$1349 (-1314 to -1385)	-$1316 (-1281 to -1351)	-$958 (-928 to -989)
Usual Care	$1639 (1596 to 1681)	0.04476 (0.04419 to 0.04533)	-$1547 (-1506 to -1589)	-$1514 (-1473 to -1555)	-$1156 (-1120 to -1193)
Chapter 6					
Coated Sutures	$305 (303 to 307)	0.04474 (0.04418 to 0.0453)	-$202 (-200 to -204)	-$165 (-163 to -167)	$239 (241 to 237)
Wound Irrigation	$358 (356 to 361)	0.04476 (0.04419 to 0.04532)	-$255 (-253 to -258)	-$218 (-216 to -221)	$185 (187 to 182)
Usual Care	$398 (396 to 401)	0.04476 (0.04419 to 0.04533)	-$296 (-293 to -298)	-$259 (-256 to -261)	$144 (146 to 141)

PI: Prediction Interval; NMB: Net Monetary Benefit; QALY: Quality Adjusted Life Year

For the PSA comparison in terms of CEACs, the Coated Sutures strategy had the highest number of PSA iterations indicating that it was the most cost-effective strategy in both Chapter 5 (Figure 5.5) and Chapter 6 (Figure 6.4). Across the two models, the strategy curves were relatively flat across the range of WTP thresholds.

For the VOI Analysis, the per-patient EVPI was reduced (Appendix Table A6.25) with the ROSSINI re-analysis estimates. In Chapter 5, the EVPPI results indicate there was value in reducing uncertainty associated with treatment effectiveness but little to no value in reducing uncertainty associated with SSI utilities or SSI cost parameters. This was the same as in the current Chapter for treatment effectiveness with a lower EVPPI for treatment effectiveness. In contrast to Chapter 5, there was some value in reducing uncertainty associated with the SSI utilities although it was minimal.

6.11 Updated model based economic evaluation Discussion

A preliminary economic evaluation was updated with estimates from the ROSSINI re-analysis to re-assess the cost-effectiveness of interventions to reduce SSI. Using costs and quality of life estimates specific to general surgery patients and adjusting for potential confounders, the intervention of Coated Sutures was cheaper and more effective than a Wound Irrigation or Usual Care strategy. The results were robust to both deterministic and probabilistic sensitivity analysis. This echoes the result recommendations from the preliminary economic evaluation with the original estimates in Chapter 5. The VOI analysis still indicated that there was value associated with the elimination of parameter uncertainty although it was much smaller than the estimates in Chapter 5. However, the transferability issues to LMIC settings remain. The ROSSINI estimates are from a UK setting where the costs and outcomes are likely to vary from different income settings.

6.12 Conclusion

The re-analysis confirmed the additional cost and decrement associated with SSI with differences compared to the original analysis of ROSSINI. With the development of new cost and quality of life estimates, the preliminary economic model presented in Chapter 5 was updated to re-assess the impact on the cost-effectiveness results . With updated estimates from the ROSSINI re-analysis on the additional cost and utility decrement associated with SSI incorporated into the preliminary economic evaluation developed in Chapter 5, interventions to reduce SSI remained cheaper and more effective than Usual Care. The next step is to develop LMIC specific estimates using primary research to incorporate the costs (Chapter 7) and outcomes (Chapter 8) in a final update to the model-based economic evaluation (Chapter 9).

Chapter 7:

The costs of SSI in LMICs

7.1 Introduction

The next step is to collect primary data on the costs of Surgical site infection (SSI) in Low and Middle Income Country (LMIC) settings alongside an SSI reducing trial in LMICs. The preliminary economic models in Chapter 5 and 6 found that an SSI reducing intervention was cost-effective compared to usual care. However, the preliminary economic models used cost estimates from a UK source which may not be transferrable to an LMIC setting. The purpose of this Chapter is to generate postoperative cost estimates of patients by SSI in LMIC settings which will then be used to later refine the preliminary economic model.

The chapter is structured as follows: First, a brief overview of the health care systems of the countries included in the analysis will be presented to set the scene for the findings. Second, a background with the chapter aims are listed. Third, the methods of the cost sub-study are listed with results presented on the costs faced by patients by SSI status and across countries and specific subgroups. Lastly, the findings are discussed, and the chapter is concluded with the thesis next steps.

The results presented here have been adapted from the following peer reviewed paper:

Monahan, M., Glasbey, J., Roberts, T.E., Jowett, S., Pinkney, T., Bhangu, A., Morton, D.G., de la Medina, A.R., Ghosh, D., Ademuyiwa, A.O. and Ntirenganya, F., 2023. The costs of surgical site infection after abdominal surgery in middle-income countries: Key resource use In Wound Infection (KIWI) study. Journal of Hospital Infection, 136, pp.38-44.

7.1.1 Healthcare systems of countries included in cost sub-study

India healthcare system

Healthcare in India is delivered through both private and public providers. India has become a major choice for inbound medical tourism owing to the low cost of healthcare [344]. The majority of private providers are focused on urban areas of India [345]. While public healthcare provision is free of charge as per the constitution, healthcare labour and infrastructures shortages in public hospitals [346] has led many patients to pay out-of-pocket for private healthcare [347]. India has relatively low levels of healthcare expenditure (2.96% in 2020) as a percentage of Gross Domestic Product (GDP) compared to the east Asia and Pacific countries (5.36%; excluding high income countries) [348]. Around half of the healthcare spending in 2020 derived from patient out-of-pocket spending on health [349]. Health insurance is limited with 37% of the Indian population covered [350], and the contribution from private and government insurance schemes to total healthcare spending is modest (8.13% in 2015-16) [351] . Rural areas suffer from unequal access to essential surgery care [352]. India falls short of all the Global Surgery indicators (timely access to essential surgery, specialist surgical workforce density, surgical volume, perioperative mortality rate, protection against impoverishing expenditures, and protection against catastrophic expenditures) as recommended by the Lancet Commission on Global Surgery [353,354]

Mexico health care system

Healthcare in Mexico is delivered through both private and public providers. Inbound medical tourism is a major industry in Mexico due to the proximity to the USA and Canada [355]. Healthcare expenditure was 5.5% of GDP in 2019 which is lower than most Central America and South America countries [356]. 38.8% of the healthcare spending in 2020 derived from patient out-of-pocket spending on health [357]. 72.9% of the population is covered by either

public or private healthcare insurance in 2019 [356]. As individuals can only access healthcare providers covered by their insurance, the segmentation of coverage can restrict access to healthcare or force individuals to pay out-of-pocket for more healthcare provision choices [358]. It was estimated that 81.7% of the population have timely access to essential surgery with lower surgical workforce density and surgical volume as recommended by the Lancet Commission on Global Surgery [306,353]. The study also found geographic clusters in Mexico of individuals with low proportions of timely access to surgical care that would most benefit from surgical access improvements [306].

Ghana health care system

Healthcare in Ghana is delivered through both private and public providers. Government spending is below average compared to sub-Saharan Africa (3.99% versus 4.92%) [348]. 30.7% of current health expenditure was derived from patient out-of-pocket spending in 2020 [348]. Close to 70% of the population is covered by either public or private healthcare insurance in 2021 [359]. Ghana faces challenges around insufficient health care expenditure, healthcare labour and infrastructure [360]. It is estimated that 71.4% of the population can access essential surgery within 2 hours [361].The challenge of timely and effective access to surgical care is more acute in rural areas where surgical care provision often is delivered by non-surgeons [303,362], and where patients have to pay up to 91% of direct surgical provision costs out-of-pocket [363]. The annual rate of 869 surgeries per 100,000 population is much lower than the 5000 surgeries per 100,000 population global surgery indicator benchmark as recommended by the Lancet Commission on Global Surgery [303,353].

Nigeria health care system

Healthcare in Nigeria is delivered through both private and public providers. Government spending is below average (4.6%) compared to sub-Saharan Africa (7.2%) and patient out-of-

pocket spending on health constitutes 80% of the total expenditure on health [364]. The share of private health insurance to total health expenditure is minimal (0.8%) compared to the sub-Saharan Africa (21%)[365].Corruption in the healthcare system is widespread [366], and there is outbound medical tourism by those who can afford to pay to circumvent domestic healthcare delivery issues [367]. Like other parts of the healthcare system, access to surgery care in Nigeria is unequal owing to problems around affordability, levels of infrastructure and healthcare professional staff and geographic distribution of these services [368]. A survey of four states in Nigeria found that a surgical provision was inadequate compared to global surgery indicator benchmarks in surgical volume, timely access to surgery and specialist surgical workforce density as recommended by the Lancet Commission on Global Surgery [353,369].

7.1.2 Background

Quantifying the costs associated with an SSI is a vital component in the economic assessment of interventions to reduce these complications [147]. To date, evidence on the magnitude of the cost burden of SSI in LMICs has been limited to single-centre studies with differences in study design impeding comparability [370]. Single-centre settings are only representative of the single centre and country setting and therefore reduces generalisability. In Chapter 3, many of the LMIC SSI studies undertook SSI detection and cost collection only up to hospital discharge. Therefore, the lack of post-discharge follow-up severely limits the validity of these studies as SSI commonly occurs after discharge [371] and the additional costs associated with SSI are shown to persist beyond discharge and 30 days [372]. Consequently, a reliable estimate of the cost burden of SSI in LMICs does not currently exist. Reducing surgical site infections in low-income and middle-income countries (FALCON) was a randomised control

trial (RCT) undertaken in seven LMIC countries (Benin, Mexico, Rwanda, Nigeria, Ghana, India, South Africa) assessing the effectiveness of interventions to reduce SSI [373,373].

The Key resource use In Wound Infection (KIWI) study was carried out within the FALCON trial in order to estimate the cost burden associated with SSI. The specific objectives of KIWI were to:

(1) measure the additional within-hospital resource use for patients with SSI compared to patients without SSI and attach unit costs to this additional resource use;
(2) identify and measure the resource use for patients who have SSI detected after hospital discharge;
(3) explore the relative cost burden for patients with Contaminated-Dirty operations compared to patients with Clean-Contaminated surgeries; and
(4) explore the healthcare needs and resource use of patients with an unresolved SSI at 30 days and beyond.

7.2 Methods

7.2.1 FALCON trial

KIWI was a study within the FALCON trial. FALCON [280,373] was a pragmatic, 2x2 factorial, stratified, multi-centre RCT, evaluating measures to reduce SSI rates in patients undergoing surgery with an abdominal incision. The primary clinical outcome for the FALCON trial was SSI up to 30 days after surgery. Patients were stratified by their predicted wound contamination (Clean-Contaminated or Contaminated-Dirty wounds). Patients with abdominal skin incision ≥5cm were randomised between (1) 2% alcoholic chlorhexidine and non-coated suture, (2) 2% alcoholic chlorhexidine and triclosan-coated suture, (3) 10%

aqueous povidone-iodine and non-coated suture, and (4) 10% aqueous povidone-iodine and triclosan-coated suture. FALCON included patients undergoing emergency or elective surgery, for any operative indication, including trauma surgery.

7.2.2 Setting

Participating FALCON centres in India, Ghana, Nigeria, and Mexico were included in KIWI. The list and type of hospitals is shown in Table 7.1. SSI was defined using the Centers for Disease Control and Prevention (CDC) criteria as per the FALCON trial [374] and was assessed at hospital discharge and at 30 days post-surgery time points for all patients.

7.2.3 Population

Consecutive adult patients recruited to the FALCON trial were eligible for the KIWI study. A minimum target of 100 consecutive patients per country was planned, with at least two hospitals per country invited to participate. No formal sample size calculation was used for the KIWI study. Consideration of sample size for economic endpoints in randomised control trials are rare [375], complex [376] and there is no agreed approach on the calculations [377].

7.2.4 Data collection up to 30-day follow-up

Resource use for SSI and no SSI patients was collected using additional Case Report Forms (CRFs) within the FALCON trial completed at hospital discharge (FALCON Hospital Resource Use Form) and as close to 30 days post-surgery as possible (FALCON Post-Discharge Resource Use Form, Figure 7.1). These forms were purposely aligned with the data collection points within the FALCON trial to minimise burden.

Table 7.1 Participating hospitals

Site	Hospital type	Description
Ghana		
Techiman Holy Family Hospital	District	Religious hospital with a bed capacity of 330
Komfo Anokye Teaching Hospital	Central	Government hospital with a bed capacity of 1200
Goaso Municipal Hospital	District	Government hospital with a bed capacity of 106
Effia-Nkwanta Hospital	Central	Government hospital with a bed capacity of 416
Cape Coast teaching hospital	Central	Government hospital with a bed capacity of 400
India		
Christian Medical College Ludhiana	Central	Charitable hospital with a bed capacity of 775
Christian Medical College Vellore	Central	Charitable hospital with a bed capacity of 1000
Madhipura Christian Hospital	District	Charitable hospital with a bed capacity of 35
Mexico		
Hospital Español Veracruz	Central	Private hospital with a bed capacity of 40
Hospital General de Boca Del Rio	Central	Private hospital with a bed capacity of 40
Hospital Regional, Veracruz	Central	Teaching hospital with a bed capacity of 240
Nigeria		
Lagos University teaching hospital	Central	Referral hospital with a bed capacity of 761
University of Ilorin Teaching Hospital	Central	Referral hospital with a bed capacity of 650

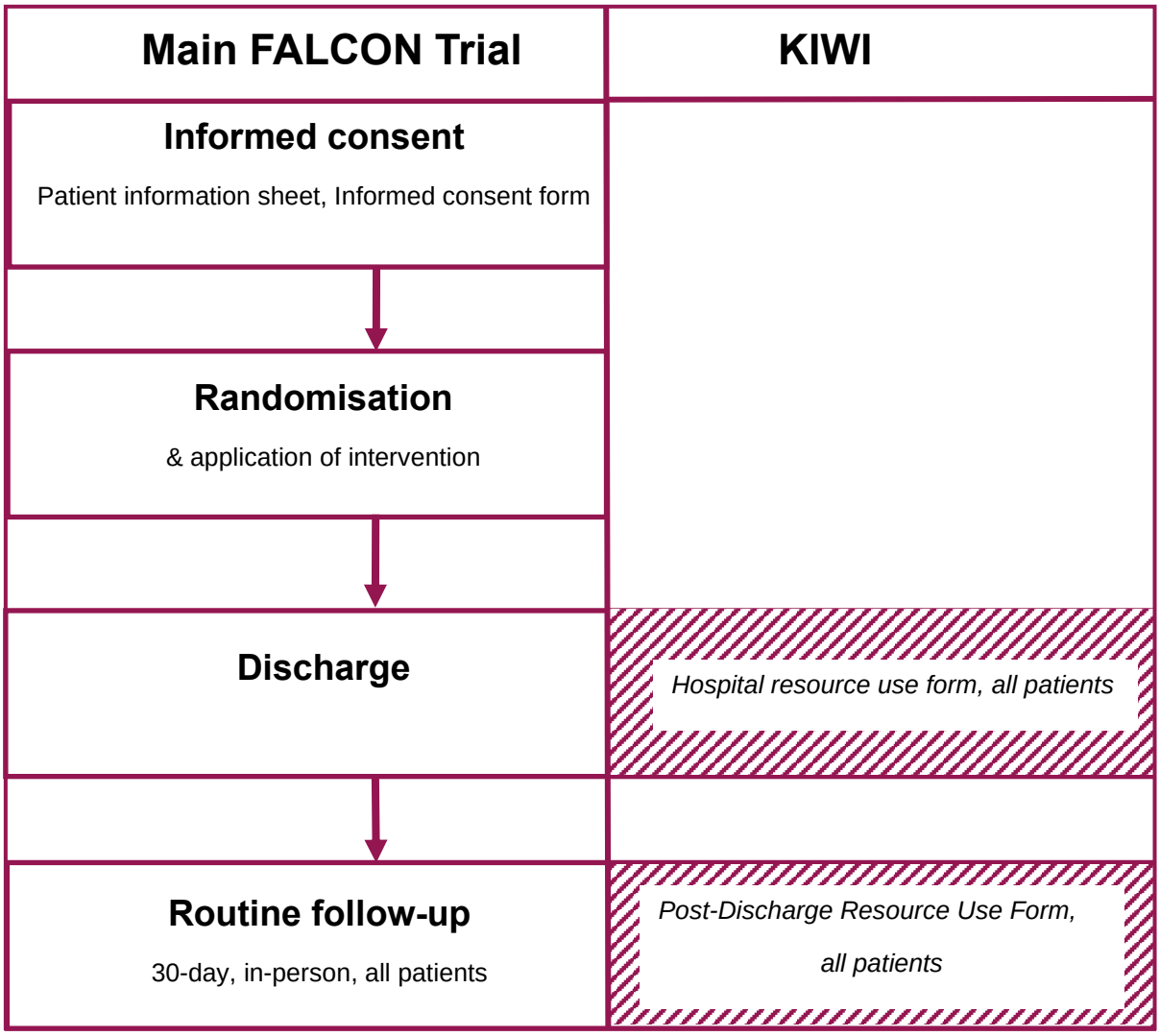


Figure 7.1 KIWI CRF timepoints

The FALCON Post-Discharge Resource Use Form collected information up to 30 days post-surgery. Relevant data included any post-discharge consultation and consumable costs along with any travel costs and income loss from attending post-discharge healthcare visits. The costs associated with travel and lost income for family members who accompanied patients were also recorded where applicable.

Inpatient resource use up to 30 days post-surgery was collected via a dedicated FALCON hospital resource use form (see Appendix A7.1). This was designed in partnership with international surgeons involved in the care of abdominal surgery patients and specifically

aimed to collect relevant cost data on resource items that would be likely to vary between patients with and without SSI in the local contexts in which these were measured. After some iterative development, the resource use questionnaires were piloted with the first five patients in each country to ensure consistency of reporting and that no relevant costs were missed.

Inpatient resources items collected were postoperative length of stay, wound dressing changes, days on antibiotics for treating a suspected wound infection, laboratory investigations, and healthcare resource use (e.g., antibiotics, painkillers) associated with patient discharge. The laboratory investigations were number of Full Blood Count results, Urea and Electrolytes results, Liver Function Test results, C-reactive Protein results, Microbiology (Wound Swab) results and imaging used to diagnose suspected SSI. The choices for imaging for suspected SSI diagnosis was a computed tomography scan and/or ultrasound scan.

When the prospective recruitment for KIWI commenced, the host trial had finished recruiting predicted Clean-Contaminated cases and was only recruiting predicted Contaminated-Dirty cases. To collect information on the Clean-Contaminated cases, retrospective data collection via telephone interview was undertaken in India and Mexico. To minimise recall bias, consecutive Clean-Contaminated patients who had most recently completed follow-up were contacted. Electronic patient records were used to complete the hospital resource use forms for the retrospective cases.

7.2.5 Data collection beyond 30-day follow-up

For patients with an unresolved SSI at 30 days post-surgery, additional telephone follow-up was completed 14 days later (as close to postoperative day 45 as practical) to collect resource use information related to their ongoing wound infection. For patients with an unresolved

wound infection at 45-days after surgery, a final third telephone call was completed 14-days later (as close to postoperative day 60 as practical). To maximise the sample size, the analysis on the post-discharge costs of unresolved wound infection included those with missing hospital resource forms.

7.2.6 Valuation of resource use data

For inpatient resource use valuation, hospital unit cost information at each participating centre was collected by the trial staff. Post-discharge costs were collected in post-discharge CRFs. Costs were expressed in Euros with a cost year of 2020. Costs were adjusted by their country's Purchasing Power Parity (PPP) conversion factor [378]. Where a country's PPP conversion factor was unavailable, an implied conversion factor from the International Monetary Fund was used instead [379].

7.2.7 Perspective

The primary analysis adopted the perspective of the health service provider. Within this perspective, direct medical costs (e.g., hospital length of stay, lab investigations, reoperations, and antibiotics) were included. A secondary analysis was conducted which adopted a societal perspective which included direct non-medical costs (travel costs) and indirect costs (productivity loss costs) incurred by the patient and their family.

7.2.8 Analysis

The postoperative mean costs faced by patients with SSI and without SSI respectively were presented on a per-country basis and stratified by predicted surgery type (Clean-Contaminated, Contaminated-Dirty). Mean costs were presented due to their relevance to resource allocation decisions (i.e., mean per patient cost multiplied by number of patients equals the total cost). Postoperative costs were further subdivided into inpatient and post-

discharge costs. Where extended follow-up was carried out on patients with unresolved wound infection, the costs are shown at 45 days and 60 days post-surgery. The costs of patients who had suffered an inpatient SSI versus those who suffered an SSI after hospital discharge were also explored. For Contaminated-Dirty cases, a sensitivity analysis compared the cost differences between retrospective and prospective cases.

As cost differences can be explained by factors other than the presence of an SSI, a regression analysis was undertaken to assess if SSI was a statistically significant determinant of healthcare costs. The regression analysis used a multilevel Generalised Linear Model with a log-link and gamma distribution and adjusted for patient characteristics (age, gender, emergency/elective, predicted contamination, SSI). The covariates of age [321], sex [322], smoking status [323], diabetic status [324], elective or emergency surgery [321], surgical contamination [326] have all been previously shown to be associated with higher postoperative healthcare costs. A multilevel Generalised Linear Model is recommended for data across multiple countries because it can account for hierarchical nature of the data [380]. The gamma distribution and log-link were chosen as it had the lowest Akaike information criterion relative to the other possible distribution and link specifications (see Appendix Table 7.1)

A complete-case analysis was undertaken, where patients with missing CRFs were removed. Imputation for missing data was not undertaken as the data was unlikely to be missing at random. The analysis was undertaken in STATA 17. No discounting of costs was undertaken as the time horizon was less than a year [66].

7.2.9 Ethical approval

Ethical approval for data collection up to 30 days was approved within the main FALCON protocol (ERN_180230) at the University of Birmingham and in the countries where the trial was recruiting. Data collection of patients beyond 30 days required a protocol amendment and ethical approval. Extended follow-up received university ethics (ERN_18-0230A) as well as local ethics approvals. Ethical approval for protocol amendments for extended follow up in participating countries was affected by the onset of COVID-19 and was delayed by postponement of ethics committee meetings and/or de-prioritization of non-COVID research studies. Only Ghana had ethical approvals for the extended follow up of patients.

7.3 Results

Prospective recruitment for KIWI was open in India (June 2020 to October 2020), Nigeria (April 2020 to October 2020), Mexico (May 2020 to October 2020) and Ghana (May 2020 to October 2020). Due to COVID-19, no prospective study enrolment of Contaminated-Dirty cases was possible in Mexico as the centres were closed for recruitment. To overcome this, we included Contaminated-Dirty cases in the retrospective analysis along with the Clean-Contaminated cases in Mexico. The number of participating centres varied by country [India (n=3), Ghana (n=5), Nigeria (n=2) and Mexico (n=3)]. Figure 7.2 shows the patient flowchart of those included in the KIWI sub study.

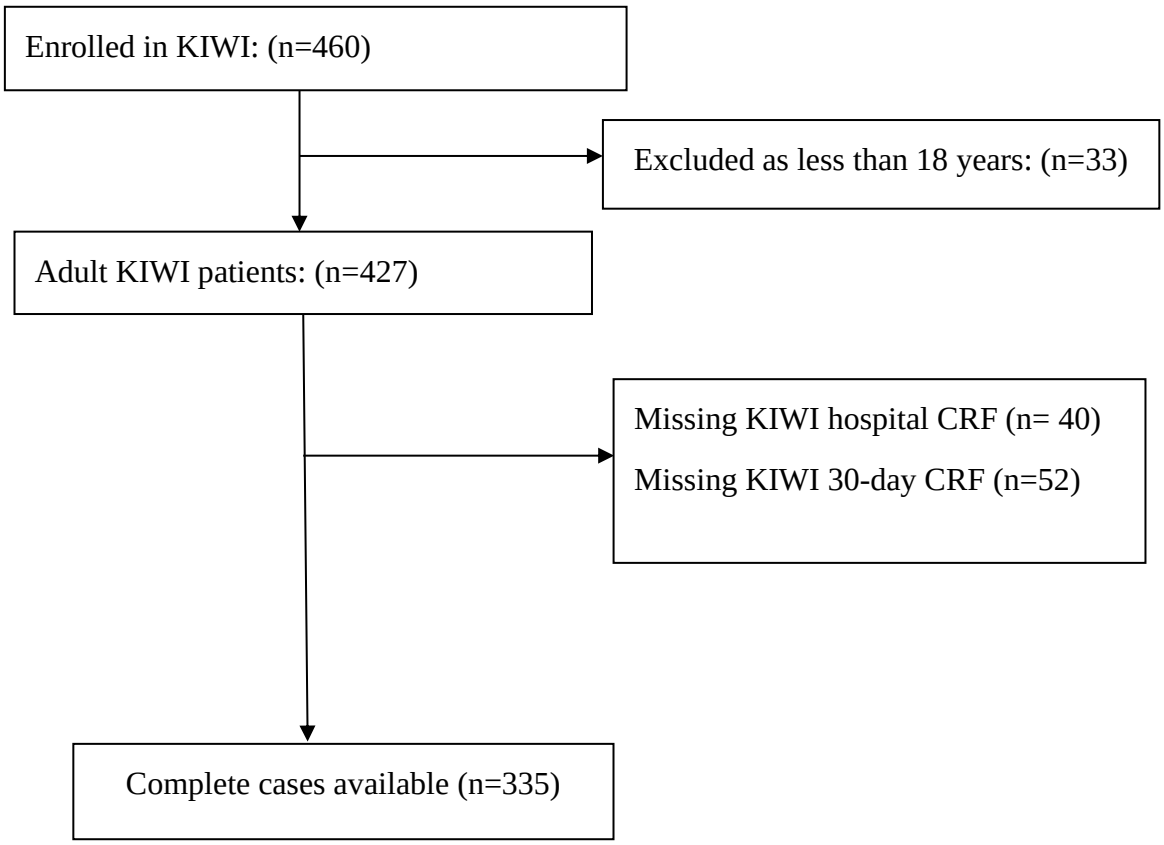


Figure 7.2 KIWI flowchart

7.3.1 Patient characteristics

Table 7.2 and Appendix Table A7.2 show the patient characteristics, and indication for surgery of those included in the study. The breakdown of the main operation is shown in Table Appendix A7.3. Clean-Contaminated cases (n=186) were collected retrospectively in India and Mexico. Clean-Contaminated cases were mainly female (88%), and 67% of Clean-Contaminated cases underwent caesarean section. Most Clean-Contaminated cases (67%) were contacted beyond 6 months of their initial recruitment to the trial. For the Contaminated-Dirty cases, patients were mainly male, older, and had a higher proportion of SSI (27% versus 7%) compared to the Clean-Contaminated cases. The proportion of SSI at postoperative day 30 was also higher in Contaminated-Dirty cases (16%) compared to Clean-Contaminated cases (3%). Inpatient SSIs were more common than outpatient SSIs in both Clean-Contaminated cases and Contaminated-Dirty cases.

India had the largest sample size (n=144), and Nigeria had the lowest sample size (n=4). Ghana had the largest number of Contaminated-Dirty cases whilst India had the largest number of Clean-Contaminated cases. In Mexico, only one patient in each contamination arm suffered an SSI.

Table 7.2 Patient characteristics

Predicted contamination	Clean-Contaminated			Contaminated-Dirty				
	Overall	Mexico	India	Overall	Ghana	India	Mexico	Nigeria
	n (%)							
Sex								
Male	22(12)	10(12)	12(12)	98(64)	66(65)	30(65)	0(0)	2(50)
Female	160(88)	74 (88)	86(88)	55 (36)	35 (35)	16 (35)	2 (100)	2 (50)
Total	182(100)	84(100)	98(100)	153(100)	101(100)	46(100)	2(100)	4(100)
Surgical Site Infection (SSI)								
No	170(93)	83(99)	87(89)	111(73)	81(80)	27(59)	1(1)	2(50)
Yes	12(7)	1(1)	11(11)	42(27)	20(20)	19(41)	1(50)	2(50)
Inpatient Surgical Site Infection	9	0	9	33	13	18	0	2
Outpatient Surgical Site Infection	3	1	2	9	7	1	1	0
Unresolved wound infection at postoperative day 30	3%	0%	5.1%	16%	9.9%	28.3%	0%	25%
Length of Stay in days *Mean (SE)*	4.98(0.3)	2.79(0.3)	6.85(0.4)	8.88(0.6)	7.90(0.7)	10.54(1.1)	8.5(1.5)	14.25 (5.6)
Age in years *Mean (SE)*	34.8 (0.9)	36.1(1.3)	33.6(1.2)	42.2 (1.3)	41.1 (1.6)	44.2(2.5)	42(3)	49.3(3.2)
Timing of 1st Post-discharge follow-up								
Prospective (up to 40 days FU)	0(0)	0(0)	0(0)	122(80)	96(95)	24(52)	0(0)	4(100)
Retrospective: 40 days to 6 months	60(33)	2(2)	58(59)	12(8)	5(5)	7(15)	0(0)	0(0)
Retrospective: 6 months to 12 months	79(43)	39(46)	40(41)	17(11)	0(0)	15(33)	2(100)	0(0)
Retrospective: Beyond 12 months	43(24)	43(51)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)

7.3.2 Clean-Contaminated postoperative resource use and costs

Postoperative and post-discharge resource use is shown for surgical patients with Clean-Contaminated wounds in Tables 7.3-7.4. In India, patients with an SSI had longer postoperative length of stays, more investigations and wound dressing changes compared to patients without an SSI. There was a large difference in patients having post-discharge healthcare visits in Mexico (4%) compared with India (87%).

Postoperative and post-discharge costs are shown for Clean-Contaminated patients in Table 7.5. Hospital investigations were the largest contributor of inpatient post-operative costs in India while it was the lowest contributor in Mexico. Overall, an SSI increased total healthcare postoperative costs by 75.3% in the Clean-Contaminated cases (€959 versus €547) (Table 7.6). Broadening the cost perspective to include travel costs and income loss from the post-discharge visits increased the additional costs associated with an SSI (€1,064 versus €656).

Table 7.3 Inpatient and discharge resource use for Clean-Contaminated cases

	Mexico		India	
	No SSI (n=83)	SSI (n=1)	No SSI (n=87)	SSI (n=11)
Inpatient resource Use				
Postoperative Length of Stay in days, Mean (SE)	2.8 (0.26)	2 (-)	6.4 (0.27)	10.36 (2.11)
Number of Wound dressings changes, Mean (SE)	3.63 (0.26)	3 (-)	6.56 (0.24)	11.00 (2.32)
Number of Full Blood Count results, Mean (SE)	0.86 (0.15)	0 (-)	1.59 (0.09)	2.09 (0.39)
Number of Urea and Electrolytes results, Mean (SE)	0.72 (0.11)	0 (-)	0.38 (0.09)	1.73 (0.45)
Number of Liver Function Test results, Mean (SE)	0.25 (0.07)	0 (-)	0.50 (0.07)	1.27 (0.30)
Proportion of Ultrasound scan use	0%	0%	0%	9%
Proportion of CT scan use	1%	0%	2%	1%
Number of C-reactive Protein results, Mean (SE)	0 (-)	0 (-)	0.12 (0.04)	0.55 (0.21)
Number of Microbiology (Wound Swab) results, Mean (SE)	0.01 (0.01)	0 (-)	0.26 (0.07)	0.78 (0.22)
Discharge				
Pain killer medications	100%	100%	34%	73%
Antibiotics for a wound infection	4%	0%	3%	36%
Wound dressings	99%	100%	6%	45%

Table 7.4 Post Discharge Resource Use for Clean-Contaminated cases

	Mexico		India	
	No SSI (n=83)	SSI (n=1)	No SSI (n=87)	SSI (n=11)
Healthcare visits				
Hospital, Count (%)	3 (4)	0 (-)	75 (86)	10 (91)
Community doctor, Count (%)	2 (2)	0 (-)	3(3)	1(9)
Community nurse or other community worker, Count (%)	0 (0)	0 (-)	1 (1)	1 (9)
Home visits, Count (%)	0 (0)	0 (-)	3 (3)	0 (0)
Hospital visit accompanied by companion/family member, Count (%)	3 (100)	-	72 (96)	10 (100)
Community doctor visit accompanied by companion/family member, Count (%)	-	-	-	-
Community nurse or other community visit worker accompanied by companion/family member, Count (%)	-	-	-	-
Purchase of wound/dressings or medication, Count (%)	6 (7)	0 (-)	5 (6)	3 (27)

Table 7.5 Postoperative and post discharge costs for Clean-Contaminated cases

	Mexico		India	
	No SSI (n=81)	SSI (n=1)	No SSI (n=87)	SSI (n=11)
Cost of Postoperative Length of Stay, wound dressings, antibiotics; Mean (SE)	€594 (67)	€951 (-)	€403 (18)	€713 (150)
Cost of Investigations; Mean (SE)	€20 (4)	0 (-)	€44 (7)	€115 (26)
Cost of Discharge (Wound dressings, antibiotics, painkillers); Mean (SE)	€4 (1)	€3 (-)	€2 (1)	€18 (6)
Healthcare visit consultation costs; Mean (SE)	0 (-)	0 (-)	€13 (4)	€114 (73)
Community doctor charge; Mean (SE)	€117 (89)	0 (-)	€33 (19)	€17 (-)
Community nurse or other community worker visit charges; Mean (SE)	0 (-)	0 (-)	0 (-)	0 (-)
Home visit charges; Mean (SE)	0 (-)	0 (-)	€18 (5)	0 (-)
Wound dressings and medication charges; Mean (SE)	€66 (23)	0 (-)	€152 (97)	€28 (7)
Travel costs; Mean (SE)	€3 (2)	0 (-)	€10 (2)	€15 (6)
Income loss; Mean (SE)	€27 (16)	0 (-)	€75 (21)	€100 (44)

Table 7.6 Total postoperative costs of SSI (€) for Clean-Contaminated cases

	Overall		Mexico		India	
	No SSI (n=170)	SSI (n=12)	No SSI (n=83)	SSI (n=1)	No SSI (n=87)	SSI (n=11)
Post-operative inpatient costs, Mean (SE)	€532 (36)	€855 (151)	€619 (68)	€954 (-)	€450 (23)	€846 (165)
Post-discharge healthcare costs, Mean (SE)	€15 (4)	€104 (61)	€8 (5)	0 (-)	€22 (7)	€113 (66)
Total post-operative healthcare costs, Mean (SE)	€547 (36)	€959 (179)	€627 (67)	€954 (-)	€471 (25)	€959 (196)
Travel and income loss, Mean (SE)	€58 (14)	€106 (41)	€30 (17)	0 (-)	€85 (21)	€115 (44)
Societal costs, Mean (SE)	€605 (38)	€1064 (203)	€656 (68)	€954 (-)	€557 (33)	€1074 (222)

7.3.3 Contaminated-Dirty postoperative resource use and costs

For the surgical cases with a Contaminated-Dirty wound, information on the postoperative and post discharge resource use is provided in Tables 7.7-7.8. Postoperative and post-discharge costs are shown in Tables 7.9-7.10 for Contaminated-Dirty cases. Due to low sample size, the Contaminated-Dirty cases of Mexico (n=2) and Nigeria (n=4) are presented in Appendix Table A7.4 for completeness. Hospital investigations were the largest contributor of inpatient post-operative costs in Ghana and India. Most patients in India and Ghana had post-discharge healthcare visits. Post-discharge costs for patients with an SSI in both India and Ghana were at least double those compared to patients without an SSI. Overall, an SSI increased total healthcare postoperative costs by 66.6% in the Contaminated-Dirty cases (€828 versus €497) (Table 7.10). The inclusion of travel costs and income loss associated with post-discharge visits widened the cost difference between patients with and without an SSI, respectively (€1,074 versus €678).

Table 7.7 Inpatient and discharge resource use for Contaminated-Dirty cases

	Ghana		India	
	No SSI (n=81)	SSI (n=20)	No SSI (n=27)	SSI (n=19)
Inpatient resource use				
Postoperative Length of Stay in days, Mean (SE)	7.04 (0.69)	11.35 (1.82)	10.29 (1.83)	10.89 (0.65)
Wound dressings changes, Mean (SE)	2.86 (0.66)	4.40 (0.69)	8.37 (1.36)	12.26 (0.83)
Full Blood Count results, Mean (SE)	1.42 (0.08)	1.40 (0.15)	1.96 (0.49)	2.42 (0.41)
Urea and Electrolytes results, Mean (SE)	1.18 (0.07)	1.31 (0.12)	2.26 (0.48)	2.26 (0.47)
Liver Function Test results, Mean (SE)	1.07 (0.07)	1 (0)	1.07 (0.21)	0.84 (0.14)
Proportion of Ultrasound scan use	7%	40%	0%	9%
Proportion of CT scan use	0%	0%	2%	0%
C-reactive Protein results, Mean (SE)	1.2 (0.2)	1 (0)	0.30 (0.10)	0.26 (0.10)
Microbiology (Wound Swab) results, Mean (SE)	1 (0)	1 (0)	0.27 (0.17)	0.95 (0.16)
Discharge				
Pain killer medications	59%	75%	67%	95%
Antibiotics for a wound infection	68%	80%	7%	84%
Wound dressings	98%	100%	15%	90%

Table 7.8 Post discharge resource use for Contaminated-Dirty cases

	Ghana		India	
	No SSI (n=81)	SSI (n=20)	No SSI (n=27)	SSI (n=19)
Hospital, Count (%)	59 (73)	13 (65)	12 (44)	15 (79)
Community doctor, Count (%)	7 (9)	5 (25)	3 (11)	1 (5)
Community nurse or other community worker, Count (%)	30 (37)	7 (35)	0 (0)	4 (21)
Home, Count (%)	4 (5)	4 (20)	0 (0)	4 (21)
Hospital visit accompanied by companion/ family member, Count (%)	23 (28)	8 (40)	12 (44)	15 (79)
Community doctor visit accompanied by companion/family member, Count (%)	0 (0)	0 (0)	4 (15)	3 (16)
Community nurse or other community visit worker accompanied by companion/family member, Count (%)	0 (0)	0 (0)	2 (7)	0 (0)
Purchase of wound/dressings or medication, Count (%)	71 (88)	20 (100)	3 (11)	10 (53)

Table 7.9 Postoperative and post discharge costs for Contaminated-Dirty cases

	Ghana		India	
	No SSI (n=81)	SSI (n=20)	No SSI (n=27)	SSI (n=19)
Cost of Postoperative Length of Stay, wound dressings, antibiotics; Mean (SE)	€306 (38)	€543 (95)	€620 (114)	€755 (48)
Cost of Investigations; Mean (SE)	€36 (5)	€71 (9)	€131 (26)	€122 (13)
Cost of Discharge (Wound dressings, antibiotics, painkillers) ; Mean (SE)	€24 (2)	€28 (4)	€5 (2)	€36 (3)
Healthcare visit consultation costs; Mean (SE)	€12 (2)	€44 (20)	€11 (2)	€13 (2)
Community doctor charge; Mean (SE)	€19 (5)	€5 (1)	€11 (3)	€12 (-)
Community nurse or other community worker visit charges; Mean (SE)	€13 (3)	€8 (2)	0 (-)	€2 (-)
Home visit charges; Mean (SE)	€69 (30)	€80 (40)	0 (-)	€10 (1)
Wound dressings and medication charges; Mean (SE)	0 (-)	0 (-)	€16 (4)	€32 (4)
Travel costs; Mean (SE)	€17 (3)	€26 (7)	€15 (7)	€27 (7)
Income loss; Mean (SE)	€195 (52)	€214 (68)	€64 (30)	€95 (41)

Table 7.10 Total postoperative costs of SSI (€) for Contaminated-Dirty cases

	Overall		Ghana		India	
	No SSI (n=111)	SSI (n=42)	No SSI (n=81)	SSI (n=20)	No SSI (n=27)	SSI (n=19)
Post-operative inpatient costs, Mean (SE)	€461 (45)	€763 (58)	€366 (38)	€642 (98)	€756 (131)	€913 (53)
Post-discharge healthcare costs, Mean (SE)	€36 (36)	€66 (6)	€44 (8)	€100 (27)	€8 (2)	€32 (6)
Total post-operative healthcare costs, Mean (SE)	€497 (66)	€828 (14)	€410 (40)	€742 (107)	€763 (132)	€945 (55)
Travel and income loss, Mean (SE)	€181 (39)	€169 (39)	€212 (52)	€239 (70)	€79 (33)	€121 (40)
Societal costs, Mean (SE)	€678 (55)	€997 (70)	€623 (59)	€981 (117)	€843 (139)	€1066 (82)

7.3.4 Extended follow-up

Information on the costs by patients in Ghana with an unresolved wound infection by 30, 45 and 60 days is shown in Table 7.11 . For patients with an unresolved wound infection, they continued to incur additional post-discharge costs although there was 42.9% follow up at the postoperative 45 day telephone follow-up.

Table 7.11 Costs for SSI Ghana patients with extended Follow up for unresolved Wound Infection (incomplete cases)

	Postoperative SSI resource use at 30 days	Postoperative resource use at 45 days	Postoperative resource use at 60 days
Sample Size (n)	32	6	2
Ongoing wound infection (r/n)	14/32	2/6	2/2
Patient Travel costs, Mean (SE)	€12 (3)	€32 (15)	€25 (3)
Patient Income loss, Mean (SE)	€117 (42)	0 (0)	0 (0)
Healthcare visit consultation costs, Mean (SE)	€23 (8)	€11 (5)	0 (0)
Wound dressings and medication, Mean (SE)	€58 (15)	€11 (4)	€11 (2)
Total healthcare costs, Mean (SE)	€81 (19)	€32 (9)	€11 (2)
Companion travel costs, Mean (SE)	€7 (2)	€29 (16)	€25 (3)
Companion income loss, Mean (SE)	€34 (15)	0 (0)	0 (0)

7.3.5 Sensitivity analysis

Table 7.12 shows the results of the sensitivity analysis on the costs by SSI timing. Inpatient SSIs were more expensive compared to SSIs which developed post-discharge. Comparing prospective to retrospective cases, postoperative inpatient costs were much higher in the retrospective cases while post-discharge healthcare costs were slightly higher in the prospective cases (Table 7.13). The multilevel model results are shown in Table 7.14. Being female, the presence of an SSI, being an emergency admission, and being a Contaminated-Dirty case were all statistically significant variables in affecting the total postoperative healthcare costs. Using the margins command, the average marginal effect of an SSI was €229. A Contaminated-Dirty SSI was predicted to be more expensive (€251) compared to a Clean-Contaminated SSI (€210).

Table 7.12 Inpatient versus outpatient SSI Sensitivity analysis

	Clean-Contaminated		Contaminated-Dirty	
	Inpatient SSI	Outpatient SSI	Inpatient SSI	Outpatient SSI
Sample size	9	3	33	9
Postoperative inpatient costs, Mean (SE)	€907 (194)	€699 (193)	€839 (58)	€483 (134)
Post-discharge healthcare resource use, Mean (SE)	€133 (79)	€16 (9)	€59 (15)	€89 (37)
Total postoperative healthcare costs, Mean (SE)	€1040 (228)	€715 (191)	€898 (62)	€572 (143)
Travel and income loss, Mean (SE)	€100 (43)	€123 (122)	€133 (36)	€300 (123)
Societal costs, Mean (SE)	€1140 (259)	€839 (261)	€1031 (79)	€872 (148)

Table 7.13 Costs of prospective versus retrospective patients with and without SSI

	Prospective SSI (n=25)	Retrospective SSI (n=14)	Prospective No SSI (n=97)	Retrospective No SSI (n=17)
Postoperative inpatient costs, Mean (SE)	€669 (59)	€888 (285)	€399 (28)	€901 (106)
Post-discharge healthcare resource use, Mean (SE)	€79 (23)	€28 (6)	€38 (7)	€45 (8)
Total postoperative healthcare costs, Mean (SE)	€748 (64)	€916 (284)	€437 (29)	€946 (112)
Travel and income loss, Mean (SE)	€193 (59)	€160 (63)	€184 (44)	€134 (44)
Societal costs, Mean (SE)	€941 (72)	€1075 (277)	€620 (47)	€1080 (136)

Table 7.14 Multilevel Generalised Linear Model with gamma distribution and log-link function of total postoperative costs

Variables	Coefficient	Standard Error	P-value	95% Confidence Interval	
Female Sex	-0.2366	0.0582	0.000	-0.3507	-0.1225
Male Sex (reference category)	-	-	-	-	-
Emergency (unplanned admission)	-0.3093	0.0666	0.000	-0.4398	-0.1788
Elective (planned admission, reference category)	-	-	-	-	-
SSI	0.4187	0.0678	0.000	0.2857	0.5516
Predicted Contaminated-Dirty wound	0.1766	0.0861	0.04	0.0079	0.3453
Predicted Clean-Contaminated wound (reference category)	-	-	-	-	-
Age	0.0023	0.0018	0.207	-0.0013	0.0059
Intercept	6.0145	0.2222	0.000	5.5791	6.45

7.4 Discussion

7.4.1 Statement of principal findings

SSI is associated with additional postoperative costs in patients undergoing abdominal surgery across Ghana, Mexico, Nigeria, and India. The overall mean additional postoperative costs with SSI were higher in Clean-Contaminated cases compared to Contaminated-Dirty cases. Looking at the inpatient resource use, the additional investigations and hospital length of stay for a patient with an SSI compared to patient without an SSI was generally higher in the Clean-Contaminated cases compared to the Contaminated-Dirty cases.

Collected postoperative costs considered both direct healthcare costs and indirect costs arising from post-discharge healthcare resource use. Patients with an SSI had higher costs in both postoperative inpatient costs and post-discharge costs compared to patients without an SSI. Even after controlling for different variables in a multilevel Generalised Linear Model analysis, SSI was a statistically significant variable in determining postoperative healthcare costs. The predicted cost of an SSI after covariate adjustment by wound contamination arm was lower than the overall unadjusted costs.

Postoperative inpatient costs constituted most the total healthcare costs in both Clean-Contaminated and Contaminated-Dirty cases. An exploratory investigation in Ghana showed that the costs of unresolved SSI persist beyond 30 days with the 45- and 60- postoperative day post-discharge costs in addition to the 30 postoperative day post-discharge costs. This is an important finding because 37.5% of prospective patients with an SSI were unresolved at 30 days post-surgery, potentially underestimating the true postoperative costs of SSI by limiting the data collection window.

7.4.2 Strengths and weaknesses

This represents the first multi-continental study assessing the postoperative costs associated with SSI. Resource use was collected in standardised forms within a trial setting, allowing comparability of findings across the countries. This study helps address some of the literature gaps by providing cost information on surgical patients beyond discharge in low resource settings. Participating countries had more than one centre participating to increase generalisability of the findings.

There are several study limitations. The use of retrospective data collection for Clean-Contaminated cases may have affected the post-discharge healthcare estimates due to recall bias [381]. Another study limitation was the absence of any low-income countries. Thus, the additional costs of SSI could not be generalised to these settings. Another limitation is the adoption of implied PPP exchange rate for the comparative cost results. This risks the possibility of measurement error bias if the implied PPP exchange rate differed from the true PPP rates. The low sample size and event rate in Nigeria and Mexico respectively further limits the precision and the reliability of the estimates in these countries. Lastly, the SSI cost differences between countries may be influenced by other factors including the clinical processes and the types of hospitals (charity, private, government).

7.4.3 Comparison with other studies

Previous studies have looked at the additional cost of SSI in Mexico [189], India [188] and Ghana [382]. These were all single centre studies with the India and Mexico studies only considering postoperative costs up to discharge. The additional cost of a patient with an SSI compared to a patient without an SSI varied considerably with it being 20.2% higher in the Ghana study [382] and 270.4% higher in the India study [188] (not reported in Mexico study [189]). The Ghana study looked at both direct and indirect costs up to 30 days post-surgery in

a teaching hospital. They found that the average additional cost of SSI was €210 in direct costs and €119 in indirect costs in a mix of Clean-Contaminated and Contaminated-Dirty patients. This compares with an average additional of €332 in direct costs and €160 in indirect cost in the present study (Contaminated-Dirty patients only). The prospective data collection in the current study was undertaken during the COVID-19 pandemic which may have affected the generalisability of the SSI incidence, inpatient and post-discharge resource use of surgical patients compared to studies undertaken in non-pandemic times.

7.4.4 Implications for practice

The host FALCON trial did not show benefit of the interventions in terms of SSI prevention [373]. However, SSI represents an additional financial burden in surgical patients. Investments in developing systems of safe surgery that reduces SSI will help reduce the financial burden of patients in low resource settings. Future research can use the present study estimates of the costs of SSI with effectiveness data to assess the cost-effectiveness of SSI prevention interventions in different country settings using decision analytic modelling to inform resource allocation decisions. Further, the joint parameter uncertainty of the decision analytic model, taken from the mean and SE of the model input estimates, can be assessed using probabilistic sensitivity analysis [383].

To help address retrospective data collection and lack of low income country limitations, a planned cost study within another multinational RCT assessing interventions to reduce SSI [384] includes prospective data on Clean-Contaminated cases and the inclusion of Rwanda to explore the costs of SSI in this income setting. Given the additional costs beyond postoperative 30-day period, future research should consider extending cost follow-up for patients with SSI in all countries to capture all relevant costs and consequences for these patients.

7.5 Conclusion

The costs associated with SSI were successfully collected across multiple LMIC countries within a surgical RCT setting. These values will be used in the updated model-based economic evaluation in Chapter 9. The next steps are to develop quality of life valuations associated with SSI for use in the updated model-based economic evaluation.

Chapter 8:

Eliciting health state valuations associated with SSI

8.1 Introduction

Chapter 7 reported the primary research estimating the additional cost of Surgical Site Infection (SSI) in a multicontinental Low- and Middle- Income Countries (LMIC) trial. To assess the value for money of an intervention aimed to reduce SSI within an LMIC model-based economic evaluation, the impact of SSI on quality of life is also needed. The impact of SSI on quality of life in utility values is required for the calculation of Quality Adjusted Life Years (QALYs) in the Cost per QALY approach. The systematic review undertaken in Chapter 4 detailed the utility weights associated with SSI in the literature and did not find any utility values from LMICs.

The impact of SSI on quality of life in terms of a disability weight is required for the calculation of Disability Adjusted Life Years (DALYs) in the Cost per DALY averted approach. However, there are no disability weights to reflect the health-related quality of life for individuals with an SSI and this prevents DALYs from being estimated.

To undertake economic analyses of global trials, both QALY and DALY health outcome measures would be of relevance. For utilities, no validated instruments measures such as the EQ-5D or the SF-6D to calculate utilities from patients were available in all the countries (Nigeria, Ghana, Mexico, India) where the cost sub-study was conducted (reported in Chapter 7). In addition, there are several challenges associated with the measurement of severity specific SSI utilities from indirect methods which has limited the current literature. In the systematic review reported in Chapter 4, the patient level studies using indirect methods all had a low SSI sample size and the highest sample size using such methods was 35 [164].

Low sample sizes of SSI can affect the reliability and precision of overall utility estimates, and this is before any consideration of subgroups by SSI severity. Measurement of utilities associated with SSI was also notable with respect to the challenges of measurement due to differing times of SSI onset and wound resolution, and the requirement to have multiple postoperative timepoints to capture this and the non-uniform impact of SSI throughout the duration of the infection.

This chapter presents the background, methodology and results of primary research undertaken to elicit Health State Valuations for SSIs. This primary research is undertaken in a UK context but appears to be the first to identify any valuations of quality of life or decrements to quality of life in any context for abdominal surgery patients with and without SSI, using established methods. These valuations are sought and derived in order to identify a ballpark level of quality of life decrement that can be used in future modelling studies. The appropriateness, including the strengths and limitations of their application to LMICs settings is considered in the discussion of this chapter.

To overcome the lack of validated patient utility measures and challenges with the measurement of severity specific SSI utilities from indirect methods, preferences on SSI health states were elicited from direct valuation techniques using a convenience sample of members of the general public. The aim was to generate Health State Valuations associated with SSI for use as outcome measures for the model-based economic evaluation in Chapter 9. The specific objectives are to:

1. Construct a set of vignettes to represent a range of health state descriptions of various degrees of severity for SSI;

2. Explore with the general public, the values attached to the different severity levels of SSI using direct methods of Health State Valuations via remote administration;
3. Assess if participants would view representative photos of the health state vignettes and whether the photos aligned with expectations of the health state based on the text descriptions.

The chapter is structured as follows: a theoretical overview on health state vignettes is described first to give context of choices for the empirical study methods section. The empirical study is referred to as the AVOCET Study (**A V**aluation **O**f postoperative **C**omplication h**E**alth s**T**ates). The health state utilities elicited are then presented along with a discussion on the study's contribution and how the research fits in the context of the existing literature. The chapter concludes with a summary and describes how the utility results will be used as parameter estimates in the decision model in Chapter 9.

8.1.1 Health state vignettes overview

To quantify the utilities and/or disability weights of SSI, the health state can be valued using direct or indirect approaches. As reported in Chapter 4, indirect health state valuations were the most common way to generate SSI utility decrements, with valuations of completed health status instruments by patients, or a proxy completion by someone else on their behalf, to provide an estimate of the patient's quality of life experience.

Generation of utility values based on direct measures of approach have long existed. This approach is typically most necessary when there is difficulty in accessing a sufficiently large sample size of patients , or pinpointing particular attributes within a treatment process or a health condition [385]. The direct method approach stipulates valuations be based on a purpose-built descriptions of a health state (vignettes) [88]. In health state valuation, vignettes are normally presented in text form although other modes that have been used instead as a

replacement or to supplement the text description includes use of video, images and medical device props [385]. Types of direct valuation approaches include Standard Gamble (SG), Time Trade Off (TTO) and the visual analogue scale (VAS) reported in Chapter 2. Outside of health state valuation, vignettes are used in different research areas such as the assessment of clinical decision making [386,387], societal attitudes [388,389], and as a means to collect of qualitative data in healthcare [390].

When constructing a vignette for the health state valuation, the starting point is understanding what should be described in the health state. Different definitions exist on what encapsulates health [391] with the most famous example included in the founding constitution of the World Health Organisation (WHO) in 1948. Its holistic interpretation defines health as "a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity" [392:pg1]. As the purpose of the health state valuation is to use the outcome measure to inform resource allocation decisions, the scope of the vignette content should be aligned to the interests of decision makers [88]. However, along with other aspects of vignette-based methodology there is no published guidelines on what salient content to include in the health state description for decision makers [385].

In contrast, guidance does exist on to the preferred indirect measures of utility measurement for cost-utility analysis by national Health Technology Assessment bodies. The EQ-5D was the favoured single indirect measure for cost-utility analysis in pharmacoeconomic guidelines for all thirteen countries that had a recommended single utility instrument measure [393]. Where multiple indirect measures were recommended, the EQ-5D was still one of the endorsed measures with French and Chilean guidelines also preferring the EQ-5D measure to be carried out alongside the HUI-3 and DALYs, respectively. Given the popularity of the EQ-5D as the utility outcome measure for decision makers, it can be inferred that the health

attributes are aligned to the interests of decision makers. The five domains concern pain, mobility, usual activities, pain/discomfort and anxiety/depression with three or five levels of responses depending on the version used.

The Gates Foundation recommend the use of DALYs for economic evaluations in LMICs [74]. Vignettes are used by the Global Burden of Disease authors in the Disability Weight component of the DALY. The vignettes are descriptions of one to three sentences focused on describing the main effects and symptoms associated with each health condition using consistent wording and accessible lay language. These descriptions were created as an iterative process in collaboration with experts who were part of the Global Burden of Disease Project [394]. Beyond the Global Burden of Disease Project, other studies have derived disability weights for different disease areas. Study approaches to developing lay health descriptions for disability weights include using content from multi-attribute utility instruments or condition-specific quality of life measures [395].

The sources of information for vignette content can come from the clinical literature, patient experiences, and expert opinion [385]. The goal of the vignette content is to accurately reflect the typical patient experience and ensure that it can be fully comprehended and understood by the participant completing the health state valuation exercise. Thus, the target audience needs to be kept in mind when synthesising the information from different clinical and non-clinical sources into a health state description.

8.1.2 The role of labelling vignettes

The decision on whether to attach a clinical name to a health state has possible implications on the valuation [396]. Naming or labelling the health state can provide meaningful context to the participant to better understand what they are valuing [88]. However, this can allow

preconceptions on disease or illnesses that do not form part of the vignette being introduced when valuing the health state [396]. Stigma against certain clinical conditions could provoke negative responses by the participant beyond the reported vignette symptoms. One example outside health state valuation was a study where, against the backdrop of the AIDS epidemic in the United States, mental health professionals rated the same clinical vignettes of hypothetical patients but with differences in the clinical condition label, either AIDS or Leukaemia [397]. Despite the symptoms being identical across the vignettes, the surveyed mental health professionals when considering the AIDS patient were statistically significantly less likely to accept them for treatment, refer them to another therapist, and make physical contact with them compared to those who rated the vignette of the leukaemia patient. Other findings included a greater unwillingness for the participant to socially interact with the patient with AIDS compared to the leukaemia patient, and that the AIDS patient was perceived as less deserving of sympathy than the Leukaemia patient. Another non-health state valuation example on the role of labelling vignettes was in the area of mental illness; a systematic review assessing the use of diagnostic labels for vignettes versus generic unlabelled vignettes uncovered an heterogenous effect of increasing, decreasing, or not having an measurable impact on participants' social responses on stigma towards people with mental illness [398].

There is mixed evidence on the impact of labelling on health state values for utilities across clinical conditions [396,399] with no identified studies assessing the issue for surgical conditions. Indeed, there was only one published health state valuation study in the area of surgery, which looked at postoperative SSI in orthopaedic surgery [236]. The authors did not provide justification for the unlabelled approach they took with the health states. For

disability weights in DALYs, the vignettes in the global burden of disease project studies were unlabelled.

Another aspect in using labelled SSI health states is undertaking a health state valuation study during a global pandemic, as in the case of this doctoral study. The stigma of COVID-19 [400] placed infectious diseases at the forefront of many people's minds. Health states labelled with infections may evoke fears of infectiousness to participants even if SSIs are not themselves contagious.

8.1.3 Vignette content perspective

For a text vignette, a choice is required on whether to take a first person, second person or third person perspective. A third person perspective allows distance between the participant and the vignette, whilst a first person or second person perspective draws the health state experiences closer to the participant. Little is written within health state valuation literature for guidance on the vignette's perspective. In healthcare qualitative studies, a distanced point of view can be especially useful for when the vignette contains sensitive or upsetting topics [390].

For the third person perspective, there is the option to incorporate gender to the described patient. Outside of health state valuation literature, there is mixed evidence on whether gendered vignettes could influence responses. For medical professionals, studies have indicated that General Practitioner treatment recommendations differ for male and female vignettes of patients with depressive symptoms [401], and patients with alcohol-related problems [402] while emergency department nurses gave priority for triaging male patients over female patients with identical myocardial infarction symptoms [403]. General Practitioner's certainty of heart failure diagnosis was higher for female vignettes [404]

whereas male vignettes had a higher diagnosis certainty of having Type 2 Diabetes [386], and clinicians ascribed different diagnostic labels by gender for patient vignettes with vulnerable narcissism symptomatology [405]. For non-medical professional respondents, gendered vignettes shaped perceptions of anorexia [406], mental health disorders [407], psychosis stigma [408], obesity stigma [388], and mobility problems [409]. Other studies found no effect on responses for gendered vignettes in areas such as health system responsiveness [410], managers' evaluations on the suitability of sickness absence [411], and nurse pain management decisions [387].

8.1.4 Vignette format

For health state valuations, the content of a text-based vignette is usually expressed through either a narrative or structured format [88]. A narrative format builds up a picture of the patient experience, and descriptions of the health state is normally conveyed using paragraphs. Structured vignettes aim to present information succinctly and efficiently using bullet points to describe key aspects of the health condition. They prioritize clarity and ease of understanding over storytelling in the narrative format. Matza et al. [385] recommends the structured format for vignettes in order to maximise comprehension. There are trade-offs in the length of the vignette and providing a salient description of the health state. An overly long description of a health state risks participants skipping parts of the description and excluding these elements in the valuation task, whilst short bullet points may not provide sufficient description of the health state and therefore participants may need to supplement the content gaps with their imagination of what they think the omitted aspects would be when valuing the health state.

The possible formats expand for non-text forms of vignettes. For example, production quality in video vignettes can affect the realism of the portrayal [412]. Likewise, the production choices of image or photo-based vignettes can influence what will be valued by the participant, although it would be difficult to encapsulate an entire health state within an image or series of images. Examples of non-text vignettes in health state valuations are almost exclusively in addition to text vignettes rather than as a standalone replacement [385]. The purpose of the supplementary material is to better clarify, and aid comprehension of, the health states described in the text vignettes. Consideration on the number of health states vignettes to be valued is a function of the length of the vignettes, duration allotted for interview, and valuation task(s). Complexity of the vignettes may reduce the number of health states valued with full consideration by the participant as the cognitive effort makes further valuations burdensome. These pitfalls can be mitigated using pilot work beforehand to test the feasibility of undergoing the health state valuation tasks within the intended conditions.

8.1.5 Vignette mode of delivery

There are variety of ways to administer a health valuation task using vignettes. It can be done with the aid of interviewer, or alone for self-completion. The task can be done online or offline. The benefit of an interviewer-led task for participants is that the interviewer(s) can be a resource for clarifying specifics relating to the valuation task, reducing the number of missing responses or illogical responses from participants unclear about the valuation task. A study comparing face-to-face interviewer administration versus online self-completion for a TTO task found that the pattern of responses differed by mode of administration [413]. Whether there would be a difference with an online interviewer versus offline interviewer was not examined in the study. A health state valuation which undertook both online and offline interviewer-led interviews (due to COVID-19 disruption) found similar TTO results for both

groups, although this was not an intended research question at the study's outset [414]. For social care quality of life preference elicitation using best–worst scaling, the Adult Social Care Outcomes Toolkit (ASCOT) service user measure gave similar results between the face-to-face interview and online survey groups after adjustment of sample characteristics [415].

The setting for which the valuation exercise is taking place is an important factor to consider. Offline face-to-face and self-completion health valuation exercises can be done in a controlled environment with a lack of distractions for the participant. Online face-to-face interviews, and online or postal self-completion run the risk of outside distractions or participants seeking to supplement vignettes with external reading. Funding considerations can restrict the sample size for either method which has implications on the reliability of the estimates. Online health valuation exercises may introduce selection bias of participants requiring to have a certain minimum standard of technological literacy which may affect the generalisability of the results [414]. The importance of this issue can depend on the target population whose preferences we want to determine for the health state valuations.

8.1.6 Who should be doing the valuations?

The normative question on who ought to be valuing health outcome measures is an unresolved methodological debate [416]. The answer is consequential as patients, the general population, and clinicians all provide different valuations for health state values [417]. A meta-analysis of indirect valuation studies found a small to moderate difference in health state valuations between patients and non-patients (non-patients here encompassing the general public, professionals, or proxies) [418]. Indeed, preferences across different aspects of health has been shown to diverge significantly by clinicians and patients [419].

There are many arguments that patients should be valuing health outcome measures [420]. One is that patients are better informed and knowledgeable about the health state versus the general public. In one study, general public focus groups in the UK participating in health state valuation exercises expressed difficulties of imagining what it would be like to live in the health states especially the vignettes with mental health problems [421]. A patient's higher level of comprehension from personal experiences of the health condition relative to the general public can be argued to provide a more realistic health state valuation as patients have first-hand knowledge on how the condition affects health. On the other hand, the greater knowledge can result in situations where patients value aspects drawing from their personal experiences that are unrelated to the vignette content and thus, a different health state is valued than what was offered. This is analogous to the problem of labelling health state vignettes.

Another argument for using patients compared to the general public is that patients are less prone to focussing effects. This is where participants are overly fixated on condition specific symptoms of the vignette at the expense of considering the broader health aspects presented in the vignette which can lead to higher utility decrement scores [422].

The role of patient adaptation with a health condition has been argued to be an advantage for health state valuation and a drawback to others. Patient adaptation is the tendency of a patient participant to value health states higher than non-patients as the negative symptoms in the vignettes are perceived to be partially or wholly surmountable over time [423]. This belief can arise due a patient's personal experiences with the health condition. An exception to the higher scoring vignettes by patients versus non patients occurred in a meta-analysis of TTO studies in the area of depression [424]. Anchoring vignettes for self-reported health has been suggested to reconcile patients valuations with non-patients [425,426]. Patient adaptation is

argued to being a positive feature as the adjustments to the health condition in the vignette are an important insight that the general public cannot adequately anticipate when valuing the health state [420].

Lastly, the patient perspective for valuation is important as any treatment change as result of the health state valuation exercise may directly affect them [420]. However, the chance to benefit from a change in treatment provision may lead to patients gaming the valuation and distorting their true health state value preferences. The importance of a patient's perspective in healthcare services is also recognised in the ideals of healthcare coproduction with healthcare providers and users interacting and working together to improve healthcare outcomes [427].

Those in favour of using the general public to value health outcomes offer arguments related to the advantage of a societal perspective informing resource allocation decisions, the absence of patient adaptation, the lack of vested interest in the valuation of outcomes, and measurement advantages in ease in recruitment relative to patients [420]. In practice, the role of valuation of indirect measures of utility measurements is undertaken by the general population [273,428–430].

Finally, there are a number of arguments for the use of clinician's preferences for healthcare valuation outcomes. They share the similar advantage to patients, with the medical knowledge of the health state condition, whilst not having personal experience of living in the health state. They also share a vested interest in shaping the health state valuations to promote more resources to their condition speciality. By the nature of a medical qualification, the valuation views would be coming from a highly educated population unrepresentative of the wider society.

Whichever group is used for the health state valuations, demographic characteristics of the sample can affect the valuations making representativeness of the target population (be it patients, general population, or clinicians) important for the results generalisability. The age of participants may influence health state valuation tasks where preferences for different aspects of health are valued differently by age groups. For example, older adults were more likely to value functional independence in daily living and social interaction more than younger adults, and older adults had weaker preferences on avoiding pain/discomfort and morbidities in comparison to younger adults [431]. Another study found that older participants compared to younger participants were willing to trade off a reduced life expectancy over mental health impairments and fatigue [432]. Other study findings included that men compared to women were less willing to trade off reduced life expectancy for quality of life morbidity, and that there were preference differences by ethnicity in areas such as depression, mobility, and sleep impairment [432].

8.2 Empirical Study Methods

8.2.1 Text vignette construction

For this study the health state vignettes were developed iteratively with input from surgeons; PhD supervisors; literature on the qualitative research of patients' quality of life with an SSI, and a patient representative. Different severity levels of SSI were considered to take account the diversity of experiences of the postoperative complication. Examples from the health state valuation literature were also used for vignette formatting and length [236,433,434].

The initial draft of health state vignettes started with EQ-5D-5L attributes for descriptions of the health states. All the attributes were used except for anxiety and depression which was purposely left for the participant to infer in the valuation exercises. Then the literature on the patient experiences on their quality of life with SSI was searched for salient aspects of experiencing an SSI. From a qualitative research systematic review [206], the patient experience of SSI impacted both physical health (sudden intense pain and wound discharge) and psychological health (emotional distress, feelings of the symptoms onset being dismissed by healthcare pre diagnosis). An SSI affected the ability to carry out everyday tasks [435] and was associated with mobility issues [205]. Given that no comparable group of surgical patients without SSI were interviewed, it is unclear from these studies how many of these negative consequences can be attributed solely to an SSI or from the experience of post-surgical recovery.

After updating the descriptions in consultation with PhD supervisors, two surgical trainees were presented with the health state vignettes and invited to give feedback on how well they felt SSI was represented. After further refinement, a patient representative with previous experience of major surgeries was approached to give a patient perspective on the vignettes. This was arranged via a Zoom call (22nd April 2021) and a subsequent email with feedback on the proposed health state descriptions. Refinements included the use of accessible language in the vignettes aligning with a 9-11 year old reading age in the UK [436], an additional severe health state with vacuum dressings, and alternative word suggestions for the scar description.

A conscious effort was made to ensure the vignettes were generic to make the SSI quality of life impact applicable to UK and LMIC contexts. This entailed avoiding explicit mentions of the UK post-operative patient pathways in terms of resource use (e.g., number of district nurse visits, length of stay) and focus more on the impact on the patient's emotional and physical

health. A structured format was taken with symptoms listed in bullet points. The health states were purposely unlabelled and in a third person perspective. Each vignette had a fifty year old person with no identified gender to avoid possible gender bias. The vignettes did not include probabilistic statements to avoid introducing participant interpretation variability in the perceived likely outcome with uncertain descriptions for the health state valuation [385]. As SSI is a temporary health state with fluctuations related to the onset, duration, and severity of symptoms, each health state vignette avoided any mention of duration so as to value the health state as is. This then opened up the possibility of later attaching duration and combining health states for different SSI health profiles separately. For example, a patient's series of health states could be: No SSI for 7 days; Mild SSI for 3 days; Moderate SSI for 8 days, then back to Mild SSI for 5 days, before returning to No SSI health state for the remainder of the month. This is an alternative to the path state method which combines descriptions across explicit periods of time and has had mixed success when compared to the QALY model [437].

Six health state vignettes of surgical patients with and without SSI were developed plus an additional full health state for the TTO valuation task. The names of each Health States A-F are shown below with label that corresponds to the health state in brackets:

- Health State A (No SSI)
- Health State B (Mild SSI)
- Health State C (Moderate SSI)
- Health State D (Severe SSI)
- Health State E (Severe SSI plus vacuum dressing)
- Health State F (Severe SSI plus bowel coming through)

The labels in brackets were not shown in the interviews, only Health State A, Health State B etc. More informative labels were initially considered substituting the term infection for problem (for example, “No wound problem”, “Mild wound problem”, “Moderate wound problem”). However, a potential issue arose with these labels that was identified when piloting the questionnaires. The informative labels of Mild, Moderate, and Severe could influence responses in the EQ-5D-5L if participants perceived the label as being applicable across all the health domains. For example, moderate wound problems may indicate moderate problems with mobility, self-care, usual activities etc. Thus, neutral labels were applied to each health state to avoid this issue.

8.2.2 Health state photographs

For the six health state vignettes of surgical patients, the empirical study explored the use of photographs as an additional descriptor. To find photographs to accompany the health states, a pragmatic search of the literature was undertaken using variations of the following search terms: “photograph”, “postoperative” and “wound infection”. This included journal articles (case reports, full text, and letters) with wound infection photographs in a main text figure(s) or within the supplementary material, stock image websites, internet search engine image searches, and dissertations or theses. Citation pearl searching from sourced journal articles was undertaken to identify additional relevant material [438]. The photograph was required to include a surgical incision located at the abdomen to align with the text-based descriptions. Photographs needed to be of sufficient high quality to be reproduced for the empirical study to be clearly distinguishable after scaling where applicable. A variety of different skin tones were sought to reflect the diversity of surgical patients.

The copyright of potentially eligible photographs was assessed to ensure that they could be reused for the empirical study. Where it was specified that permission was needed for reproduction of the photographs or there was ambiguity in the article, permission was sought from the journal and authors for access rights. Using the sample of potential images obtained from the search, the eligibility of each image to a health state was assessed by a clinician and images were then attributed to their most suitable health state vignette. For consistency, three photographs were used per health state vignette.

8.2.3 Valuation approach

A TTO, EQ-5D-5L, and VAS techniques were chosen as the direct valuation approaches. The TTO was chosen over the standard gamble due to its more frequent use in direct valuation studies [385], its comparability advantage to the EQ-5D-5L due to its use in preference elicitation for EQ-5D-5L value sets [422], and possible accuracy advantages over standard gamble [439]. The EQ-5D-5L was chosen due to its convenience, conciseness, and popularity as a recommended utility measurement for health technology assessments. The EQ-5D-5L also included the VAS which participants also completed. After initial piloting with four health economics colleagues, a 24-month time horizon with monthly increments was chosen for the TTO scenarios. This was preferred as it provided 24 possible levels in integer format, and longer time horizons (5 years, 10 years) was felt to be too long to reside in the described health states, whereas a shorter time horizon of 1 year was associated with a reluctance to trade off any life expectancy. A two-stage chained TTO [91] was initially considered as SSI is a temporary health state rather than a chronic health state. Reasons for using a two-stage chained TTO for valuations of temporary health states include that the temporary health state is a treatment process (e.g. chemotherapy for cancer), or that the health state assessed was

associated with mild impairments of health related quality of life [92]. Ultimately a conventional TTO was selected as many of the motivations for using a two-stage chained TTO were less applicable to SSI health states. In addition, the conventional TTO method had been successfully used previously in another direct valuation study of SSI [236].

8.2.4 Redcap survey platform

The empirical study used the online Redcap (Research Electronic Data Capture) survey platform. Redcap is a web based application used for online research data collection [440,441]. Redcap was used for the FALCON trial and the KIWI sub study (see Chapter 7) along with other trials in the Birmingham Global Surgery Unit portfolio. The Global Surgery Unit's Redcap projects were held on University of Birmingham servers. Redcap allowed for real-time data entry and automated export of selected data to common statistical support packages such as STATA. The project was registered at the EuroQol research foundation website and was granted permission to use the Redcap version of EQ-5D-5L [442]. The VAS used a vertical slider to depict the possible health score responses with a box underneath to indict the level of health score chosen. Categorical variables with single answers used radio buttons as response options. For the current age in years demographic variable, numerical integer values were only allowed to be entered.

The Participant Information Sheet, Consent Form and Main Questionnaire were all created in Redcap. Appendix A8.1 displays a word copy version of the Participant Information Sheet. A survey queue allowed a flow of forms and had inbuilt features such as the required completion of all the compulsory consent form items before the main interview questionnaire could begin.

8.2.5 Interview structure

The arrival of COVID-19 made face to face sessions challenging. Instead, Zoom teleconferencing software was used for remote administration of the consent form and questionnaire. The recent widespread acceptance of teleconferencing software during the pandemic made the mode of administration resilient in the face of changing regional lockdown measures. Interviews were done on a 1:1 basis with interviewer and interviewee. The interviewer shared their screen with the online questionnaire and the participant verbally indicated the answers to the questions which the interviewer then inputted their responses. Interviews had a time slot of one hour allotted to give participants time to do the tasks without feeling time pressure. Participants had the option of doing the interview without the camera on while the interviewer had the video on during the zoom interview unless there were bandwidth issues.

The main questionnaire was split into four sections and followed a similar structure to previous direct valuation studies [433,434]. The first section of the main questionnaire recorded information on a participant's demographics. Participants were asked their age, identified gender, whether the gender they identify with was the same as the sex they had registered at birth, their main activity, their ethnic group, level of education, and history of having surgery. The categories on ethnic group asked were taken from the UK census high-level ethnic groups [443]. The second section introduced the EQ-5D-5L and VAS. To familiarise themselves with the instruments, participants were first asked to complete them with their own health before the vignettes were introduced. The vignette and the instrument were presented side by side on the same screen. Health States were presented in chronological order starting with Health State A and ending with Health State F.

Section 3 of the questionnaire contained the TTO exercises. A summary of the valuation task instructions was provided, and the interviewer was at hand to answer any clarifying questions that the participant had. To present the TTO in Redcap, a slider similar to the VAS was initially considered. However, only the minimum, maximum and midpoint values were able to be labelled using Redcap slider which made the task more visually challenging for the participant. Instead, a table of values were used with each time period labelled so participants could indicate their indifference value and where above and below their health state preferences [433]. Each Health State was compared to a "Full Health State" for the TTO exercise (see Figure 8.1).

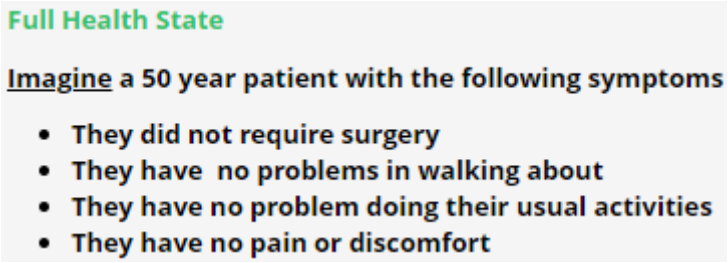


Figure 8.1 Full Health State

The last section was an optional section for participants to look at health state photographs with the vignettes. For each Health state (A-F), they were asked if they wished to look at photographs of typical patients in the described Health state. As the photographs were optional, a branching logic was used to ensure that the photographs were hidden unless the participant agreed to see them. For those who wanted to look at the images, they were asked based on the photographs, whether the health state looked as expected, looks worse than expected, or the health state looks better than expected. A "piping" Redcap feature was also used which allowed previous participant answers from the EQ-5D-5L, and the TTO to be

reshown here for context (the piping feature did not function for the VAS responses). As this last section was optional, the participants did not undergo the valuation exercises again to prevent gaming from stating not to view the photographs to finish the interview earlier rather than not wishing to view the photographs in the first place.

At the start of the interview, it was emphasised that participation was voluntary, and that the data generated were anonymous. It was made clear that participants could withdraw from the study within two weeks of the interview completion and that their data would also be withdrawn from the study. This information was included in the participant information sheet and consent form.

8.2.6 Interviewers recruitment and selection

To share the workload of the interviews, a job description was created at the University of Birmingham casual worker platform Worklink. Four students were recruited as interviewers. They were: (1) a first year Department of Economics PhD student; (2) a final Year MSci Biochemistry student; (3) a registered nurse enrolled in a MSc in Clinical Oncology; and (4) a MSc Political Psychology of International Relations student. Worklink interviewer training was done via Zoom on 16th February 2022. Worklink interviewers had access to the survey link only and could not access the Redcap project interface, nor did they possess editing or viewing rights to completed records.

8.2.7 Sample

While anyone in the UK adult general population who could had access to and operate Zoom software was eligible to take part, the advertising was targeted at a convenience sample of undergraduate and postgraduate students at the University of Birmingham in the UK. As the valuation exercises are cognitively challenging, an educated sample group had the advantage

of minimising participant difficulty with the tasks versus the general population. A target sample size of 100 participants was chosen for pragmatic reasons given time and financial constraints.

Advertisement of the study included participant information sheet printouts at notice boards across the university campus and emails to programme administrators at the undergraduate and postgraduate level. A prior warning was given in the participant information sheet form informing potential participants that both the text based and photograph-based health state descriptions are graphic in nature. The email to the programme administrators included both a document of the participant information sheet form plus an online viewable version that was accessed via a persistent URL link. This was created using a separate Redcap project and availed of a custom named URL ("https://redcap.link/AVOCET_PIS") which redirected to a Redcap website. A student academic experience intern at the University Student Services made contact and with permission, the study recruitment was posted as "Instagram stories" from the School of Sport, Exercise and Rehabilitation Sciences account and the School of Geography, Earth, and Environmental Sciences account (see Figure 8.2). Emails to different programme administered were staggered to avoid demand bottlenecks in the opening weeks of recruitment.

Participant data underwent pseudo-anonymization through the assignment of an identification code, and the interviewer retained a key to identify an individual's data in case of participant withdrawal or if the participant expressed a desire to be informed about the published summary of results on the optional section of the consent form. For participants who completed the interview, their email address was used for the purpose of emailing the voucher.

Online shopping vouchers (£15) were emailed to the participants after the completion of the interview. Participants who chose to withdraw during the research interview were not compensated. Participants who chose to withdraw after the research interview did not lose the financial compensation. It was not expected for there to be any unacceptable psychological discomfort from study participation. However, if such discomfort were to arise, the interviewer would pause the session and inquire if the participant wished to proceed. Participants had the option to discontinue the interview without providing a specific reason. Ethical approval (ERN_21-1542) was granted by the University of Birmingham on the 15th November 2021. Funding for the empirical work was provided by a University of Birmingham preliminary data award and a discretionary NIHR chair funding budget.



Figure 8.2 Screenshot of Health Valuation Study Instagram story

8.2.8 Analysis

The analysis was undertaken in STATA 17[444]. Demographic details were shown first with information on the participant's self-rated health using the EQ-5D-5L and the VAS. A crosswalk algorithm was used to convert the EQ-5D-5L values to utilities [445]. The VAS scores were divided by one hundred for comparability of results. Results were presented separately by valuation technique and across the different health state vignettes. Paired t-tests were used to assess statistically significant mean differences between the SSI decrements within a valuation technique. Paired t-tests were also used to assess a given SSI decrements (e.g. mild SSI disutility) across valuation techniques. Linear correlation across techniques was assessed using the Pearson's Product Moment Correlation Coefficient. The categories to denote the strength of the association between the valuation techniques were: "no relationship" (Correlation Coefficient <0.2), "weak relationship" (Correlation Coefficient: 0.2-0.5), "moderate relationship" (Correlation Coefficient: 0.5-0.7), and "strong relationship" (Correlation Coefficient: >0.7).

Logical inconsistencies on the preferences towards more severe Health States was assessed within each technique. This was judged in the following cases: (1) for any of the SSI Health States (Health States B-F) being valued higher than the No SSI health state (Health State A); (2) for the Mild SSI health state (Health State B) to be valued higher than the other SSI health states (Health States C-F); (3) for the Moderate SSI health state (Health State C) to be valued higher than the other more severe SSI health states (Health States D-F); (4) for the Moderate SSI health state (Health State C) to be valued higher than the other more severe SSI health states (Health States D-F); (5) for the Severe Health State (Health State D) to be valued higher than the Severe Health State plus bowel coming through (Health State F). The exclusion of any illogical responses was assessed in a sensitivity analysis.

Across the three techniques, associations between the demographics and the utility scores per health state were examined using a Generalised Linear Model. As in Chapter 6, this approach was taken because of the flexibility in selecting different distribution types and link functions to best match the utility data distribution [319]. Models were fitted using maximum likelihood estimation. Age group (Under 25 years, 25 years and above), Gender, Education Status, prior surgical experience, self-EQ-5D-5L score, and ethnicity were used as covariates. These were selected as age [446–448], education [449], gender[450], ethnicity [451], prior experience of health condition [452], and the participant's health status[453] were significant predictors of health state valuations in the literature.

Selection of the family distribution was made using the modified Park test [122,335]. The coefficient from modified Parks test indicates the distribution (Gamma, Gaussian, Poisson, Inverse Gaussian) that best reflects the mean and variance relationship. Where the modified Park test resulted in a negative coefficient >-0.5, the data was transformed into utility decrements and retested [122,335]. Once the preferred family distribution was selected, link power functions from the range of -2 to 2 were tested in 0.1 increments using the Pearson's correlation test, the Pregibon link test and the Modified Hosmer and Lemeshow test [122,336]. For all link functions that had non-significant p-values (greater than 0.05) from the goodness of fit tests, the best fitting link function was chosen on the basis of the lowest Akaike information criterion score. Where there were convergence issues for all the tested link functions of a preferred family distribution, the second-best family distribution was selected. Huber-White sandwich estimators were used to generate robust standard errors to account for variance heterogeneity [339].

The proportion of participants willing to see the health state vignettes photographs was then presented, along with the percentage of participants who, in light of the photographs, thought

that the health state was better than expected, as expected, or worse than expected. Subgroup analysis explored differences across age groups, gender, surgical experiences, and if interview was conducted by a Worklink interviewer. In the regression and subgroup analyses, ethnicity categories were collapsed into the "other ethnic group" where there were fewer than five participants in the category. For other variables, categories with fewer than five participants were excluded in the regression and subgroup analyses for anonymity purposes.

8.2.9 Health state vignettes

The health state vignettes developed for the valuations are shown in Figures 8.3-8.7. The accompanying health state photographs utilised in the optional last section of the interview are displayed in Appendix A8.2.

Health State A

Imagine a 50 year patient with the following symptoms

- ☐ They had abdominal surgery with a cut up and down the tummy. The operation goes well.
- ☐ They need assistance with walking
- ☐ They have some problems with usual activities
- ☐ They have occasional pain
- ☐ The scar will heal quite neatly (a straight line)

Figure 8.3 Health State A description

Health State B

Imagine a 50 year patient with the following symptoms

- ☐ They had abdominal surgery with a cut up and down the tummy. The operation goes well.
- ☐ They need assistance with walking
- ☐ They have some problems with usual activities
- ☐ They develop a wound problem. There is redness and swelling on a small area around the skin surface where the surgery occurred. This area is hot to the touch
- ☐ They will have occasional pain to begin with. It becomes more painful at the site of the infection
- ☐ A small amount of pus needs to be drained from the wound, leaving a small hole in the wound
- ☐ The wound discharges pus which stains clothing and bedding
- ☐ They require their wound dressings changed every day
- ☐ The scar will heal quite neatly (a straight line)

Figure 8.4 Health State B description

Health State C

Imagine a 50 year patient with the following symptoms

- ☐ They had abdominal surgery with a cut up and down the tummy. The operation goes well.
- ☐ They need assistance with walking
- ☐ They develop a wound problem. There is redness and swelling on a large area of the skin surface where the surgery occurred. This area is hot to the touch.
- ☐ They feel generally unwell and they have a fever.
- ☐ They will have occasional pain to begin with. They have more severe pain at the site of the infection (along most of the wound)
- ☐ They have more problems with usual activities
- ☐ A large amount of pus needs to be drained from the wound, leaving a large hole in the wound
- ☐ The wound discharges pus which stains clothing and bedding
- ☐ The pus is foul smelling
- ☐ They require their wound dressings changed every day
- ☐ Their scar will be raised and heal slightly wider than normal (an island of scar tissue)

Figure 8.5 Health State C description

Health State D

Imagine a 50 year patient with the following symptoms

- ☐ They had abdominal surgery with a cut up and down the tummy. The operation goes well.
- ☐ They need assistance with walking
- ☐ They develop a wound problem. To begin with, there is redness and swelling on a large area of the skin surface where the surgery occurred. This area is hot to the touch.
- ☐ The skin edges burst open from top to bottom and continuously drain foul-smelling pus
- ☐ They have severe pain all across the tummy and will be bed bound (have difficulty getting out of bed)
- ☐ They cannot do their usual activities
- ☐ The wound discharges pus which stains clothing and bedding
- ☐ They require their wound dressings changed every day
- ☐ Their scar will be raised and heal wider than normal (an island of scar tissue)

Figure 8.6 Health State D description

Health State E

Imagine a 50 year patient with the following symptoms

- ☐ They had abdominal surgery with a cut up and down the tummy. The operation goes well.
- ☐ They need assistance with walking
- ☐ They develop a wound problem. To begin with, there is redness and swelling on a large area of the skin surface where the surgery occurred. This area is hot to the touch.
- ☐ The skin edges burst open from top to bottom and continuously drain foul-smelling pus
- ☐ They have severe pain all across the tummy and will be bed bound (have difficulty getting out of bed)
- ☐ They cannot do their usual activities
- ☐ The wound discharges pus which stains clothing and bedding
- ☐ They require their wound dressings changed every day
- ☐ They need a foam dressing that is placed directly on the wound that is then sealed using adhesive film and vacuum pump (vacuum dressing) to help the wound heal
- ☐ Their scar will be raised and heal wider than normal (an island of scar tissue)

Figure 8.7 Health State E description

Health State F

Imagine a 50 year patient with the following symptoms

- ☐ They had abdominal surgery with a cut up and down the tummy. The operation goes well.
- ☐ They need assistance with walking
- ☐ They develop a wound problem. To begin with, there is redness and swelling on a large area of the skin surface where the surgery occurred. This area is hot to the touch.
- ☐ The skin edges burst open from top to bottom and continuously drain foul-smelling pus
- ☐ The tough edges of the bottom of the wound come apart, allowing the bowel to come through
- ☐ They have severe pain all across the tummy and will be bed bound (have difficulty getting out of bed)
- ☐ They cannot do their usual activities
- ☐ The wound discharges pus which stains clothing and bedding
- ☐ They require their wound dressings changed every day
- ☐ Their scar will be raised and heal wider than normal (an island of scar tissue)

Figure 8.8 Health State F description

8.3 Results

8.3.1 Sample characteristics

The interviews took place from February 2022 to May 2022. Figure 8.9 provides a study recruitment flowchart. One participant did not complete the interview due to a lecture clash. Participant demographic details are shown in Table 8.1. Participants mainly identified as female (75%), and were young, with a median age of 21 years old. Nearly all participants' identified with their sex registered at birth (97%). The majority of the participants were students (89%) and all were educated to either an undergraduate degree level (64%) or a postgraduate degree level (36%). White (58%) was the commonest reported ethnic group followed by Asian or Asian British (22%), Black/ African / Caribbean /Black British (10%), Mixed/ multiple ethnic groups (6%), and other ethnic group (4%). Less than half of participants had any experience of surgery (45%) and the mean duration of interview was 28 minutes. No participants withdrew their data following their interview.

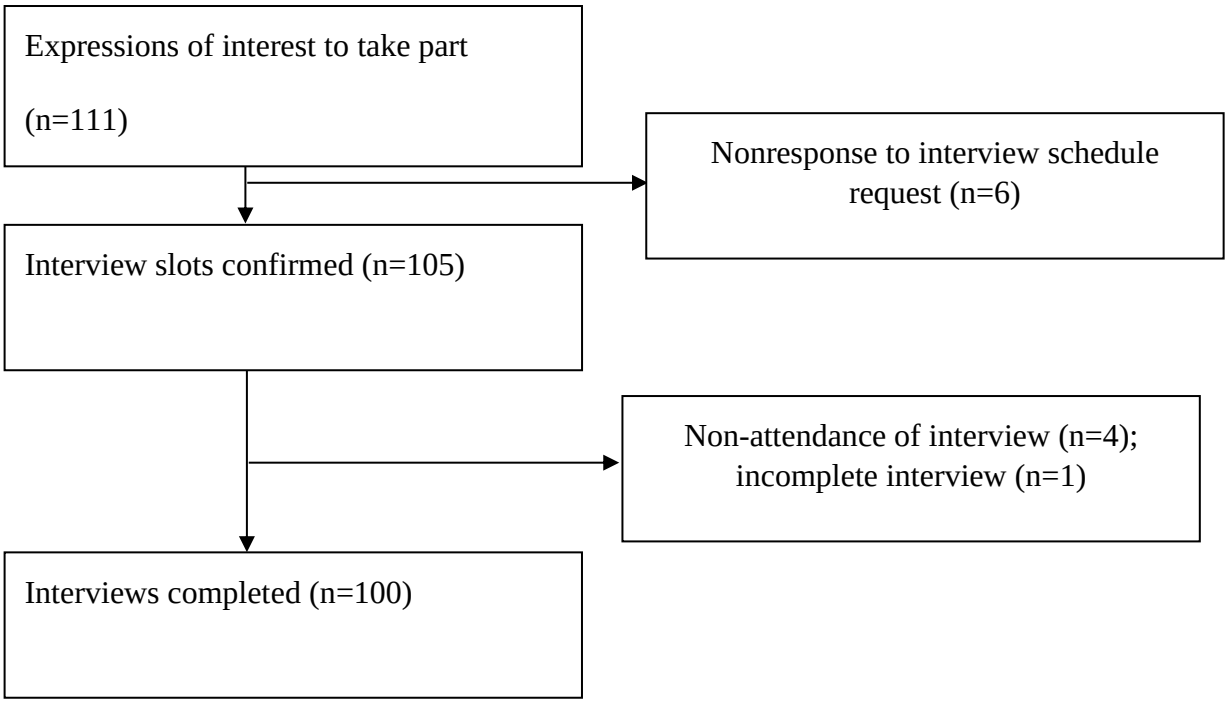


Figure 8.9 Flowchart of AVOCET participant recruitment

Table 8.1 Participant characteristics (n=100)

Variable	Value
Current age in years	
Mean	24.11
Median	21
Standard deviation	7.59
Min	18
Max	61
25% Percentile	20
75% Percentile	26
What gender do you identify with?	
Female	75%
Male	24%
Other	1%
Identified with gender same as sex registered at birth	
Yes	97%
No	1%
Prefer not to say	2%
Ethnic group	
White	58%
Asian or Asian British	22%
Black/African/Caribbean/Black British	10%
Mixed/ multiple ethnic groups	6%
Other ethnic group	4%
Prefer not to say	0%
Which of the following best describes main activity	
Student	89%
In full or part-time employment or self-employment	10%
Seeking work	1%
Retired	0%
Carer/volunteer	0%
Prefer not to say	0%

Variable	Value
Prior Experience of having Surgery	
No	55%
Yes	45%
Highest level of education (including studying for)	
Postgraduate degree	36%
Undergraduate degree	64%
Certificate or diploma	0%
Secondary school	0%
Primary school	0%
Prefer not to say	0%
Duration of interview in minutes	
Mean	28.00
Median	26.6
Standard deviation	7.03
Min	17.28
Max	54.62
25% Percentile	18.17
75% Percentile	40.55

8.3.2 Own Health EQ-5D-5L and Visual Analogue Scale

In terms of their own health, many participants reported no problems across the EQ-5D-5L domains (Figure 8.10). For self-care, there were no reported problems. and no one selected the worst response options across the five domains in relation to their own health. Most problems were reported in the Anxiety/Depression domain with 30, 8, and 4 participants stating slight problems, moderate problems, and severe problems, respectively. Table 8.2 contains the EQ-5D-5L and VAS scores for participants' own health and the health state vignettes. EQ-5D-5L mean scores (0.886) were higher than the mean Visual Analogue Scale Scores (0.828) for own health. In both instruments, some participants reported the highest possible score (i.e., 1).

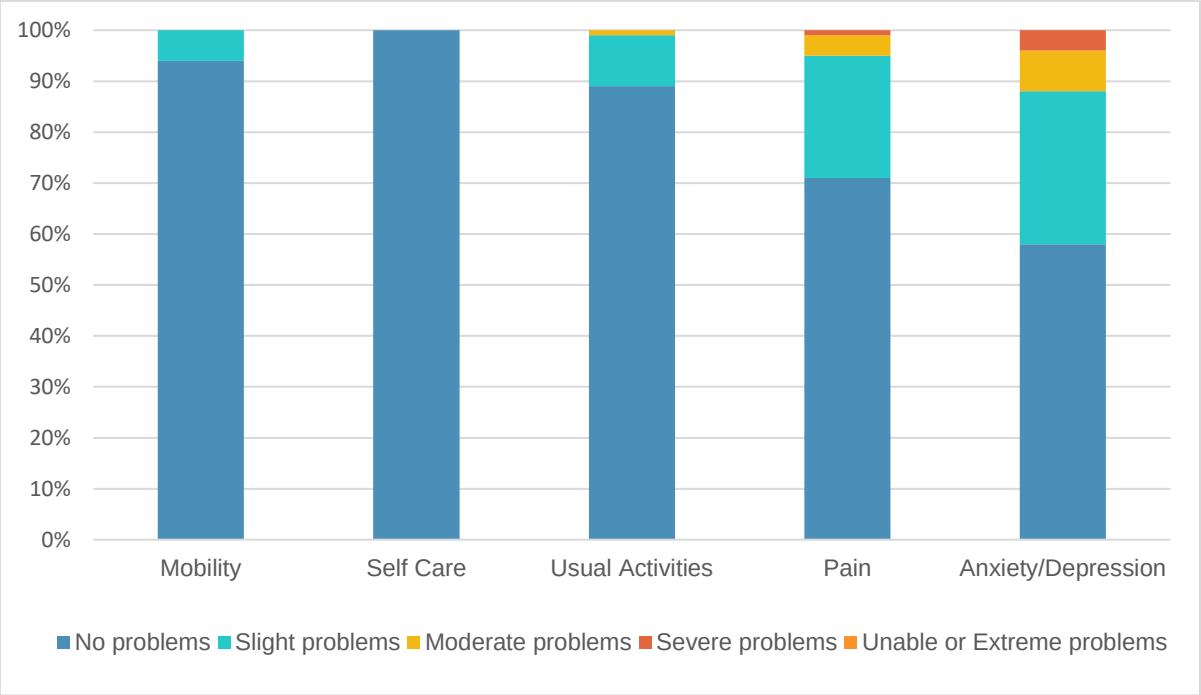


Figure 8.10 Self Health EQ-5D-5L response distributions by domain

The EQ-5D-5L response distributions by health state vignettes are shown in Appendix A8.3. For the health state vignettes, there were lower mean EQ-5D-5L scores as the severity of SSI health states increased and all SSI health states were lower compared to the health state without SSI. Furthermore, Health States D-F reported negative mean EQ-5D-5L scores. The pattern of increased SSI severity and lower score persisted in the VAS (see Table 8.3). As the VAS is bounded to zero, it was not possible to have negative scores. For each health state vignette, the VAS had a higher mean score compared to the mean EQ-5D-5L responses.

Table 8.2 EQ-5D-5L scores

Variable	Mean	Standard Deviation	25% Percentile	Median	75% Percentile	Standard Error	Min	Max
Own Health	0.886	0.124	0.837	0.879	1	0.012	0.451	1
Health State A (No SSI)	0.542	0.116	0.538	0.557	0.592	0.012	-0.106	0.735
Health State B (Mild SSI)	0.32	0.235	0.165	0.338	0.528	0.024	-0.352	0.71
Health State C (Moderate SSI)	0.105	0.241	0.036	0.155	-0.0325	0.024	-0.594	0.56
Health State D (Severe SSI)	-0.236	0.249	-0.491	-0.257	-0.033	0.025	-0.594	0.249
Health State E (Severe SSI plus vacuum dressing)	-0.279	0.237	-0.51	-0.283	-0.113	0.024	-0.594	0.231
Health State F (Severe SSI plus bowel coming through)	-0.392	0.244	-0.594	-0.257	-0.269	0.024	-0.594	0.516

Table 8.3 Visual analogue scale scores

Variable	Mean	Standard Deviation	25% Percentile	Median	75% Percentile	Standard Error	Min	Max
Own Health	0.828	0.120	0.77	0.85	0.9	0.012	0.4	1
Health State A (No SSI)	0.574	0.123	0.5	0.6	0.65	0.012	0.3	0.8
Health State B (Mild SSI)	0.437	0.134	0.35	0.45	0.5	0.013	0.15	0.78
Health State C (Moderate SSI)	0.347	0.130	0.25	0.35	0.425	0.013	0.1	0.65
Health State D (Severe SSI)	0.259	0.126	0.15	0.25	0.35	0.013	0.05	0.5
Health State E (Severe SSI plus vacuum dressing)	0.229	0.123	0.10	0.245	0.30	0.012	0	0.5
Health State F (Severe SSI plus bowel coming through)	0.168	0.119	0.05	0.15	0.25	0.012	0	0.5

8.3.3 Time Trade Off

The TTO utility scores are presented in Table 8.4. More severe SSI health states were associated with consistently lower utility score with a ~0.5 difference between the No SSI health state and the Severe SSI plus bowel coming through health state. As with the VAS, it was not possible to score below zero in valuing health states. Health State F had a mean value of 0.239 with scores ranging from 0 to 0.833. Zero meant that participant(s) considered 24 months in Health State F equivalent to zero months in Full Health (i.e., death). For Health State A and Health State B, there were instances of participants refusing to trade-off length of life for improved quality of life with resulting maximum scores of 1. Conversely, there were participants willing to trade-off many months to avoid the No SSI and Mild SSI health states (2 months). A participant justified willing to trade off many months for reasons of not wanting to be a burden on their family and friends. TTO utility scores were higher than EQ-5D-5L utility scores and Visual Analogue Scale Scores.

The worst possible scores for each instrument were given to Health State E by EQ-5D-5L, VAS, and Health State F by all instruments. None of the Health States Vignettes were assigned the best possible scores by any of the instruments.

Table 8.4 Time trade off scores

Variable	Mean	Standard Deviation	25% Percentile	Median	75% Percentile	Standard Error	Min	Max
Health State A (No SSI)	0.733	0.203	0.625	0.75	0.917	0.020	0.083	1
Health State B (Mild SSI)	0.615	0.204	0.5	0.625	0.75	0.020	0.083	1
Health State C (Moderate SSI)	0.501	0.195	0.396	0.5	0.625	0.020	0.083	0.958
Health State D (Severe SSI)	0.402	0.189	0.25	0.417	0.5	0.019	0.042	0.917
Health State E (Severe SSI plus vacuum dressing)	0.348	0.189	0.208	0.333	0.4375	0.019	0.042	0.875
Health State F (Severe SSI plus bowel coming through)	0.239	0.172	0.125	0.208	0.333	0.017	0	0.833

8.3.4 Paired t-test and correlation results

The results of the paired t-test comparing valued health state utility scores by technique is presented in Table 8.5. The null hypothesis is that the mean health utility scores between two techniques are the same while the alternate hypothesis is that mean health utility scores between two techniques are different. All the health states had significantly different means by valuation technique at a 5% significance threshold. At a 1% significance threshold, the mean difference in EQ-5D-5L value and Visual Analogue Scores for Health State A were not statistically different.

The Pearson correlation coefficients of the pairwise comparison of health state valuations by technique is shown in Table 8.6 with associated P-values. At the 5% level, the Correlation Coefficient of EQ-5D-5L and VAS were statistically significant with weak to moderate positive correlation across all the Health States. At the 5% level, the Correlation Coefficient of TTO and VAS were statistically significant across all Health States albeit with generally weaker positive correlation than the Correlation Coefficient EQ-5D-5L and VAS. For the Correlation Coefficient of EQ-5D-5L and Time-Trade Off, only Health State F has a statistically significant correlation at the 5% level.

Table 8.5 Paired t-test for equality of the means by technique

Variable	Difference	P-value	95% Confidence Interval
Own Health EQ-5D-5L versus VAS	-0.0583	0.0000	-0.0823 to -0.0345
Health State A: EQ-5D-5L versus VAS	0.0323	0.0193	0.0054 to 0.0592
Health State A: EQ-5D-5L versus TTO	0.1905	0.0000	0.1465 to 0.2340
Health State A: TTO versus VAS	0.1582	0.0000	0.1168 to 0.1996
Health State B: EQ-5D-5L versus VAS	0.1170	0.0000	0.0765 to 0.1574
Health State B: EQ-5D-5L versus TTO	0.2942	0.0000	0.2354 to 0.3529
Health State B: TTO versus VAS	0.1772	0.0000	0.1352 to 0.2192
Health State C: EQ-5D-5L versus VAS	0.2425	0.0000	0.2026 to 0.2824
Health State C: EQ-5D-5L versus TTO	0.3964	0.0000	0.3375 to 0.4553
Health State C: TTO versus VAS	0.1539	0.0000	0.1124 to 0.1953
Health State D: EQ-5D-5L versus VAS	0.4954	0.0000	0.4538 to 0.5370
Health State D: EQ-5D-5L versus TTO	0.6384	0.0000	0.5811 to 0.6957
Health State D: TTO versus VAS	0.1430	0.0000	0.1073 to 0.1787
Health State E: EQ-5D-5L versus VAS	0.5074	0.0000	0.4650 to 0.5497
Health State E: EQ-5D-5L versus TTO	0.6263	0.0000	0.5717 to 0.6808
Health State E: TTO versus VAS	0.1189	0.0000	0.0840 to 0.1538
Health State F: EQ-5D-5L versus VAS	0.5604	0.0000	0.5195 to 0.6013
Health State F: EQ-5D-5L versus TTO	0.6311	0.0000	0.5778 to 0.6845
Health State F: TTO versus VAS	0.0708	0.0001	0.0361 to 0.1054
TTO: Time Trade Off; VAS: Visual Analogue Scale			

Table 8.6 Pairwise correlations of valuation techniques

EQ-5D-5L correlation with Visual Analogue Scale						
	Health State A	Health State B	Health State C	Health State D	Health State E	Health State F
Correlation Coefficient	0.3531	0.5051	0.5511	0.5423	0.4447	0.5349
P-value	0.0003	0	0	0	0	0
EQ-5D-5L correlation with Time Trade Off						
	Health State A	Health State B	Health State C	Health State D	Health State E	Health State F
Correlation Coefficient	0.1155	0.0965	0.085	0.1523	0.1846	0.1985
P-value	0.2523	0.3395	0.4005	0.1303	0.066	0.0477
Visual Analogue Scale correlation with Time Trade Off						
	Health State A	Health State B	Health State C	Health State D	Health State E	Health State F
Correlation Coefficient	0.2501	0.2688	0.2247	0.4004	0.4295	0.3235
P-value	0.0121	0.0068	0.0246	0	0	0.001

8.3.5 Health state disutilities

To calculate the impact of the description of the SSI health states on valuations, the health state with no SSI was subtracted from each SSI health state to obtain disutilities (Table 8.7). The mean SSI disutilities were the largest across all Health States with the EQ-5D-5L. The VAS and TTO disutilities are broadly similar for Mild, Moderate, and Severe SSIs but then diverge for the Severe SSI plus vacuum dressing disutility and Severe SSI plus bowel health states. The disutilities obtained by the TTO were larger than VAS for the Severe SSI plus vacuum dressing disutility and Severe SSI plus bowel health states.

Table 8.7 Disutilities by health state valuation approach

Variable	**Mean**	**Standard deviation**	**Min**	**Max**
EQ-5D-5L disutilities				
Mild SSI disutility (Health State B- Health State A)	-0.222	0.184	-0.816	0
Moderate SSI disutility (Health State C- Health State A)	-0.437	0.204	-1.127	-0.014
Severe SSI disutility (Health State D- Health State A)	-0.778	0.239	-1.167	-0.163
Severe SSI plus vacuum dressing disutility (Health State E- Health State A)	-0.821	0.24	-1.2	-0.163
Severe SSI plus bowel disutility (Health State F- Health State A)	-0.934	0.254	-1.297	-0.044
EQ-5D Visual Analogue Scale				
Mild SSI disutility (Health State B- Health State A)	-0.137	0.067	-0.35	-0.02

Variable	Mean	Standard deviation	Min	Max
Moderate SSI disutility (Health State C- Health State A)	-0.227	0.082	-0.5	-0.1
Severe SSI disutility (Health State D- Health State A)	-0.315	0.099	-0.55	-0.15
Severe SSI plus vacuum dressing disutility (Health State E- Health State A)	-0.346	0.113	-0.65	-0.1
Severe SSI plus bowel disutility (Health State F- Health State A)	-0.406	0.126	-0.7	-0.1
Time Trade Off				
Mild SSI disutility (Health State B- Health State A)	-0.118	0.098	-0.5	0.125
Moderate SSI disutility (Health State C- Health State A)	-0.231	0.159	-0.792	0.208
Severe SSI disutility (Health State D- Health State A)	-0.33	0.182	-0.792	0.042
Severe SSI plus vacuum dressing disutility (Health State E- Health State A)	-0.385	0.202	-0.917	0.125
Severe SSI plus bowel disutility (Health State F- Health State A)	-0.493	0.213	-0.958	0.042

Paired t-tests of disutilities of health states by technique (Appendix Table A8.1) confirm statistically significant differences in mean disutilities by technique at the 5% level for all disutilities with few exceptions. The exceptions were Mild, Moderate, Severe SSIs, and Severe SSI plus vacuum dressing mean disutility differences calculated by VAS and TTO. The Severe SSI plus vacuum dressing disutility mean difference between VAS and TTO was close to statistical significance with a p-value of 0.0577.

8.3.6 Generalised linear model regression

The regression results of separate models predicting the dependent variables of the health state valuations per health state and technique are shown in Appendix Table A8.2. Decrements were used in nearly half of the regressions. The modified Parks Test per health state and technique are shown in Appendix Table A8.3. Even after adjustment to a decrement health state, there were no suitable family distributions for the Health State F EQ-5D-5L regression. The results are presented for completeness using the family distribution associated with the highest p-value in the modified Park Test. The link function diagnostics are shown in Appendix Table A8.4. All the selected link functions had non-significant p-values from the goodness of fit tests.

Most of the explanatory variables [Age group (Under 25 years, 25 years and above), gender, education status] were not statistically significant predictors across any of the vignettes and valuation techniques (Appendix Table A8.2). The participants own EQ-5D-5L score was statistically significant negative predictor of valuations of Health State A decrement and Health State B decrement and a statistically significant positive predictor of valuations of the Health State C, all using the EQ-5D-5L technique. Relative to no prior experience of having surgery, those who have had experienced surgery had a higher predicted valuations of Health State B decrement and Health State C decrement using the Time Trade Off technique.

Only certain ethnic groups across some of the health state vignettes were statistically significant predictors. Relative to the White Ethnic Reference Category, participants with a Black/ African / Caribbean /Black British Ethnicity had statistically significant lower predicted valuations for Health State E using the Visual Analogue Score technique. Relative to the White Ethnic Reference Category, Asian or Asian British participants had statistically significant lower predicted valuations for Health State B Decrement and Health State D T using the Time Trade Off technique, and statistically significant higher predicted valuations of Health State C using the Time Trade Off technique. Relative to the White Ethnic Reference Category, other ethnic group participants had statistically significant lower predicted valuations for Health State A decrement using the Visual Analogue Score.

8.3.7 Health state photographs

The number of participants who agreed to look at the photographs representing the health states is shown in Table 8.8. Nearly all participants chose to look at the photographs with N=99 (99%) of participants willing to look at Health State A photographs with some small dropout as the more severe health states are shown. A high proportion of participants (90%) were willing to look at photographs of the most severe Health State (Severe SSI plus bowel coming through).

Table 8.8 Health state photographs acceptability

Variable	N	%
Agreed to look at Health State A (No SSI) photographs	99/100	99%
Agreed to look at Health State B (Mild SSI) photographs	97/100	97%
Agreed to look at Health State C (Moderate SSI) photographs	96/100	96%
Agreed to look at Health State D (Severe SSI) photographs	95/100	95%
Agreed to look at Health State E (Severe SSI plus vacuum dressing) photographs	92/100	92%
Agreed to look at Health State F (Severe SSI plus bowel coming through) photographs	90/100	90%

For those who viewed the Health State photographs, the percentage of those who thought the photographs relative to the text vignette looked as expected, worse than expected, and better than expected is shown in Table 8.9. The majority of participants felt that the photographs for Health States A, B, and E (No SSI, Mild SSI, and Severe SSI plus vacuum dressing) looked as expected. The majority of participants felt that the photographs for Health States C, D, and F (Moderate SSI, Severe SSI, and Severe SSI plus bowel) looked worse than expected. None of the Health States had the better than expected option as the most favoured option. Indeed, the better than expected option was the least popular choice in all Health States except for Health State E where it was the second most popular choice.

Table 8.9 Health state image expectations relative to the text vignette

Variable	Looks as expected	Worse than expected	Better than expected
Health State A (No SSI)	63.64%	29.29%	7.07%
Health State B (Mild SSI)	53.61%	30.93%	15.46%
Health State C (Moderate SSI)	36.46%	59.38%	4.17%
Health State D (Severe SSI)	37.89%	57.89%	4.21%
Health State E (Severe SSI plus vacuum dressing)	55.43%	20.65%	23.91%
Health State F (Severe SSI plus bowel coming through)	33.33%	53.33%	13.33%

8.3.8 Subgroup Analyses

The results of subgroup analyses are shown in Tables 8.10-8.13. There were no statistically significant differences between age groups on health state valuations across vignettes and valuation techniques at the 5% level (Table 8.10). This was also the case for the gender subgroup analysis (Table 8.11). For prior surgical experience, the only statistically significant difference between groups was for Health State D using TTO with all other health states within the TTO having a non-statistically significant mean group difference (Table 8.12). For the Worklink Interviewer subgroup analysis, higher statistically significant mean group differences were found for Health State D and Health State E in the TTO exercises by participants interviewed by Worklink interviewers (Table 8.13). No other statistically significant differences were found in the other Health States in the TTO exercises nor in the Health States in the EQ-5D-5L and VAS results.

8.3.9 Logical inconsistencies sensitivity analysis

A comparison of the health state valuations of the full sample versus the sample excluding any logical inconsistent responses is shown in Table 8.14. The EQ-5D-5L as the first valuation task was associated with the most logical inconsistent responses. Excluding the logical inconsistent responses had little impact on the valuation results.

Table 8.10 Age subgroup analysis

	<25 years old (n=70)		>= 25 years old (n=30)		Paired t-test	
Valuation Technique and Health State	Mean	Standard Deviation	Mean	Standard Deviation	Mean Difference	P-value
EQ-5D-5L						
Health State A (No SSI)	0.555	0.073	0.512	0.178	0.043	0.0908
Health State B (Mild SSI)	0.318	0.213	0.326	0.284	-0.008	0.8844
Health State C (Moderate SSI)	0.112	0.200	0.088	0.320	0.024	0.6522
Health State D (Severe SSI)	-0.238	0.249	-0.233	0.254	-0.005	0.9251
Health State E (Severe SSI plus vacuum dressing)	-0.278	0.246	-0.280	0.220	0.002	0.9654
Health State F (Severe SSI plus bowel coming through)	-0.383	0.244	-0.413	0.246	0.030	0.5751
Visual Analogue Scale						
Health State A (No SSI)	0.566	0.130	0.594	0.103	-0.028	0.2948
Health State B (Mild SSI)	0.425	0.135	0.466	0.130	-0.040	0.1678
Health State C (Moderate SSI)	0.337	0.126	0.372	0.139	-0.036	0.2117
Health State D (Severe SSI)	0.246	0.121	0.291	0.134	-0.045	0.1020
Health State E (Severe SSI plus vacuum dressing)	0.215	0.117	0.260	0.134	-0.045	0.0925
Health State F (Severe SSI plus bowel coming through)	0.156	0.122	0.197	0.109	-0.041	0.1167
Time Trade Off						
Health State A (No SSI)	0.727	0.215	0.746	0.172	-0.019	0.6688
Health State B (Mild SSI)	0.601	0.206	0.646	0.200	-0.045	0.3182
Health State C (Moderate SSI)	0.492	0.197	0.524	0.192	-0.032	0.4557
Health State D (Severe SSI)	0.395	0.190	0.419	0.186	-0.025	0.5493
Health State E (Severe SSI plus vacuum dressing)	0.346	0.185	0.351	0.201	-0.006	0.8936
Health State F (Severe SSI plus bowel coming through)	0.237	0.164	0.244	0.192	-0.008	0.8420

Table 8.11 Gender subgroup analysis

	Identified as Female (n=75)		Identified as Male (n=24)		Paired t-test	
Valuation Technique and Health State	Mean	Standard Deviation	Mean	Standard Deviation	Mean Difference	P-value
EQ-5D-5L						
Health State A (No SSI)	0.533	0.129	0.571	0.055	-0.038	0.1612
Health State B (Mild SSI)	0.318	0.241	0.341	0.218	-0.024	0.6664
Health State C (Moderate SSI)	0.121	0.235	0.078	0.243	0.043	0.4454
Health State D (Severe SSI)	-0.229	0.253	-0.244	0.236	0.015	0.7990
Health State E (Severe SSI plus vacuum dressing)	-0.277	0.239	-0.272	0.232	-0.005	0.9266
Health State F (Severe SSI plus bowel coming through)	-0.398	0.240	-0.364	0.258	-0.034	0.5581
Visual Analogue Scale						
Health State A (No SSI)	0.564	0.123	0.606	0.122	-0.043	0.1417
Health State B (Mild SSI)	0.428	0.135	0.468	0.132	-0.040	0.2086
Health State C (Moderate SSI)	0.341	0.125	0.373	0.144	-0.031	0.3092
Health State D (Severe SSI)	0.255	0.124	0.278	0.135	-0.023	0.4332
Health State E (Severe SSI plus vacuum dressing)	0.226	0.120	0.245	0.133	-0.019	0.5184
Health State F (Severe SSI plus bowel coming through)	0.167	0.116	0.180	0.129	-0.014	0.6268
Time Trade Off						
Health State A (No SSI)	0.727	0.192	0.752	0.240	-0.025	0.6100
Health State B (Mild SSI)	0.613	0.201	0.623	0.221	-0.010	0.8373
Health State C (Moderate SSI)	0.500	0.197	0.509	0.195	-0.009	0.8512
Health State D (Severe SSI)	0.401	0.196	0.408	0.171	-0.007	0.8779
Health State E (Severe SSI plus vacuum dressing)	0.350	0.191	0.349	0.185	0.001	0.9813
Health State F (Severe SSI plus bowel coming through)	0.247	0.185	0.219	0.128	0.028	0.4844

Table 8.12 Prior surgery experience subgroup analysis

	No Prior surgery experience (n=55)		Prior surgery experience (n=45)		Paired t-test	
Valuation Technique and Health State	Mean	Standard Deviation	Mean	Standard Deviation	Mean Difference	P-value
EQ-5D-5L						
Health State A (No SSI)	0.540	0.125	0.544	0.106	-0.004	0.8607
Health State B (Mild SSI)	0.335	0.236	0.302	0.237	0.033	0.4822
Health State C (Moderate SSI)	0.104	0.244	0.106	0.240	-0.003	0.9572
Health State D (Severe SSI)	-0.221	0.253	-0.255	0.247	0.035	0.4934
Health State E (Severe SSI plus vacuum dressing)	-0.245	0.243	-0.320	0.226	0.075	0.1184
Health State F (Severe SSI plus bowel coming through)	-0.371	0.268	-0.417	0.210	0.046	0.3475
Visual Analogue Scale						
Health State A (No SSI)	0.575	0.114	0.574	0.133	0.001	0.9825
Health State B (Mild SSI)	0.434	0.132	0.442	0.137	-0.008	0.7689
Health State C (Moderate SSI)	0.344	0.127	0.352	0.135	-0.008	0.7511
Health State D (Severe SSI)	0.251	0.125	0.269	0.128	-0.019	0.4664
Health State E (Severe SSI plus vacuum dressing)	0.222	0.121	0.236	0.127	-0.014	0.5681
Health State F (Severe SSI plus bowel coming through)	0.165	0.124	0.173	0.114	-0.009	0.7227
Time Trade Off						
Health State A (No SSI)	0.714	0.231	0.755	0.160	-0.040	0.3256
Health State B (Mild SSI)	0.586	0.224	0.650	0.171	-0.064	0.1166
Health State C (Moderate SSI)	0.467	0.208	0.544	0.171	-0.077	0.0494
Health State D (Severe SSI)	0.366	0.182	0.446	0.189	-0.080	0.0332
Health State E (Severe SSI plus vacuum dressing)	0.323	0.174	0.377	0.204	-0.053	0.1609
Health State F (Severe SSI plus bowel coming through)	0.214	0.148	0.270	0.195	-0.057	0.1011

Table 8.13 Worklink interviewer subgroup analysis

	Non-Worklink Interviewer (n=53)		Worklink Interviewer (n=47)		Paired t-test	
Valuation Technique and Health State	Mean	Standard Deviation	Mean	Standard Deviation	Mean Difference	P-value
EQ-5D-5L						
Health State A (No SSI)	0.545	0.105	0.538	0.128	0.007	0.7667
Health State B (Mild SSI)	0.346	0.234	0.291	0.236	0.055	0.2483
Health State C (Moderate SSI)	0.131	0.240	0.076	0.241	0.055	0.2591
Health State D (Severe SSI)	-0.240	0.259	-0.232	0.241	-0.009	0.8597
Health State E (Severe SSI plus vacuum dressing)	-0.274	0.237	-0.284	0.241	0.010	0.8310
Health State F (Severe SSI plus bowel coming through)	-0.394	0.255	-0.389	0.232	-0.005	0.9170
Visual Analogue Scale						
Health State A (No SSI)	0.563	0.125	0.587	0.120	-0.024	0.3226
Health State B (Mild SSI)	0.437	0.139	0.438	0.129	-0.001	0.9618
Health State C (Moderate SSI)	0.351	0.133	0.344	0.129	0.007	0.7978
Health State D (Severe SSI)	0.257	0.128	0.261	0.126	-0.005	0.8596
Health State E (Severe SSI plus vacuum dressing)	0.231	0.126	0.226	0.121	0.005	0.8414
Health State F (Severe SSI plus bowel coming through)	0.169	0.126	0.168	0.112	0.001	0.9670
Time Trade Off						
Health State A (No SSI)	0.701	0.215	0.768	0.183	-0.066	0.1018
Health State B (Mild SSI)	0.576	0.216	0.658	0.182	-0.082	0.0454
Health State C (Moderate SSI)	0.469	0.199	0.537	0.186	-0.068	0.0823
Health State D (Severe SSI)	0.367	0.190	0.441	0.181	-0.074	0.0485
Health State E (Severe SSI plus vacuum dressing)	0.330	0.192	0.367	0.186	-0.037	0.3330
Health State F (Severe SSI plus bowel coming through)	0.219	0.178	0.262	0.164	-0.042	0.2227

Table 8.14 Logical inconsistencies sensitivity analysis

	Full Sample (n=100)		Logical inconsistencies excluded (n varied by health state)		
Valuation Technique and Health State	Mean	Standard Deviation	Mean	Standard Deviation	Number of excluded responses
EQ-5D-5L					
Health State A (No SSI)	0.542	0.116	0.542	0.116	0
Health State B (Mild SSI)	0.32	0.235	0.338	0.228	6
Health State C (Moderate SSI)	0.105	0.241	0.124	0.232	10
Health State D (Severe SSI)	-0.236	0.249	-0.234	0.247	14
Health State E (Severe SSI plus vacuum dressing)	-0.279	0.237	-0.287	0.233	3
Health State F (Severe SSI plus bowel coming through)	-0.392	0.244	-0.431	0.210	12
Visual Analogue Scale					
Health State A (No SSI)	0.574	0.123	0.574	0.123	0
Health State B (Mild SSI)	0.437	0.134	0.440	0.131	1
Health State C (Moderate SSI)	0.347	0.130	0.350	0.129	3
Health State D (Severe SSI)	0.259	0.126	0.259	0.122	4
Health State E (Severe SSI plus vacuum dressing)	0.229	0.123	0.226	0.122	2
Health State F (Severe SSI plus bowel coming through)	0.168	0.119	0.166	0.116	3
Time Trade Off					
Health State A (No SSI)	0.733	0.203	0.745	0.200	5
Health State B (Mild SSI)	0.615	0.204	0.621	0.207	5
Health State C (Moderate SSI)	0.501	0.195	0.510	0.195	8
Health State D (Severe SSI)	0.402	0.189	0.402	0.188	5
Health State E (Severe SSI plus vacuum dressing)	0.348	0.189	0.343	0.185	1
Health State F (Severe SSI plus bowel coming through)	0.239	0.172	0.237	0.171	2

8.4 Discussion

8.4.1 Statement of principal findings

This chapter has developed utility estimates associated with Surgical Site Infection. Bespoke Health State vignettes of different severity levels of SSI were developed using a variety of sources with matching photographs to align with the text-based vignettes. The vignettes were remotely valued using a predominately UK student population using direct methods. The online mode of administration was feasible and had a high interview completion rate. A range of utilities were obtained for each of the health states with more severe Health States having utilities that were statistically significant from the preceding health state across valuation techniques. Mean utility health states were highest for the TTO techniques while the lowest mean utility health states were from the EQ-5D-5L.

While Health States themselves differed significantly between techniques, SSI disutilities between VAS and TTO decrements had non-statistically significant differences in except for Severe SSI plus bowel Health State. The lower EQ-5D-5L mean utility health states is not surprising as the functional descriptions were partly derived from the EQ-5D-5L response levels which gave little room for interpretation in many of the domains. In addition, negative utility values were possible in the EQ-5D-5L which was not the case for the VAS or TTO. Owing to the overlapping descriptions, the purpose of the EQ-5D-5L was to familiarise the participants with the health state vignettes rather than to use the utility estimates at face value for a model-based economic evaluation.

GLM regression and subgroup analyses did not find an association between participant characteristics and the valuation scores. Excluding logically inconsistent responses had little impact on the results. Subgroup analysis uncovered few statistically significant differences, but these were likely chance findings as they were inconsistent across health state vignettes

and techniques. As the majority of participants were undergraduate students, the age group cut offs for the subgroup was quite young (25 years and above, under 25 years) which may explain why there were no material differences in health state valuations. A relatively large number of participants (45%) had prior surgical experience, but this was not found to be a driver in differences in valuation scores to those who had no surgical experience. It could be that the type of surgical experience could be important (minor/major surgery or site of operation) for health state valuations, but this was not explored in this study.

There was high acceptability of the SSI photographs, with a large proportion of participants were willing to view photographs of the Health State. Given the graphic nature of the photographs, it was surprising how many participants agreed to view the photographs. Within the participant information sheet, there were warnings of the health state descriptions so self-selection of participants who are less averse to graphic text and photographs cannot be ruled out.

While participants did not redo the valuation tasks with additional information gained from the Health State photographs, many participants found the more severe SSI health states worse than they expected. This suggests that they could have underestimated the severity of the health states based on the text vignettes alone and consequently their SSI utility values may have been lower with the addition of the photographs. Alternatively, the majority of participants who viewed the milder health states (No SSI, Mild SSI) thought the photographs were as expected, from which it could be inferred that the health state valuations on text vignettes alone would be unlikely to vary significantly with the addition of the photographs.

8.4.2 Strengths and limitations

This study represents the first direct health state valuation study for SSI in abdominal surgery. It is also the first study to use photographs of a surgical health state to explore their use as a supplement to text-based vignettes. The diversity of the SSI experience was specifically explored in the valuations and were found to be distinct from one another at a statistically significant 5% level. The SSI health state vignettes followed best practice in the literature on the development and valuation of the vignette [385]. Three separate valuation techniques were used to derive utilities for the health states and allowed for an assessment on how valuations differed by method. The online mode of administration gave participants flexibility of being able to do the interview in the setting of their choosing, and they did not have to physically turn up to an interview venue and follow precautionary COVID-19 meeting procedures. The 1:1 interview design maximised opportunity for participants to ask clarifying questions during the interview to minimise comprehension errors. The online design of the interview with the Redcap Survey Platform allowed for previous answers to be seamlessly displayed for participants at the health state photographs section to quickly refresh memories and give context of how they had valued the health states using EQ-5D-5L and TTO.

The selection of family distributions and link functions for the Generalised Linear Model was made on the basis of goodness of fit tests to ensure that the model was not misspecified. Nearly all the health states were able to use a family distribution that had a non-significant modified Parks test p-value. All the link functions used in the Generalised Linear passed the Pearson's correlation test, the Pregibon link test and the modified Hosmer and Lemeshow test, indicating there was not a lack of fit issue with the link function.

However, there are several limitations associated with the study. The empirical study used a UK convenience population of participants with a university education who were mainly in their twenties. This may have implications on the representativeness of findings compared to the general population. A previous study in the UK valuing EQ-5D-3L states with VAS found that respondents with a degree had a higher median valuation for 31 of the 43 states relative to those with intermediate or no educational qualifications [449]. In the same study, age did not have a significant effect on the valuations using VAS. Another UK study by the same authors found that age had an impact on TTO valuations but not for SG valuations; higher TTO valuations were found in the 18-40 years groups compared to the other older age groups [446,447].

The online mode of administration was not inclusive to those who did not have access to a laptop or smartphone with video capabilities. There were other downsides associated with online 1:1 interview format. The lack of a controlled environment on the participant side meant that there were a variety of places participants selected for the zoom interview including a bedroom, canteen, train station, and a university communal space. Some of these environments may be less conducive than others for focusing on valuation tasks. Another aspect of the environment beyond the interviewer's control was the possibility of participants seeking out sources in addition to the described health state during the interview. For example, one participant stated that they had Googled images of the vacuum dressings as they were valuing Health State E. This issue would also be present in unsupervised self-completion of valuation tasks. Another issue was the timing of the interviews and the health state photographs. At least one of the refusals to view the more severe SSI health state photographs was because of the combination of the afternoon interview timing and the participant's reluctance to be put off their lunch on seeing a severe SSI photograph.

With the health state photographs, it was not possible to have a standardized patient with differences only in wound infection profile. Different shapes of the patient stomach and other aesthetic characteristics may have influenced participants expectation answers compared to the text vignettes alone.

There are also limitations with the design of the questionnaire. The questionnaire was piloted with health economist colleagues. Piloting the questionnaire with lay people instead of health economists may have led to feedback which improved the questionnaire design and comprehension for those undertaking the questionnaire from a health economics naïve perspective. As the health states were presented in chronological order, the valuations may be subject to question order bias where the subsequent valuations of the health states may be influenced by valuations of preceding health states [454].

Lastly, while no explicit mention of post-operative patient pathways in terms of resource use was mentioned in the vignette descriptions to make the health states applicable across income groups, the UK participants may have still inferred that the healthcare would be applicable to the UK context, and that wound dressings would be most likely be changed by a medical professional and not a family member.

8.4.3 Comparison with other studies

Previous studies have looked at the health state valuations of EQ-5D-3L profiles using both TTO and VAS [455]. The finding in the present study that TTO valuations were higher than VAS valuations concurs with a Swedish study [456] and was at odds with a EQ-5D value sets of UK and Spain where TTO was higher only for milder states and lower than VAS for severe health states [455].

Other utility estimates for SSI were found in the systematic review in Chapter 4 and the ROSSINI re-analysis in Chapter 5. The majority of these studies in the review had

methodological issues including non-adjustment of preoperative utility scores, lack of multiple and consistent timepoints and no covariate adjustment of patient characteristics. This makes comparison with the present study difficult. The findings of selected studies without major methodological issues are compared below.

For the indirect studies, the TTO mild SSI disutility (-0.118) is nearly identical to the original ROSSINI utility estimate (-0.119) and larger than the meta-analysis utility estimate of SSI studies with EQ-5D (-0.08) that was reported in the discussion of Chapter 4 [276]. However, the original ROSSINI utility estimate is likely a calculation error, the meta-analysis utility estimates would not be restricted to just mild or superficial SSIs, and both estimates had not been adjusted for baseline utility scores between groups. Inclusion of the TTO moderate SSI disutility (-0.231) and severe SSI disutility (-0.33) would result in a greater difference than the meta-analysis. The TTO moderate and severe SSI disutilities were not comparable to deep SSI disutility estimates from the Parker study (-0.102 from EQ-5D-3L; -0.031 from SF-6D) and the aforementioned meta-analysis (−0.10).

The TTO SSI disutilities are also not in line with the ROSSINI re-analysis utility value in Chapter 6 (0.056 decrement from Generalised Linear Model with Poisson distribution). However, all the above comparisons assume that the duration of the disutilities generated from the AVOCET study last for the entire month when SSI onset rarely begins at day 1 and ends on day 30. Thus, the size difference may be overstated before duration is taken into account.

The other direct health state valuation SSI study in the literature [236] had a larger sample of 201 participants with a higher mean age of 46.2 years, a near equal split by identified gender, and a higher proportion from a White ethnic/racial background compared to the present empirical work. Their study reported disutilities with a joint surgery superficial wound

infection to be -0.03, a deep infection followed by Debridement, antibiotics and implant retention to be -0.18, and deep infection (two-stage revision arthroplasty) to be -0.32. In addition, they reported spine surgery health states infection disutilities of requiring and not requiring surgery to be -0.03 and -0.16, respectively. The differences in valuation scores apart from the different site of the infection may be from the use of path states where the symptoms of the health state gradually improved until a return to normal functioning at 6 months; participants then valued the 6 months of symptoms and 6 months of normal functioning over the 1 year time period. Here, the health states were purposively valued without any change in symptoms to obtain the utility values of living in the health state rather than a post-surgery recovery profile.

8.4.4 Implications for practice

As mentioned earlier, supplementing photographs to text-based vignettes for health state valuation was associated with high acceptability and suggested potentially lower valuations for more severe SSI health states. Participants value the health state that they have comprehended. A challenge with text vignettes is around providing enough detail for participants to accurately comprehend the health state description without employing simplifying heuristics while not having the text vignette excessively long so that participants end up skipping parts of the description and excluding these elements in the valuation task. The introduction of photographs represents a route to increase the comprehension of a health state with visual information and consolidate the participants understanding. The combination of text and pictures has been advocated in educational research as synergies in cross-referential connections to verbal (text) and non-verbal (images) processing has been hypothesised to more effectively encode information for learners [457].

To better understand how the information from the text and non-text aspects of a vignette are processed by participants, including the duration spent looking at the photograph and the visual attention that participants give to different aspects of the photograph and text, the use eye-tracking technology could be explored. Eye-tracking technology has been previously applied in assessing how individuals attend and process information in discrete choice experiments [458].

Wound photography already exists in clinical practice to help evaluate postoperative wound healing assessment with best practice guidance available on capturing and presenting the images [459]. Remote wound monitoring using self-reported SSI symptoms and wound photographs by patients on smartphones has been shown to be feasible in UK abdominal surgery patients [460] and is currently being explored in LMIC surgical patients [461]. The evidence on the addition of wound photography increasing diagnostic accuracy compared to text alone is mixed. For surgeons, the addition of wound photographs to online text based clinical vignettes increased specificity and decreased sensitivity for detection of SSIs [462].

With the ongoing research on the use of wound photographs, there is an opportunity to amass a library of images of the wound trajectory of postoperative patients across different settings and ethnicities. As light skin tones were predominantly featured in the SSI wound photography literature when searching for suitable photographs for the present study, a collection of surgical photographs of different skin tones could better represent the impact of SSI across patients from different ethnicities. Wound photographs by postoperative day could also provide indications on the fluctuations in SSI severity from onset to complete wound healing which can then combined with severity specific utility data to model the quality of life trajectory of SSI patients in economic evaluations.

The SSI utility estimates generated in the study varied considerably depending on the severity and the valuation technique used. For severity, this underlines the importance of looking at the severity of SSI for research and not just a binary Yes/No which has been a routine categorisation of SSI for clinical trials. The usefulness of distinguishing severity of SSI will be explored in an upcoming SSI trial (SWANN MARLIN) where the present study vignettes (text and photographs) are being adapted for clinicians to allocate SSI patients into mild/moderate/severe SSI categories and assess if the categorisation can delineate patient outcomes and costs.

As a UK convenience population was used, future research to explore difference in preferences in a more representative general UK population along with general populations in different income settings. Previous studies has demonstrated the successful use of the TTO technique for the valuation of EQ-5D sets across general populations in different income settings [463–467]. Lastly, as patients will differ by body type with an SSI, future research could explore the use of using the same actors for each health state with different SSI depicted using cosmetics and prosthetics to assess if keeping the portrayed patients consistent across health states has any impact on the valuations.

8.5 Conclusion

This chapter reported the elicitation of Health State Valuations associated with SSI. Descriptions of SSI were associated with statistically significant quality of life decrement. Due to their theoretical grounding, the TTO estimates will be used as the base case model input values for the model-based cost-utility analyses in Chapter 9. The TTO utility estimates will be used in the calculations of QALYs by strategy in the Cost per QALY approach in Chapter 9. For the Cost per DALY averted approach in Chapter 9, the TTO utility estimates

will be rescaled into Disability weights and form part of an SSI DALY. The VAS estimates will be used in a sensitivity analysis in both approaches.

Chapter 9:

An updated model-based economic evaluation

9.1 Introduction

This chapter refines the preliminary economic evaluation model presented in Chapter 5 using information from the primary data collection reported in Chapters 7 and 8. The preliminary economic evaluation model used existing information from the literature on the costs (Chapter 3) and quality of life impact of Surgical Site Infection (SSI) (Chapter 4). Results from the model suggested that SSI reducing interventions were cheaper and more effective than the Usual Care strategy. Due to robustness issues associated with the model inputs in Chapter 5, the preliminary model-based economic evaluation was then updated using estimates from the ROSSINI trial re-analysis which was presented in Chapter 6. The decision recommendation did not change given the re-analysis estimates presented at the end of Chapter 6. Using the primary research undertaken on Costs (Chapter 7) and Quality of life (Chapter 8) associated with SSI, the model is now to be updated with an LMIC focus to assess the costs and consequences of different interventions evaluated in the FALCON trial [280,373].

9.1.1 Overview of the FALCON trial

The FALCON randomised control trial (RCT) [373] assessed the clinical effectiveness of different skin preparation methods (2% Alcoholic Chlorhexidine versus 10% Aqueous Povidone–Iodine) and different facial closure methods (Triclosan-coated suture versus Non-coated sutures) in reducing SSI in abdominal surgical patients across seven LMICs (Ghana, India, Nigeria, Mexico, Benin, Rwanda, and South Africa). For skin preparation methods, alcohol based solutions are considered to have superior antiseptic properties over aqueous based solutions and this may reduce the risk of developing an SSI [468]. For fascial closure

methods, non-coated suture material can be colonized by bacteria that can raise the risk of an SSI; Triclosan-coated sutures are treated with an antibacterial agent effective against many common organisms linked to the development of an SSI [282].

The FALCON RCT [373] considered the clinical effectiveness of the interventions for two different types of surgical patients delineated according to their predicted wound contamination (Clean-Contaminated, Contaminated-Dirty). The clinical effectiveness was assessed separately by wound contamination type due to probable heterogeneous effects in the interventions mechanisms of action and underlying risk of SSI across the surgery types [373]. The FALCON RCT was characterised by a 2x2 factorial design which randomised patients into receiving both interventions, either intervention, or none of the interventions [469] and allowed for the separate treatment comparison by skin preparation method or fascial closure method assuming that there is no interaction effect between skin preparation methods and fascial closure methods. Fortunately, no statistically significant interaction effect between interventions was detected in the FALCON trial [373]. The FALCON trial recruited 5788 patients, of which 3091 patients had an anticipated Clean-Contaminated wound, and 2697 patients had an anticipated Contaminated-Dirty wound. The trial did not find a statistically significant difference in preventing SSI by skin preparation method nor by fascial closure method in both wound contamination types [373].

9.1.2 Chapter aim and structure

The aim of the chapter is to assess the cost-effectiveness of the interventions of the FALCON RCT. Cost-effectiveness is assessed separately for surgical patients with either Clean-Contaminated or Contaminated-Dirty wounds, and by setting (considering India, Ghana, and Mexico). A Cost per Quality Adjusted Life Year (QALY) approach and Cost per Disability Adjusted Life Year (DALY) averted approach was taken. The Key resource use In Wound

Infection (KIWI) sub study, carried out within the FALCON RCT [373] and detailed in Chapter 7, was limited to data collection in middle-income countries. As such, cost-effectiveness assessment within this Chapter is specific to these country settings.

Despite the lack of statistically significance associated with the FALCON trial interventions, a strategy could potentially be considered cost-effective compared to Usual Care even after a full assessment of parameter uncertainty. This was documented with the Wound Irrigation strategy in the preliminary model-based economic evaluations in Chapter 5 and Chapter 6.

This chapter details the methods of the model-based economic evaluation first with the analytic approaches for each setting. Then the deterministic and probabilistic results are summarised, with a discussion of the principal findings, strengths and limitations, comparison with other studies, and implications for practice.

9.2 Methods

The patient population considered by the model-based economic evaluation is adult patients undergoing abdominal surgery. The model-based economic evaluation assessed the cost-effectiveness of SSI reducing measures separately in (i) Clean-Contaminated patients in India, (ii) Contaminated-Dirty patients in India, (iii) Clean-Contaminated patients in Mexico, and (iv) Contaminated-Dirty patients in Ghana. The model-based economic evaluation did not consider Contaminated-Dirty patients in Mexico and Nigeria due to small sample size ($n<5$).

9.2.1 Model comparators

The following strategies were compared in the model-based economic evaluation and had been assessed in the FALCON trial:

- 2% Alcoholic Chlorhexidine strategy: (2% Alcoholic Chlorhexidine solution skin preparation and non-coated sutures for fascial closure)

- Triclosan-coated Sutures strategy: (10% Aqueous Povidone–Iodine skin preparation and Triclosan-coated Sutures for fascial closure)
- Usual Care strategy: (10% Aqueous Povidone–Iodine solution skin preparation and non-coated sutures for fascial closure).

A separate comparator combining 2% Alcoholic Chlorhexidine and triclosan-coated sutures was assessed in a deterministic sensitivity analysis and probabilistic sensitivity analysis. The FALCON interventions were assumed to only affect the SSI risk and none of the other clinical probabilities in the model.

9.2.2 Model structure

The model structure is shown in Figure 9.1 and is the same structure used in the preliminary model-based economic evaluation. Like the preliminary model-based economic evaluation, the updated model-based economic evaluation also represents the decision problem using a decision tree in TreeAge 2023 [278]. The postoperative pathway was assumed not to differ by predicted contamination status and Low- and Middle- Income Countries (LMIC) setting (Ghana, Mexico, India).

In the model-based economic evaluation, surgical patients in all strategies faced a postoperative risk of an SSI. For patients who did not suffer an SSI, they could suffer a death or survive until the end of the time horizon. For patients who suffered an SSI, it could be one of three severity levels: Superficial SSI, Deep Incisional SSI, and Deep Organ Space SSI. Thereafter, a patient with an SSI could die or survive until the end of the time horizon. The time horizon for the model was selected to be 30 days, in line with the trial data effectiveness endpoint data, cost data and preliminary model-based economic evaluation.

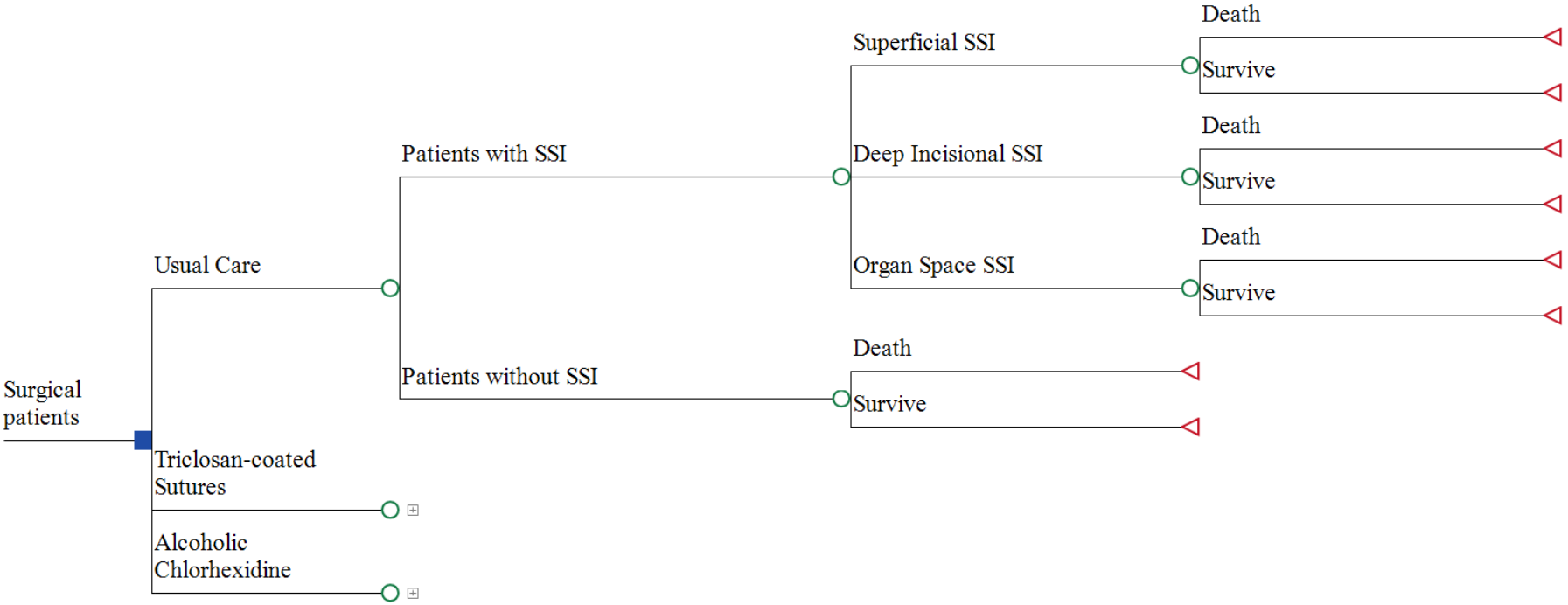


Figure 9.1 Model structure

9.2.3 Model input parameters

The model input parameters are displayed in Table 9.1, Table 9.2, and Table 9.3. The tables contained values used for the deterministic and probabilistic analyses values along with the sources for the model inputs.

Costs

Country specific costs for Mexico, India, and Ghana are shown in Table 9.1. The primary analysis adopted the perspective of a disaggregated societal perspective where healthcare and societal costs were separately reported [1]. Costs are reported in 2020 international dollars.

The intervention costs for India and Mexico were obtained by the country hub managers involved in the FALCON trial. As the intervention costs had not arrived in time for PhD submission, the costs were estimated using a relative cost index of model predictions of healthcare costs from the WHO CHOICE [470]. The additional cost of SSI by country was taken from the KIWI sub-study which is reported in Chapter 7 and converted from international Euros to international dollars. A per country and per wound contamination unadjusted cost was used in the base case analysis. The components of the additional cost associated with SSI included cost included inpatient healthcare resource use (postoperative length of stay, antibiotics, wound dressing changes, laboratory investigations), healthcare resource use (antibiotics for a wound infection, wound dressings, painkillers) at hospital discharge, and post-discharge healthcare resource use (healthcare visits, wound dressings, and medication). As the one patient with SSI in Mexico did not report post-discharge societal costs and some patient without SSI had incurred costs, an additional SSI for this setting is shown in the model to decrease societal costs.

Table 9.1 Model cost parameters (international dollars 2020)

Variable	Deterministic Value (Int$)	PSA Distribution	PSA parameters	Source
India				
2% Alcoholic Chlorhexidine Cost	$13.33	Gamma	α=44.44 λ= 17.78	FALCON trial [373]
10% Aqueous Povidone–Iodine Cost	$9.56	Gamma	α= 44.44; λ = 44.44;	FALCON trial [373]
Cost of Triclosan-coated Sutures	$21.24	Gamma	α= 44.44; λ = 8.889	FALCON trial [373]
Cost of Uncoated Sutures	$19.54	Gamma	α= 44.44; λ = 29.630	FALCON trial [373]
Additional Healthcare Cost of Clean-Contaminated SSI	$691(139)	Normal	μ= 691; σ= 139	FALCON KIWI [373,471]
Additional Healthcare Cost of Contaminated-Dirty SSI	$257 (232)	Normal	μ= 257; σ= 232	FALCON KIWI [373,471]
Additional Societal Cost of Clean-Contaminated SSI	$42 (88)	Normal	μ= 42; σ= 88	FALCON KIWI [373,471]
Additional Societal Cost of Contaminated-Dirty SSI	$60 (74)	Normal	μ= 60; σ= 74	FALCON KIWI [373,471]
Mexico				
2% Alcoholic Chlorhexidine Cost	$15.97	Gamma	α= 44.44; λ = 17.78	FALCON trial [373]
10% Aqueous Povidone–Iodine Cost	$12.25	Gamma	α= 44.44; λ = 44.44;	FALCON trial [373]
Cost of Triclosan-coated Sutures	$45.84	Gamma	α= 44.44; λ = 8.889	FALCON trial [373]

Variable	Deterministic Value (Int$)	PSA Distribution	PSA parameters	Source
Cost of Non-coated Sutures	$28.03	Gamma	α= 44.44; λ = 29.630	FALCON trial [373]
Additional Healthcare Cost of Clean-Contaminated SSI	$463 (876)	Normal	μ= 463; σ= 876	FALCON KIWI [373,471]
Additional Societal Cost of Clean-Contaminated SSI	-$42 (218)	Normal	μ= -42; σ= 218	FALCON KIWI [373,471]
Ghana				
2% Alcoholic Chlorhexidine Cost	$5.53	Gamma	α= 44.44; λ = 17.78	FALCON trial [373]
10% Aqueous Povidone–Iodine Cost	$3.97	Gamma	α= 44.44; λ = 44.44;	FALCON trial [373]
Cost of Triclosan-coated Sutures	$8.81	Gamma	α= 44.44; λ = 8.889	FALCON trial [373]
Cost of Non-coated Sutures	$8.11	Gamma	α= 44.44; λ = 29.630	FALCON trial [373]
Additional Healthcare Cost of Contaminated-Dirty SSI	$470 (137)	Normal	μ= 470; σ= 137	FALCON KIWI [373,471]
Additional Societal Cost of Contaminated-Dirty SSI	$38 (156)	Normal	μ= 38; σ= 156	FALCON KIWI [373,471]
PSA: Probabilistic Sensitivity Analysis; SSI: Surgical Site Infection				

Clinical parameters

Clinical parameters are listed in Table 9.2. The probability of an SSI at 30 days post-surgery along with the treatment effectiveness for each strategy by predicted wound contamination, was taken from the FALCON trial [373]. There was a higher risk of SSI with patients with a predicted Contaminated-Dirty wound contamination (30%) relative to patients with a predicted Clean-Contaminated wound contamination (15%). The treatment effectiveness relative risks were adjusted by urgency of surgery (elective, emergency), Age (less than 18 years, greater than or equal to 18 years), the other randomised treatment allocated within the factorial trial design, and centre. While all the point estimates of the relative risks were below 1 indicating a lower probability of SSI for the interventions, these were statistically non-significant with the 95% Confidence Intervals crossing 1. Treatment effectiveness was assumed not to vary by country.

SSI was not reported by severity level in the FALCON trial [373]. The FALCON trial also did not report the 30 day probability of death by SSI status. Instead, the model parameter values and sources from the preliminary model-based economic evaluation were used. The severity proportions of SSI were obtained from a European SSI surveillance report [20]. The 30-day mortality by SSI status was obtained from GlobalSurg2 [289].

Table 9.2 Model clinical parameters

Variable	Deterministic Value	PSA Distribution	PSA parameters	Source
SSI risk				
30 day postoperative Clean-Contaminated probability of SSI	15.53%	Beta	α=454; β=2469	FALCON trial [373]
30 day postoperative Contaminated-Dirty probability of SSI	30.03%	Beta	α=709; β=1652	FALCON trial [373]
Treatment effectiveness				
Clean-Contaminated Relative risk of 2% Alcoholic Chlorhexidine versus 10% aqueous povidone–iodine	0.97 (95% CI 0.82 to 1.14)	Log-Normal	μ= -0.0305; σ= 0.0841	FALCON trial [373]
Clean-Contaminated Relative risk of Triclosan-coated Sutures versus uncoated sutures	0.90 (95% CI 0.77 to 1.06)	Log-Normal	μ= -0.1054; σ= 0.0815	FALCON trial [373]
Contaminated-Dirty Relative risk of 2% Alcoholic Chlorhexidine versus 10% aqueous povidone–iodine	0.91 (95% CI: 0.81 to 1.02)	Log-Normal	μ= -0.0943; σ= 0.0588	FALCON trial [373]
Contaminated-Dirty Relative risk of Triclosan-coated Sutures versus uncoated sutures	0.98 (95% CI 0.87 to 1.10)	Log-Normal	μ= -0.0202; σ= 0.0598	FALCON trial [373]
SSI severity proportions				
Superficial SSI proportion	42.12%	Dirichlet	α_1=8560; $\alpha_1+\alpha_2+\alpha_3$=20322	European SSI Surveillance Report [20]

Variable	Deterministic Value	PSA Distribution	PSA parameters	Source
Deep Incisional SSI proportion	29.73%	Dirichlet	α_2=6042; $\alpha_1+\alpha_2+\alpha_3$=20322	As above
Organ Space SSI proportion	28.15%	Dirichlet	α_3=5720; $\alpha_1+\alpha_2+\alpha_3$=20322	As above
Mortality by SSI status				
30 day postoperative No SSI Death probability	1.50%	Beta	α=162; β=10665	GlobalSurg2 [289] Table 2
30 day postoperative Superficial SSI Death probability	2.86%	Beta	α=43; β=1,438	Derived from GlobalSurg2 [289], European SSI Surveillance Report [20], and Astagneau [7]
Mortality Odds Ratio Deep Incisional versus Superficial SSI	1.38 (95% CI 0.73 to 2.59)	Log-Normal	μ= 0.3207 σ= 0.3220	Astagneau[7]
Mortality Odds Ratio Organ Space versus Superficial SSI	3.46 (95% CI 2.06 to 5.84)	Log-Normal	μ= 1.242 σ= 0.2647	Astagneau[7]
PSA: Probabilistic Sensitivity Analysis; SSI: Surgical Site Infection				

Quality of life outcome parameters

Quality of life parameters for the deterministic and probabilistic analyses are listed in Table 9.3. For the base case analysis with the Cost per QALY approach, the TTO utilities were used from Chapter 8. For a patient without an SSI, the utility score for Health State A was used (Table 8.4). The SSI decrements were taken from Table 8.7. A superficial SSI decrement was assumed to be equivalent to the Health State B decrement (Mild SSI decrement). A Deep Incisional SSI decrement was assumed to be equivalent to the Health State C decrement (Moderate SSI decrement). A Deep Organ Space SSI decrement was assumed to be equivalent to the Health State D decrement (Severe SSI decrement). For utility calculation, onset of an SSI was assumed to occur at day 8 in the model. Surgical patients with SSI were assumed to have the utility of a patient without SSI for the first week and thereafter have the SSI decrement. For patients with SSI who survive, this is 23 days of an SSI decrement. Deaths were assumed to occur halfway through the model (i.e., 15 days). For patients with an SSI who died, the utility score comprised of the utility of a patient without SSI for seven days, an SSI decrement for eight days, and a value of zero for the fifteen remaining days of the time horizon.

For the Cost per DALY averted approach, information on the Years of Life Lost (YLL), Years Lived with Disability (YLD), and Disability Weights were required. DALYs were considered for patients with SSI. The YLL element comprised the life expectancy had the SSI not occurred. For the timing of the deaths for the YLL calculation, they were assumed to occur halfway through the model (i.e., 15 days). The additional mortality from SSI was taken from the 30 day postoperative probability of death for patients with SSI minus the 30 day postoperative probability of death for patients without SSI. YLL was assumed to be irrespective of SSI severity.

Table 9.3 Model quality of life outcome parameters

Variable	Deterministic Value	PSA Distribution	PSA parameters	Source
QALY analysis parameters				
No SSI health state	0.733	Beta	α= 357.91; β= 130.37	Chapter 8 Health State A Time Trade Off Score
Superficial SSI health state decrement	0.118	Normal	μ= 0.118; σ=0.010	Chapter 8 Health State B decrement
Deep Incisional SSI health state decrement	0.231	Normal	μ= 0.231; σ=0.016	Chapter 8 Health State C decrement
Deep Organ Space SSI health state decrement	0.330	Normal	μ= 0.330; σ=0.018	Chapter 8 Health State D decrement
DALY analysis parameters				
Superficial SSI disability weight	0.118	N/A	N/A	Derived from Superficial SSI decrement
Deep Incisional SSI disability weight	0.231	N/A	N/A	Derived from Deep Incisional SSI decrement
Deep Organ Space SSI disability weight	0.330	N/A	N/A	Derived from Deep Organ Space SSI decrement
India SSI Years of Life Left Clean-Contaminated (per additional SSI Death)	24.22	Fixed	N/A	Chapter 7 Table 7.1 and online DALY calculator [472]
Mexico SSI Years of Life Left Clean-Contaminated (per additional patient with SSI Death)	24.27	Fixed	N/A	Chapter 7 Table 7.1 and online DALY calculator [472]

Variable	Deterministic Value	PSA Distribution	PSA parameters	Source
India SSI Years of Life Left Contaminated-Dirty (per additional patient with SSI Death)	21.36	Fixed	N/A	Chapter 7 Table 7.1 and online DALY calculator [472]
Ghana SSI Years of Life Left Contaminated-Dirty (per additional patient with SSI Death)	20.71	Fixed	N/A	Chapter 7 Table 7.1 and online DALY calculator [472]
Mean days of wound resolution of Superficial SSI	38.17	Poisson	λ =38.17	Prada et al. [22]
Mean days of wound resolution of Deep Incisional SSI	93.83	Poisson	λ =93.83	Prada et al. [22]
Mean days of wound resolution of Deep Organ Space SSI	As above	As above	As above	Prada et al. [22]
Superficial SSI Years Lived with Disability Duration	0.1045	N/A	N/A	Derived from mean days of wound resolution of Superficial SSI
Deep Incisional SSI Years Lived with Disability Duration	0.2569	N/A	N/A	Derived from mean days of wound resolution of Deep Incisional SSI
Deep Organ Space Years Lived with Disability Duration	0.2569	N/A	N/A	Derived from mean days of wound resolution of Deep Organ Space SSI
PSA: Probabilistic Sensitivity Analysis; SSI: Surgical Site Infection				

As there are many indications for surgery in the FALCON trial [373] (see Appendix Table A8.2 for the main abdominal procedure performed on patients in KIWI sub study) along with patient demographics, it is difficult to quantify a representative life expectancy element for patients in this trial [373]. For simplification purposes, the life expectancy for the average age of surgical patients by wound contamination and country was used with an online DALY calculator [472] to estimate the YLL. The life expectancy estimates of the calculator come from life tables in the Global Burden of Disease 2016 [98]. As the FALCON trial only reported age as a categorical variable of adults and children, the information was taken from the KIWI sub study reported in Chapter 7 [471]. For example, the average age of Clean-Contaminated patients in India was 33.6 years. Inputting this in the Age of premature death due to disease section of the online DALY calculator [472] for both sexes for India gives a discounted life expectancy of 24.22 years.

The YLD calculation required the disability weight and the length of time with an SSI. The utility decrements from the TTO scores in Chapter 8 were transformed into Disability Weights by multiplying them by -1. For the duration of an SSI, a fracture-related study reported the 25th, 50th, and 75th percentiles of days of wound resolution times of SSI [22]. This was chosen as it was the only known study with severity specific wound resolution times. The mean days of wound resolution of SSI was estimated using the average of the reported median and quartiles [473]. The wound resolution days were reported by Superficial SSI and Deep Incisional or Deep Organ Space SSI groups. In the model, Deep Incisional SSI and Deep Organ Space SSIs were assigned the same duration but had different disability weights which lead to different Years Lived with Disability. As patients who died were assumed in the model to die at postoperative day 15 on average, patients with SSI who died in the model were assigned 8 days of the Years Lived with Disability after onset of an SSI.

9.2.4 Analysis

A partially split approach [111] was taken for the analyses: for each country setting, the country specific costing was used, and the treatment effectiveness from all participating countries within the FALCON trial was used. Discounting was not undertaken for the cost per QALY approach due to the thirty day postoperative time horizon. A 3% discounting rate was used for the YLL component of the Cost per DALY averted approach [74].

Results were presented by country and wound contamination strata (India Clean-Contaminated surgical patients; India Contaminated-Dirty surgical patients; Mexico Clean-Contaminated surgical patients; Ghana Contaminated-Dirty surgical patients). An incremental approach was taken with strategies ordered by increasing costs. More costly and less effective strategies were considered dominated by the comparator strategy. A strategy was considered extended dominated if the current strategy would be dominated on costs and effects by a mixture of two other strategies [299]. To reflect that fewer DALYs were preferred in the results calculation, the incremental effects of the outcome measure was inverted in Treeage for the Cost per DALY averted approach. Base case results were displayed with total costs, QALYs, and DALYs along with incremental costs, incremental QALYs, and incremental DALY averted. Total costs were rounded to the nearest dollar. QALY and DALY results were rounded to the nearest four decimal places.

For the cost per QALY approach, a country specific cost-effectiveness threshold for QALYs were used [298]. These thresholds were estimated based on the marginal productivity of health expenditure. The reported values were adjusted by a Purchasing Power Parity (PPP) conversion factor into international dollars and are shown in Table 9.4. As these were presented as a range, the upper bound was used for the base case analysis with the lower bound used for a deterministic sensitivity analysis. Interventions were considered cost-

effective if their incremental cost-effectiveness ratio was less than or equal to the country specific QALY threshold. As the cost per QALY thresholds were based on health expenditure, only healthcare costs were considered for costs in the cost-effectiveness assessment.

For the Cost per DALYs averted approach, a country specific cost-effectiveness threshold for DALYs averted were used. These supply side cost-effectiveness thresholds for each country (Table 9.4) were taken from a study [474,475] that estimated the cost-effectiveness thresholds using information on the YLL and YLD averted from health expenditure (DALYs averted is the sum of the YLL and YLD [476]). Alternative thresholds from the same study [474,475] were used in a sensitivity analysis. Interventions were considered cost-effective if their incremental cost-effectiveness ratio was less than or equal to the country specific DALY threshold. Like the Cost per QALY thresholds, only healthcare costs were considered for the cost per DALY averted thresholds due to the cost-effectiveness thresholds being derived from health expenditure.

Table 9.4 Cost-effectiveness thresholds for QALYs and DALYs

Variable	Base Case threshold	Source
Ghana QALY Cost-effectiveness thresholds	$2,043	Upper bound value from Woods et al. [298]
India QALY Cost-effectiveness threshold	$2,781	Upper bound value from Woods et al. [298]
Mexico QALY Cost-effectiveness threshold	$10,780	Upper bound value from Woods et al. [298]
Ghana DALY Cost-effectiveness thresholds	$114	Ochalek et al. [474]; DALY Approach 4 Moreno-Serra and Smith strategy [475]
India DALY Cost-effectiveness threshold	$214	Ochalek et al. [474]; DALY Approach 4 Moreno-Serra and Smith strategy [475]
Mexico DALY Cost-effectiveness threshold	$746	Ochalek et al. [474]; DALY Approach 4 Moreno-Serra and Smith strategy [475]

9.2.5 Sensitivity analyses

Deterministic and probabilistic sensitivity analyses were also undertaken to quantify the model parameter uncertainty.

Deterministic sensitivity analyses

The deterministic sensitivity analysis (DSA) included univariate sensitivity analysis, multivariate sensitivity analysis, scenario analysis, and threshold analysis. A description of the planned Deterministic Sensitivity Analysis is listed in Table 9.5. The alternative cost-effectiveness thresholds for DSA11 and DSA12 were interpreted in reference to the base case results and the base case results were not reproduced again for these scenarios.

Table 9.5 Deterministic sensitivity analysis list

Scenario number	Description
	Clinical Parameters
DSA1	The overall relative risk for Alcoholic Chlorhexidine versus Povidone–iodine (0.94) was applied to both Clean-Contaminated and Contaminated-Dirty strata
DSA2	The overall relative risk for Triclosan-coated Sutures versus Uncoated Sutures (0.94) was applied to both Clean-Contaminated and Contaminated-Dirty strata
DSA3	The overall 30 day postoperative risk of SSI (22%) was applied to both Clean-Contaminated and Contaminated-Dirty strata
	Cost Parameters
DSA4	Additional healthcare cost of an SSI from the Generalised Linear Model was used for each wound contamination strata ($298: Clean-Contaminated; $356: Contaminated-Dirty)
DSA5	Additional healthcare cost of an SSI from the unadjusted analysis was used for each wound contamination strata ($469 Clean-Contaminated; $583 Contaminated-Dirty))
	Utilities
DSA6	As SSI resolution time in days came from an orthopaedic SSI study, the mean SSI resolution time in days was halved (Superficial SSI resolution: 19.09 days; Deep Incisional and Deep Organ Space SSI: 46.92 days) [Cost per DALY averted approach only]
DSA7	The health state utilities and decrements were taken from the Visual Analogue Scores in Chapter 8 (Patient without SSI: 0.574; Superficial SSI decrement: 0.137 , Deep Incisional SSI decrement: 0.227, Deep Organ Space SSI decrement: 0.315)

Scenario number	Description
DSA8	The health state decrement trajectory associated with Deep Incisional SSI and Deep Organ SSI health states were assumed not to be constant to reflect the transient nature of an SSI: (1) for a Deep Incisional SSI, after SSI onset at day 8, a Superficial SSI decrement was applied for the first two and last two days of the 23 days of the SSI duration (2) for a Deep Organ Space SSI, after SSI onset, a Superficial SSI decrement was applied for the first two and last two days of the 23 days of the SSI duration, and a Deep Incisional SSI was applied on days 3 and 21 of the SSI duration. For the rest of the SSI duration, the applicable Deep Incisional SSI and Deep Organ SSI decrements were used for Deep Incisional SSI health state and Deep Organ SSI health state, respectively. [Cost per QALY approach only]
DSA9	The health state utilities and decrements were taken from the ROSSINI re-analysis in Chapter 6 and applied across the month (No SSI: 0.616; SSI decrement: 0.056)
	Scenario Analysis
DSA10	The cost-effectiveness of a Combined Treatment (Chlorhexidine and Coated Sutures) was assessed relative to the other strategies. The treatment effectiveness by wound contamination strata was assumed to be the product of the respective relative risks.
DSA11	The lower bound cost-effectiveness QALY thresholds were used for Ghana ($224), India ($416), and Mexico ($3,850) and applied to the base case results
DSA12	The alternative cost-effectiveness DALY thresholds were used for Ghana ($42), India ($36), and Mexico ($3,183) and applied to the base case results
DSA13	Societal costs based on numbers of days of paid employment off within a month by changes in health status were included[477] and valued by the 2020 daily minimum wage for each country [478–480]
DSA14	The time horizon was extended to 2 months, costs of SSI was increased by 10% over the extended time horizon, SSI utility decrements were expected to last an additional month and societal costs based on numbers of days of paid employment off within 6 weeks by changes in health status were included[477] and valued by the 2020 daily minimum wage for each country[478–480] [Cost per QALY approach only]
	Threshold Analysis

Scenario number	Description
DSA15	The effectiveness of the Alcoholic Chlorhexidine intervention was varied to assess the minimum level of effectiveness required to be the most cost-effective option
DSA16	The effectiveness of the Triclosan-coated sutures intervention was varied to assess the minimum level of effectiveness required to be the most cost-effective option
DSA17	The baseline SSI risk was varied to assess the minimum level of baseline 30 day postoperative probability of SSI required for any of the interventions to remain cost-effective versus Usual Care.
DSA18	The cost of SSI was varied to assess the minimum level of costs associated with SSI required for any of the interventions to remain cost-effective versus Usual Care.
DSA19	An overall quality of life decrement associated with SSI was varied to assess the minimum level of disutility associated with SSI required for any of the interventions to remain cost-effective versus Usual Care. [Cost per QALY approach only]

Probabilistic sensitivity analysis

10,000 iterations were run for the Probabilistic Sensitivity Analysis (PSA) to assess the joint parameter uncertainty of the model inputs. The same random number generator set (seeded run) was undertaken for each setting. The mean Probabilistic Sensitivity Analysis iterations were expressed using the Net Monetary Benefit (NMB) for each strategy with each additional QALY and DALYs valued at their respective countries cost-effectiveness threshold.

The 30 day postoperative probabilities of SSI by wound contamination strata, and mortality by SSI status were assigned a beta distribution with information on the count data used for the PSA parameters. SSI severity was assigned a Dirichlet distribution, and the count data was used for parameters. Treatment effectiveness relative risk ratios were assigned a log-normal distribution with parameters estimated from the reported means and 95% Confidence Intervals. The mean days of SSI resolution was assigned a Poisson distribution based on the estimated mean value for Superficial SSI, Deep Incisional SSI, and Deep Organ Space SSI.

The intervention costs were assigned Gamma distributions with an assumed standard error of 15% of the mean cost. For the additional healthcare and societal costs of SSI, normal distributions were used which allowed the possibility of no additional cost or less additional costs associated with SSI. The No SSI health state utility was assigned a beta distribution with the information on the mean and standard error parameterised using method of moments method [124]. The SSI utility decrements were assigned a normal distribution based on the mean and standard errors. The SSI utility decrements were linked to the corresponding disability weights and variability in the utility decrements in the PSA was reflected in the disability weights for the PSA in the Cost per QALY approach.

The PSA output was illustrated using incremental cost-effectiveness planes and Cost-effectiveness acceptability curves (CEAC). The incremental cost-effectiveness plane compared the incremental costs and effects of two strategies across the four cost-effectiveness quadrants and included the country-specific willingness to pay (WTP) threshold as a diagonal line with incremental iterations that would be considered cost-effective under the line and vice versa. Further, incremental iterations that were considered cost-effective and not cost-effective were coloured green and red, respectively. A confidence ellipse conveyed the region in the incremental cost-effectiveness plane where 95% of the incremental iterations resided [301].

The CEAC expressed the Net Monetary Benefits from each strategy across a range of different WTP thresholds. A separate PSA explored looking at a Combined Treatment of Triclosan-coated Sutures and 2% Alcoholic Chlorhexidine. As there was no interaction effect found in the FALCON trial between the treatments [373], the product of the separate relative risks by wound contamination strata in the PSA was used for the treatment effectiveness of the Combined Treatment.

9.2.6 Value of information analysis

A Value of Information analysis was undertaken to assess the EVPI and EVPPI using the model's PSA output across the different setting. The EVPI was first calculated on a per patient basis across a range of (WTP) thresholds.

EVPPI was calculated using a double loop Monte Carlo simulation [134]. Selected parameters of interest were grouped in the outer loop and the rest of the parameters averaged within the inner loop. The inner loop was run for 10,000 samples and the outer loop were run with 1,000

samples. The results were presented on a per patient basis. The EVPPI of following groups of parameters were assessed:

1. 2% Alcoholic Chlorhexidine and Triclosan-coated Sutures effectiveness (wound contamination specific 2% Alcoholic Chlorhexidine Relative Risk; wound contamination specific Triclosan-coated Sutures Relative Risk)
2. SSI quality of life decrements (Superficial SSI health state decrement, Deep Incisional SSI health state decrement; Deep Organ Space SSI health state decrement)
3. Additional Cost of SSI (country and wound contamination specific)

9.3 Results

9.3.1 Deterministic results

Base case results are shown in Table 9.6 for the Cost per QALY approach. Triclosan-coated Sutures was the dominant strategy in the patient group with Clean-Contaminated wounds in India. Usual Care had the lowest costs in the patient group with Clean-Contaminated wounds in Mexico, and the additional cost of either Alcoholic Chlorhexidine or Triclosan-coated Sutures was too high for the interventions to be considered cost-effective at the specified cost-effectiveness threshold. With lower costs and higher QALYs, Alcoholic Chlorhexidine was the dominant strategy in the Contaminated-Dirty wound contamination strata in India and Ghana.

Base case results are shown in Table 9.7 for the Cost per DALY averted approach. The decision recommendations were the same as the Cost per QALY approach except for Mexico. Triclosan-coated Sutures had the lowest costs and DALYs in the Clean-Contaminated wound contamination strata in India while Alcoholic Chlorhexidine had the lowest costs and DALYs in the Contaminated-Dirty wound contamination strata in India and Ghana. Due to the dominance of the strategies for the above settings, cost-effectiveness thresholds were not necessary to determine the most cost-effective option. For Mexico, either Alcoholic Chlorhexidine or Triclosan-coated Sutures could be considered cost-effective compared to Usual Care. Triclosan-coated Sutures would be the most cost-effective strategy at the Mexico $746 per DALY averted cost-effectiveness threshold. The YLL component accounted for over 95% of the DALYs across all strategies and settings.

Table 9.6 Cost per QALY base case results (international dollars 2020)

Strategy	Healthcare Cost (Int$)	Incremental Healthcare Costs (Int$)	Societal Cost (Int$)	QALY	Incremental QALY	ICER (Int$)
India Clean-Contaminated						
Triclosan-coated Sutures	127		5.87	0.058669		Dominant
Usual Care	136	9.03	6.52	0.058452	-0.00022	Dominated
Alcoholic Chlorhexidine	137	9.58	6.33	0.058517	-0.00015	Dominated
India Contaminated Dirty						
Alcoholic Chlorhexidine	103		16.40	0.0568		Dominant
Usual Care	106	3.18	18.02	0.056422	-0.00038	Dominated
Triclosan-coated Sutures	106	3.33	17.66	0.056506	-0.00029	Dominated
Mexico Clean-Contaminated						
Usual Care	112		-6.52	0.058452		
Alcoholic Chlorhexidine	114	1.56	-6.33	0.058517	0.00007	23,951
Triclosan-coated Sutures	123	9.06	-5.87	0.058669	0.00015	59,489
Ghana Contaminated-Dirty						
Alcoholic Chlorhexidine	142		10.38	0.0568		Dominant
Triclosan-coated Sutures	151	9.02	11.18	0.056506	-0.00029	Dominated
Usual Care	153	11.14	11.41	0.056422	-0.00038	Dominated
ICER: Incremental cost-effectiveness ratio; NMB: Net Monetary Benefit; QALY: Quality Adjusted Life Year						

Table 9.7 Cost per DALY averted base case results (international dollars 2020)

Strategy	Healthcare Cost (Int$)	Incremental Healthcare Costs (Int$)	Societal Cost (Int$)	DALY	Incremental DALY averted	ICER
India Clean-Contaminated						
Triclosan-coated Sutures	127		5.87	0.10573		Dominant
Alcoholic Chlorhexidine	136	9.03	6.52	0.117478	-0.011748	Dominated
Usual Care	137	9.58	6.33	0.113953	-0.008223	Dominated
India Contaminated-Dirty						
Alcoholic Chlorhexidine	103		16.40	0.20669		Dominant
Usual Care	106	3.18	18.02	0.227132	-0.02044	Dominated
Triclosan-coated Sutures	106	3.33	17.66	0.222589	-0.01590	Dominated
Mexico Clean-Contaminated						
Usual Care	112		-6.52	0.132551		
Alcoholic Chlorhexidine	114	1.56	-6.33	0.128575	0.00398	393
Triclosan-coated Sutures	123	9.06	-5.87	0.119296	0.01326	976
Ghana Contaminated-Dirty						
Alcoholic Chlorhexidine	142		10.38	0.200766		Dominant
Triclosan-coated Sutures	151	9.02	11.18	0.21621	-0.01544	Dominated
Usual Care	153	11.14	11.41	0.220622	-0.01986	Dominated
DALY: Disability Adjusted Life Year; ICER: Incremental cost-effectiveness ratio; NMB: Net Monetary Benefit						

The results of the DSA are shown in Appendix Tables A9.1-A9.27 and summarised in Tables 9.8-9.9. When overall relative risks of treatment effectiveness were used instead of relative risks by wound contamination strata (Appendix Tables A9.1-A9.4), the decision recommendations for India and Ghana did not change and the dominant strategies in the base case remained so in both the Cost per QALY and the Cost per DALY averted approaches. For the patient group with Clean-Contaminated wounds in Mexico, when the Alcoholic Chlorhexidine relative risk was lowered to 0.94, the Alcoholic Chlorhexidine strategy dominated Usual Care and would also be considered the most cost-effective strategy compared to Triclosan-coated Sutures (Appendix Tables A9.1-A9.2). When the overall relative risks of treatment effectiveness for Triclosan-coated Sutures was altered to 0.94, Usual Care remained the most cost-effective strategy for the patient group with Clean-Contaminated wounds in Mexico as per the base case analysis in the Cost per QALY approach (Appendix Table A9.3). Under this deterministic sensitivity analysis in the Cost per DALY averted approach for the same group of patients, Alcoholic Chlorhexidine overtook Triclosan-coated Sutures and became the most cost-effective strategy with an ICER of $237 per DALY averted (Appendix Table A9.4).

The decision recommendations did not change from the base case for both India and Ghana when the overall 30 day postoperative risk of SSI was applied to both wound contamination strata (Appendix Tables A9.5-A9.6). For Mexico, Alcoholic Chlorhexidine became the most cost-effective strategy with an ICER of $7,124 per QALY in the Cost per QALY approach (Appendix Table A9.5). For the Cost per DALY averted approach, Triclosan-coated Sutures remained the most cost-effective strategy for the patient group with Clean-Contaminated wounds in Mexico when the overall 30 day postoperative risk of SSI was applied (Appendix Table A9.6).

Table 9.8 Most cost-effective strategy for deterministic results (Cost per QALY approach)

	Base Case	DSA1	DSA2	DSA3	DSA4	DSA5	DSA7	DSA8	DSA9	DSA13	DSA14
India Clean-Contaminated											
Triclosan-coated Sutures	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Alcoholic Chlorhexidine											
Usual Care											
India Contaminated-Dirty											
Triclosan-coated Sutures											
Alcoholic Chlorhexidine	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Usual Care											
Mexico Clean-Contaminated											
Triclosan-coated Sutures											
Alcoholic Chlorhexidine		✓		✓							✓
Usual Care	✓		✓		✓	✓	✓	✓	✓	✓	
Ghana Contaminated-Dirty											
Triclosan-coated Sutures											
Alcoholic Chlorhexidine	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Usual Care											

Table 9.9 Most cost-effective strategy for deterministic results (Cost per DALY averted approach)

	Base Case	DSA1	DSA2	DSA3	DSA4	DSA5	DSA6	DSA7	DSA9	DSA13
India Clean-Contaminated										
Triclosan-coated Sutures	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Alcoholic Chlorhexidine										
Usual Care										
India Contaminated-Dirty										
Triclosan-coated Sutures										
Alcoholic Chlorhexidine	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Usual Care										
Mexico Clean-Contaminated										
Triclosan-coated Sutures				✓						
Alcoholic Chlorhexidine	✓	✓	✓		✓	✓	✓	✓	✓	✓
Usual Care										
Ghana Contaminated-Dirty										
Triclosan-coated Sutures										
Alcoholic Chlorhexidine	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Usual Care										

Using alternative estimates for the additional healthcare cost of an SSI did not alter the decision recommendations on the most cost-effective option (Appendix Tables A9.7-A9.10). Nor was reducing the SSI resolution time by 50% sufficient to change the most cost-effective option in any of the settings for the Cost per DALY averted approach (Appendix Table A9.11). For the utility parameters, the cost-effectiveness results were robust to alternative estimates (Appendix Table A9.12-A9.13, A9.15-A9.16) or differences in SSI trajectory (Appendix Table A9.14). The alternative cost-effectiveness thresholds applicable for different countries did not change the decision recommendations.

For the deterministic sensitivity analysis where a Combined Treatment (Chlorhexidine and Triclosan-coated Sutures) was added as a comparator, the dominance of the single treatment comparator was challenged (Appendix Table A9.17- A9.18). For the Cost per QALY approach, the decision recommendations did not change in India and Mexico although the Combined Treatment was now the most effective strategy across all settings. In Ghana, the Combined Treatment now dominated the other strategies. For the Cost per DALY averted approach, the Combined Treatment was now the most cost-effective strategy across all the settings. The addition of the Combined Treatment strategy for the patient group with Clean-Contaminated wounds in Mexico results in the Triclosan-coated Sutures being ruled out due to extended dominance from a mixed strategy of Alcoholic Chlorhexidine only, and the Combined Treatment.

Adding in the societal costs based on valuing changes in societal costs increased the total level of societal costs but it was not a large additional change after accounting for the paid number of employment days off for postoperative patients with no SSI sharing the same range as superficial SSI patients and only representing an additional 2.1 days compared to deep incisional SSI patients and deep organ space SSI patients (Appendix Tables A9.19-20). For

Mexico clean-contaminated patients, the addition of the societal costs did not outweigh the reduction in societal costs associated with SSI found in the KIWI study. Extending the time horizon by 2 months did not change the decision recommendations except for Mexico where Alcoholic Chlorhexidine now becomes cost-effective as opposed to Usual Care in the base case cost per QALY approach. The increase in societal costs were even more marginal in this scenario as the difference between paid number of employment days off for postoperative patients with no SSI and superficial SSI patients versus deep incisional SSI patients and deep organ space SSI patients only represented an additional 0.4 days.

The threshold analyses are shown in Appendix Tables A9.22-A9.30. The minimum level of treatment effectiveness varied by country, wound contamination, and approach (Appendix Tables A9.22-A9.25). The minimum level of the baseline 30 day postoperative probability of SSI required for any of the interventions to be cost-effective versus Usual Care ranged from 3.5% to 20.2% by setting in the Cost per QALY approach (Appendix Table A9.26) and ranged from 1.7% to 7.7% by setting in the Cost per DALY averted approach (Appendix Table A9.27).

For the Cost per QALY approach, the minimum level of costs associated with SSI required for any of the interventions to remain cost-effective versus Usual Care ranged from $70 in the India Clean-Contaminated wound contamination strata to $646 in the Mexico Clean-Contaminated wound contamination strata (Appendix Tables A9.28). For the Cost per DALY averted approach, the minimum level of costs associated with SSI required for any of the interventions to remain cost-effective versus Usual Care were all unrealistic and ranged from -$258 in the Mexico Clean-Contaminated wound strata and -$60 in the Ghana Contaminated-Dirty strata (Appendix Tables A9.29). Lastly, the minimum level of SSI disutility required for any of the interventions to remain cost-effective versus Usual Care in India and Ghana all had

negative values in all settings meaning that an SSI would have to increase quality of life for the Usual Care strategy to compete on cost-effectiveness. For Mexico, the overall SSI utility decrement would have to increase to 0.486 in the Cost per QALY approach.

9.3.2 Probabilistic sensitivity analysis results

The mean PSA iterations are shown in Table 9.10. As with the deterministic base case results, Triclosan-coated Sutures had the lowest costs and DALYs, and the highest QALYs in the patient group with Clean-Contaminated wounds in India. Similarly, Alcoholic Chlorhexidine had the lowest costs and DALYs, and the highest QALYs in the Contaminated-Dirty wound contamination strata for India and Ghana. For Mexico, the Usual Care strategy had the lowest costs, QALYs and DALYs averted for the patient group with Clean-Contaminated wounds.

Table 9.10 Mean PSA results (international dollars 2020)

Strategy	Healthcare Cost [Int$] (95% PI)	Societal Cost [Int$] (95% PI)	QALYs (95% PI)	QALYs NMB [Int$] (95% PI)	DALYs (95% PI)	DALY NMB [Int$] (95% PI)
India Clean-Contaminated						
Usual Care	136 (136 to 137)	6.57 (6.3 to 6.84)	0.05843 (0.05839 to 0.05846)	26 (26 to 27)	0.2107 (0.21 to 0.2114)	-181 (-182 to -181)
Triclosan-coated Sutures	127 (127 to 128)	5.93 (5.69 to 6.18)	0.05864 (0.05861 to 0.05867)	36 (35 to 36)	0.1917 (0.191 to 0.1924)	-169 (-169 to -168)
Alcoholic Chlorhexidine	137 (137 to 138)	6.41 (6.14 to 6.67)	0.05848 (0.05845 to 0.05852)	26 (25 to 26)	0.2057 (0.2049 to 0.2064)	-181 (-182 to -181)
India Contaminated-Dirty						
Usual Care	105 (103 to 106)	18.08 (17.65 to 18.52)	0.05639 (0.05635 to 0.05642)	52 (51 to 54)	0.3762 (0.3749 to 0.3774)	-185 (-186 to -184)
Triclosan-coated Sutures	105 (104 to 106)	17.75 (17.32 to 18.18)	0.05647 (0.05643 to 0.0565)	52 (51 to 54)	0.3700 (0.3687 to 0.3713)	-184 (-185 to -183)
Alcoholic Chlorhexidine	102 (100 to 103)	16.47 (16.07 to 16.87)	0.05676 (0.05673 to 0.0568)	56 (55 to 58)	0.3477 (0.3465 to 0.3488)	-176 (-177 to -175)
Mexico Clean-Contaminated						
Usual Care	113 (110 to 115)	-6.57 (-6.3 to -6.84)	0.05843 (0.05839 to 0.05846)	517 (514 to 520)	0.2385 (0.2377 to 0.2393)	-291 (-293 to -288)
Triclosan-coated Sutures	124 (121 to 126)	-5.93 (-5.69 to -6.18)	0.05864 (0.05861 to 0.05867)	508 (506 to 511)	0.217 (0.2162 to 0.2178)	-286 (-288 to -283)
Alcoholic Chlorhexidine	114 (112 to 117)	-6.41 (-6.14 to -6.67)	0.05848 (0.05845 to 0.05852)	516 (513 to 519)	0.2328 (0.2319 to 0.2336)	-288 (-291 to -285)
Ghana Contaminated-Dirty						
Usual Care	152 (152 to 153)	11.1 (10.18 to 12.03)	0.05639 (0.05635 to 0.05642)	-37 (-38 to -36)	0.3651 (0.3639 to 0.3663)	-194 (-195 to -193)
Triclosan-coated Sutures	151 (150 to 151)	10.88 (9.98 to 11.79)	0.05647 (0.05643 to 0.0565)	-35 (-36 to -34)	0.3591 (0.3579 to 0.3604)	-191 (-192 to -191)
Alcoholic Chlorhexidine	141 (141 to 142)	10.14 (9.29 to 10.98)	0.05676 (0.05673 to 0.0568)	-26 (-26 to -25)	0.3375 (0.3363 to 0.3386)	-180 (-181 to -179)
DALY: Disability Adjusted Life Year; NMB: Net Monetary Benefit; PI: Prediction Interval; QALY: Quality Adjusted Life Year						

Triclosan-coated Sutures had the highest NMB for QALYs and DALYs at the specified cost-effectiveness thresholds for the Clean-Contaminated wound contamination patient group in India. Alcoholic Chlorhexidine had the highest NMB in QALYs and DALYs at the specified cost-effectiveness thresholds for the Contaminated-Dirty wound contamination patient groups in India and Ghana. For Mexico, Usual Care and Triclosan-coated Sutures had the highest NMB for QALYs and DALYs at the specified cost-effectiveness thresholds, respectively.

The incremental cost-effectiveness planes for each setting and approach are shown in Appendix Figures A9.1-A9.24.

India Clean-Contaminated

For the Cost per QALY approach, the incremental iterations of Triclosan-coated Sutures versus Usual Care, Triclosan-coated Sutures versus Alcoholic Chlorhexidine , and Alcoholic Chlorhexidine versus Usual Care are shown in Appendix Figure A9.1, Appendix Figure A9.2 , and Appendix Figure A9.3, respectively. For each Triclosan-coated Sutures comparison there are a higher proportion of cost-effective iterations (denoted in green) than non-cost-effective iterations (denoted in red). For Triclosan-coated Sutures versus Usual Care, 82.47% of the PSA iterations indicated that Triclosan-coated Sutures was the most cost-effective strategy. For Triclosan-coated Sutures versus Alcoholic Chlorhexidine, 71.03% of the PSA iterations indicated that Triclosan-coated Sutures was the most cost-effective strategy. For Alcoholic Chlorhexidine versus Usual Care, 47.28% of the PSA iterations indicated that Alcoholic Chlorhexidine was the most cost-effective strategy.

The same pattern of incremental iterations is evident in the Cost per DALY averted approach (Appendix Figure A9.4-A9.6). For Triclosan-coated Sutures versus Usual Care, 84.28% of the PSA iterations indicated that Triclosan-coated Sutures was the most cost-effective strategy.

For Triclosan-coated Sutures versus Alcoholic Chlorhexidine, 72.4% of the PSA iterations indicated that Triclosan-coated Sutures was the most cost-effective strategy. For Alcoholic Chlorhexidine versus Usual Care, it was a near even split with 49.64% of the PSA iterations indicating that Alcoholic Chlorhexidine was the most cost-effective strategy.

The CEAC for the India Clean-Contaminated surgical patients is shown in Figure 9.2 in the Cost per QALY approach and Figure 9.3 in the Cost per DALY averted approach. At a WTP threshold of $2,781 per QALY, Triclosan-coated Sutures had the highest the proportion of iterations that were cost-effective (71.72%), followed by Alcoholic Chlorhexidine (19.55%) and Usual Care (8.73%). The flatness of the curves across the WTP thresholds reflects the incremental iterations either falling into the Northwest and Southeast quadrants. At a WTP threshold of $214 per DALY, Triclosan-coated Sutures had the highest the proportion of iterations that were cost-effective (72.31%), followed by Alcoholic Chlorhexidine (20.08%) and Usual Care (8.73%). Again, the curves were broadly flat across the WTP thresholds based on the location of the incremental PSA iterations and bore much similarity to the Cost per QALY approach.

Figure 9.2 Cost-effectiveness acceptability curve India Clean-Contaminated (Cost per QALY)

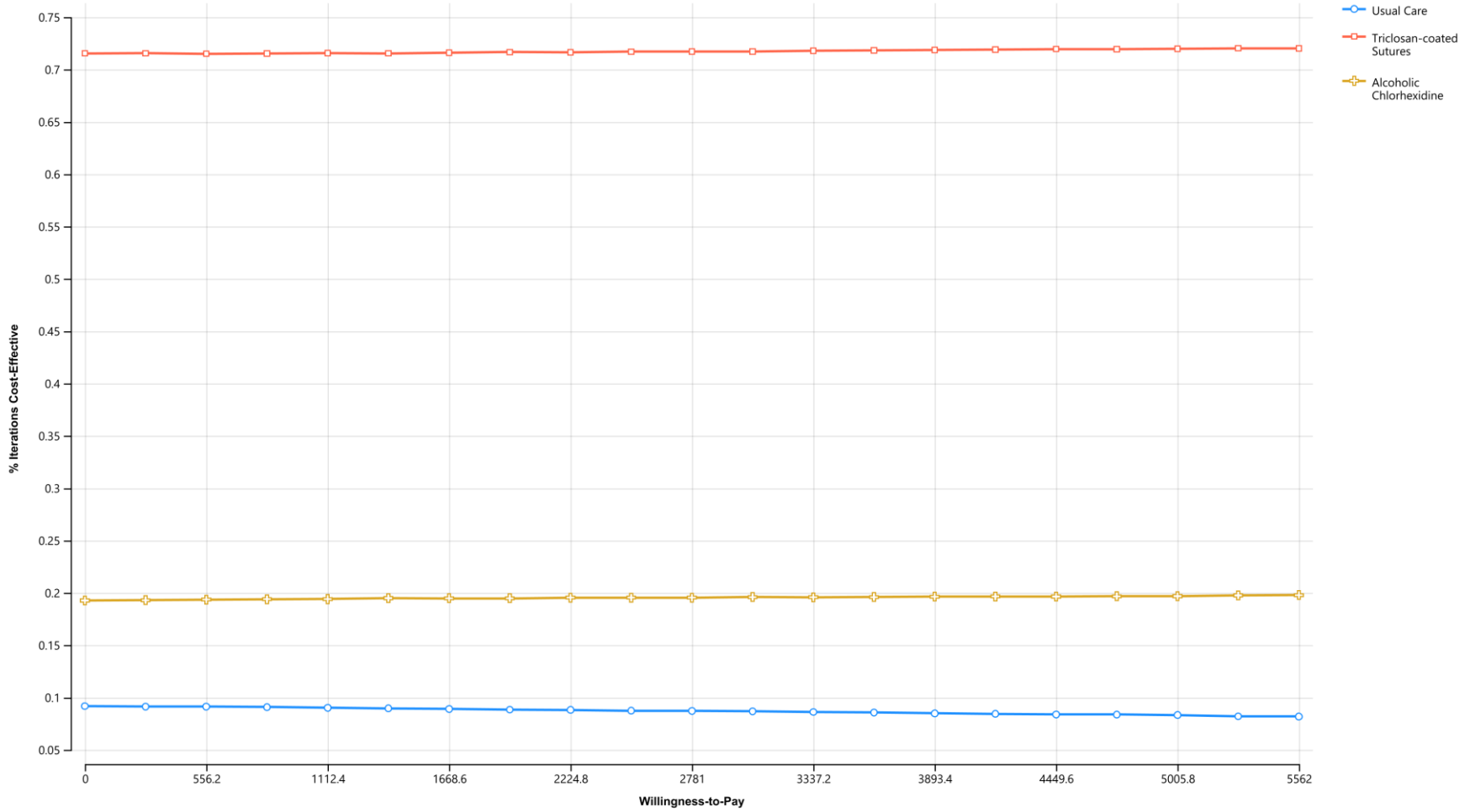
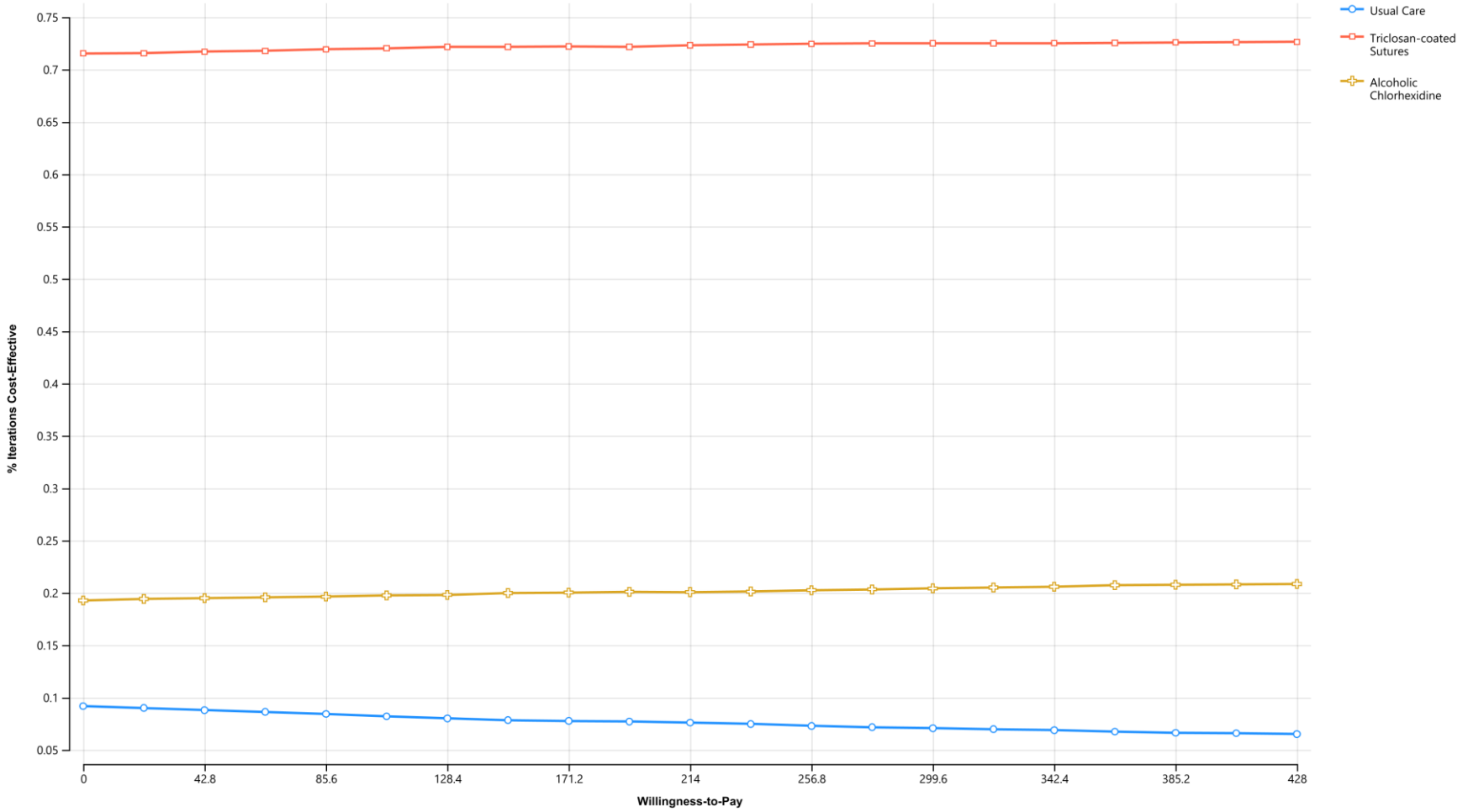


Figure 9.3 Cost-effectiveness acceptability curve India Clean-Contaminated (Cost per DALY averted)



India Contaminated-Dirty

For the Cost per QALY approach, the incremental iterations of Triclosan-coated Sutures versus Usual Care (Appendix Figure A9.7), Triclosan-coated Sutures versus Alcoholic Chlorhexidine (Appendix Figure A9.8), and Alcoholic Chlorhexidine versus Usual Care (Appendix Figure A9.9) were more scattered than the equivalent scatterplots for the patient group with Clean-Contaminated wounds in India. Here, Triclosan-coated Sutures had more iterations that were not cost-effective (illustrated in red) versus Alcoholic Chlorhexidine or Usual Care. For Triclosan-coated Sutures versus Usual Care, 41.24% of the PSA iterations indicated that Triclosan-coated Sutures was the most cost-effective strategy. For Triclosan-coated Sutures versus Alcoholic Chlorhexidine, few PSA iterations (18.04%) indicated that Triclosan-coated Sutures was the most cost-effective strategy. For Alcoholic Chlorhexidine versus Usual Care, 62.75% of the PSA iterations indicated that Alcoholic Chlorhexidine was the most cost-effective strategy. The vast majority of the cost-effective iterations of Alcoholic Chlorhexidine versus Usual Care were located in the Southeast quadrant with a few in the Northeast and Southwest Quadrant. This pattern was also displayed in the Triclosan-coated Sutures versus Alcoholic Chlorhexidine incremental cost-effectiveness scatterplot (mirrored as Alcoholic Chlorhexidine is the baseline and Triclosan-coated Sutures is the comparator).

The same pattern of incremental iterations is evident in the Cost per DALY averted approach (Appendix Figure A9.4-A9.6). For Triclosan-coated Sutures versus Usual Care, the number of PSA iterations that indicated that Triclosan-coated Sutures was the most cost-effective strategy increased under the Cost per DALY averted approach to 47.95%. For Triclosan-coated Sutures versus Alcoholic Chlorhexidine, the number of PSA iterations that indicated that Triclosan-coated Sutures was the most cost-effective strategy also increased under the Cost per DALY averted approach (26.08%). For Alcoholic Chlorhexidine versus Usual Care,

it rose to 74.11% of the PSA iterations that showed Alcoholic Chlorhexidine being the most cost-effective strategy.

The CEAC for the India Contaminated-Dirty surgical patients is shown in Figure 9.4 in the Cost per QALY approach. The percentage of cost-effective iterations from the Alcoholic Chlorhexidine strategy increased as the WTP threshold increased. The percentage of cost-effective iterations from the Usual Care strategy decreased as the WTP threshold increased. The percentage of cost-effective iterations from the Triclosan-coated Sutures strategy remained flat with a slight decrease as the WTP threshold increased. This suggests that the increase in cost-effective iterations from the Alcoholic Chlorhexidine strategy as the WTP threshold increased mainly came from iterations that would have otherwise been the most cost-effective option for Usual Care under lower WTP thresholds. At a WTP threshold of $2781 per QALY, Alcoholic Chlorhexidine had the highest the proportion of iterations that were cost-effective (49.61%), followed by Triclosan-coated Sutures (28.52%) and Usual Care (21.87%).

The CEAC for the India Contaminated-Dirty surgical patients is shown in Figure 9.5 in the Cost per DALY averted approach. Here, the percentage of cost-effective iterations from the Alcoholic Chlorhexidine strategy increased at a higher rate at the lower WTP thresholds ranges compared to the increases at the upper bounds of the WTP thresholds. Both the Triclosan-coated Sutures strategy and Usual Care strategy decreased as the WTP threshold increased. The Alcoholic Chlorhexidine strategy is the most cost-effective option even if decisions makers do not place any monetary value on DALYs averted. At a WTP threshold of $214 per DALY, Alcoholic Chlorhexidine had the highest the proportion of iterations that were cost-effective (59.44%), followed by Triclosan-coated Sutures (26.15%) and Usual Care (14.41%).

Figure 9.4 Cost-effectiveness acceptability curve India Contaminated-Dirty (Cost per QALY)

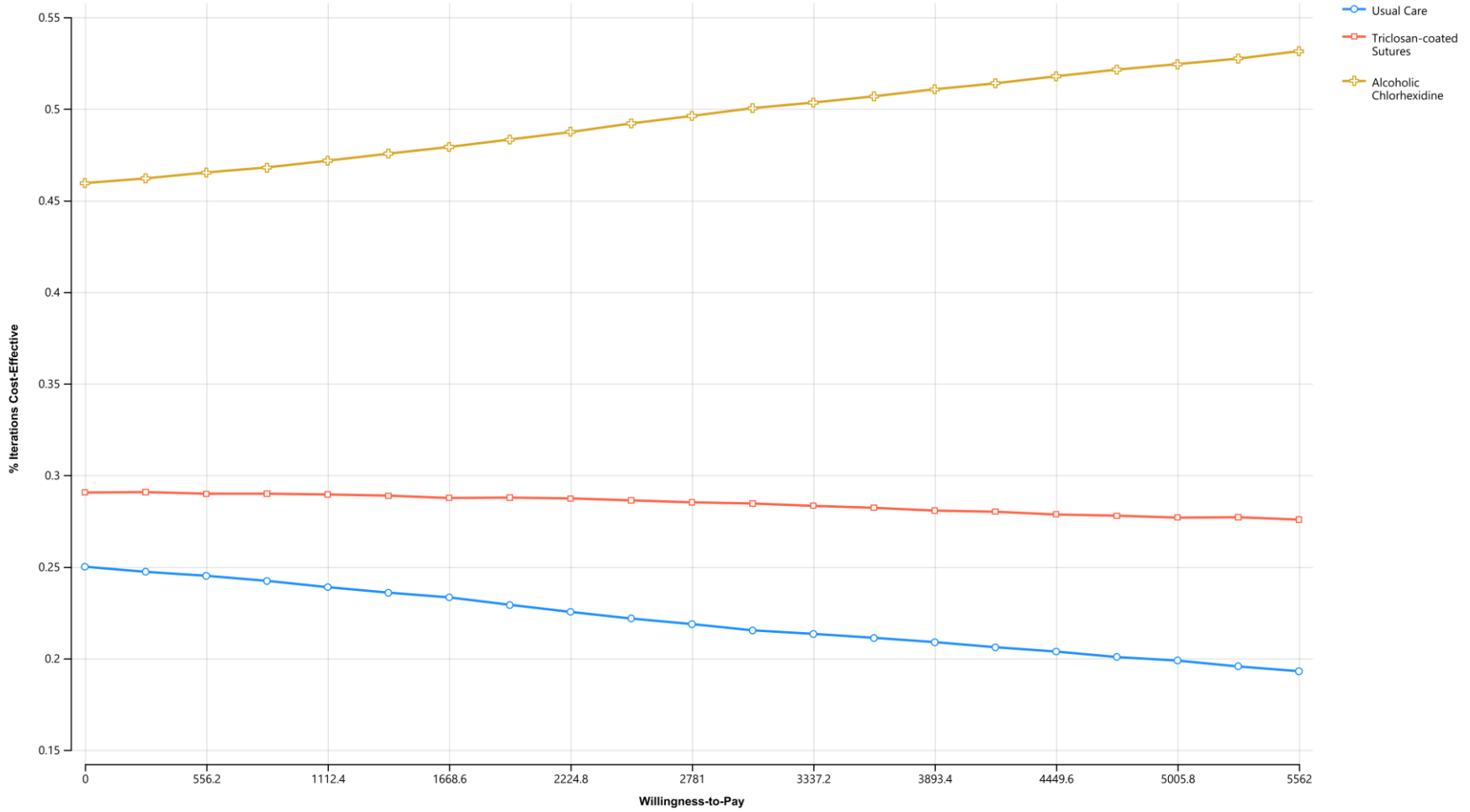
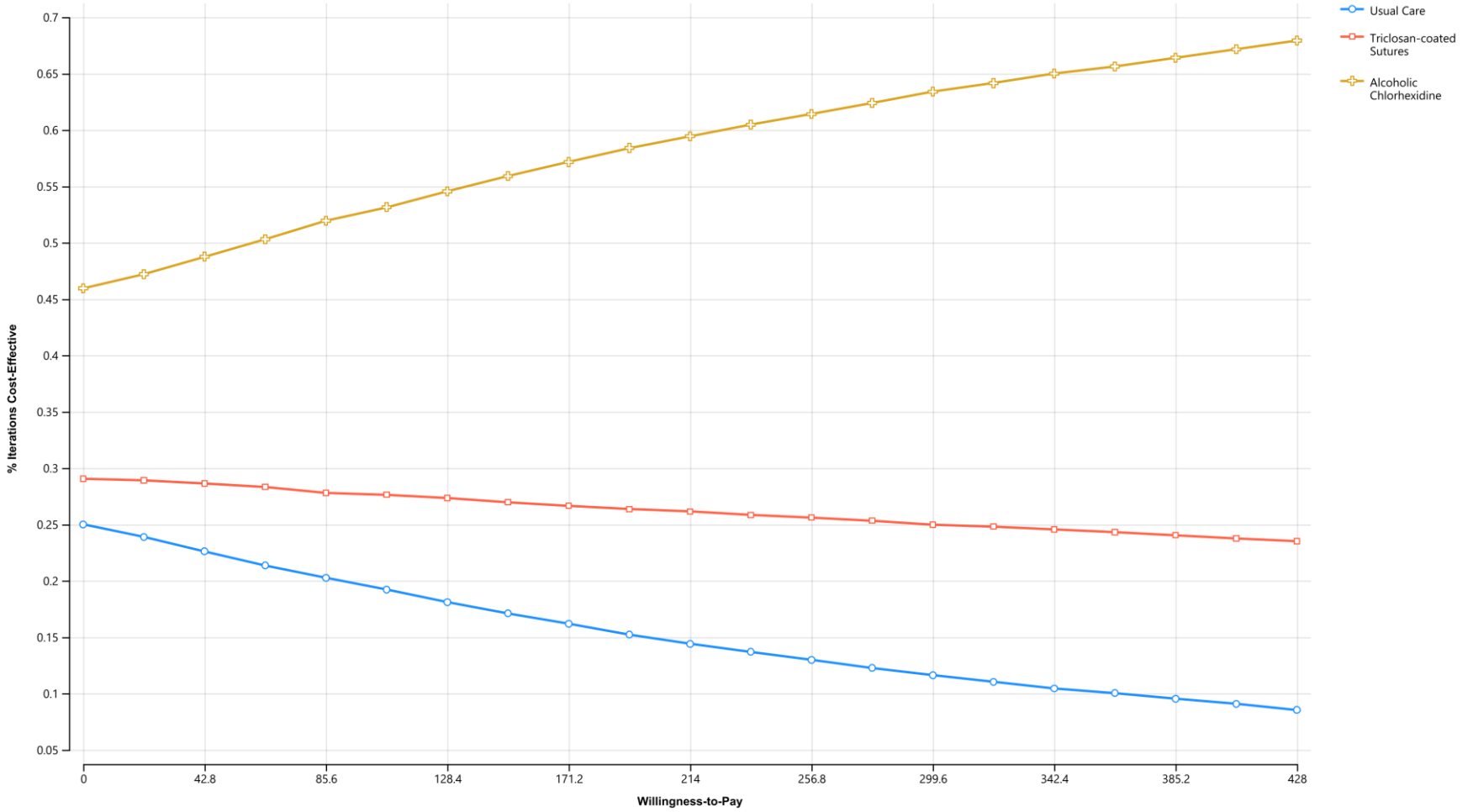


Figure 9.5 Cost-effectiveness acceptability curve India Contaminated-Dirty (Cost per DALY averted)



Mexico Clean-Contaminated

For the Cost per QALY approach, the incremental iterations of Triclosan-coated Sutures versus Usual Care, Triclosan-coated Sutures versus Alcoholic Chlorhexidine, and Alcoholic Chlorhexidine versus Usual Care are shown in Appendix Figures A9.13- A9.15. For Triclosan-coated Sutures versus Usual Care, the majority of PSA iterations were in the Northeast and Southeast quadrants indicating that Triclosan-coated Sutures were generally more effective than Usual Care. For Triclosan-coated Sutures versus Usual Care, 27.89% of the PSA iterations indicated that Triclosan-coated Sutures was the most cost-effective strategy. For Triclosan-coated Sutures versus Alcoholic Chlorhexidine, less than a third of the PSA iterations (28.62%) indicated that Triclosan-coated Sutures was the most cost-effective strategy. For Alcoholic Chlorhexidine versus Usual Care, 36.39% of the PSA iterations indicated that Alcoholic Chlorhexidine was the most cost-effective strategy.

For the Cost per DALY averted approach (Appendix Figure A9.16- A9.18), the strategies with the highest proportion of PSA iterations stays the same compared to the Cost per QALY approach. For Triclosan-coated Sutures versus Usual Care, less than half of the PSA iterations (41.75%) indicated that Triclosan-coated Sutures was the most cost-effective strategy. For Triclosan-coated Sutures versus Alcoholic Chlorhexidine, just under half the PSA iterations (40.13%) indicated that Triclosan-coated Sutures was the most cost-effective strategy. For Alcoholic Chlorhexidine versus Usual Care, 48.26% of the PSA iterations indicated that Alcoholic Chlorhexidine was the most cost-effective strategy.

The CEAC for the Mexico Clean-Contaminated surgical patients is shown in Figure 9.6 in the Cost per QALY approach and Figure 9.7 in the Cost per DALY averted approach. The strategy with the highest percentage of cost-effective iterations differed by approach. For the Cost per QALY approach, the proportion of most cost-effective iterations attributed to the Usual Care Strategy decreased as the WTP thresholds increased. Both Triclosan-coated Sutures and Alcoholic Chlorhexidine strategies increased their proportions of most cost-effective iterations as the WTP thresholds increased. The ranking order for the three strategies did not change across the observed WTP thresholds. At a WTP threshold of $10,780 per QALY, Usual Care had the highest the proportion of iterations that were cost-effective (47.54%), followed by Alcoholic Chlorhexidine (31.82%), and Triclosan-coated Sutures (20.64%).

For the Cost per DALY averted approach, all strategies intersect with each other at the observed WTP ranges. The Usual Care strategy has the highest proportion of most cost-effective PSA iterations at a zero WTP for an additional QALY threshold. The Usual Care strategy had more cost-effective iterations at the lower WTP thresholds compared to Alcoholic Chlorhexidine until a crossover point of a WTP of ~$760 for an additional DALY averted. Thereafter, Alcoholic Chlorhexidine had the highest proportion of most cost-effective PSA iterations until a crossover point with Triclosan-coated Sutures at WTP of ~$970 for an additional DALY averted. At a WTP threshold of $746 per DALY averted, Usual Care had the highest the proportion of iterations that were cost-effective (34.86%), followed by Alcoholic Chlorhexidine (34.44%) and Triclosan-coated Sutures (30.70%).

Figure 9.6 Cost-effectiveness acceptability curve Mexico Clean-Contaminated (Cost per QALY)

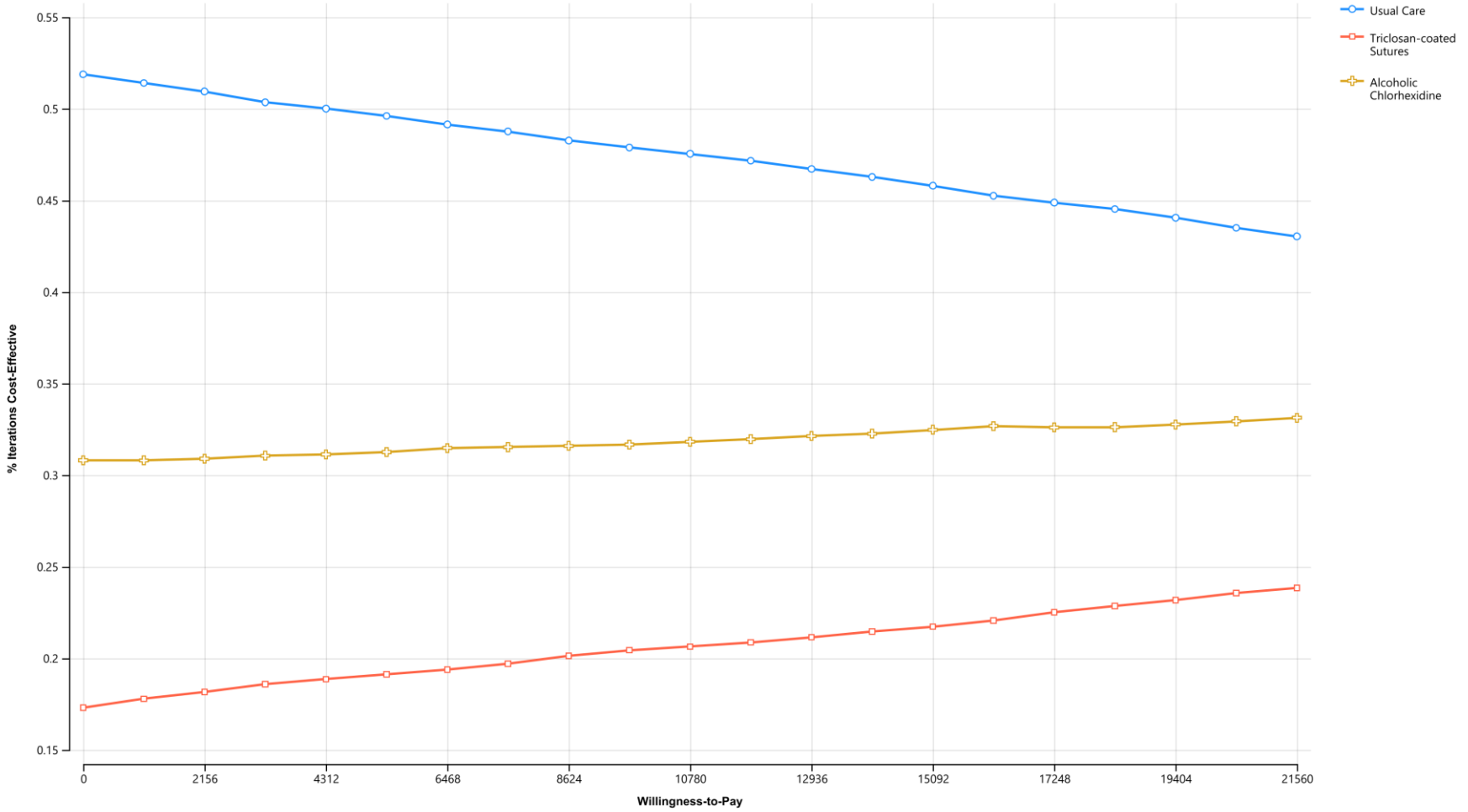
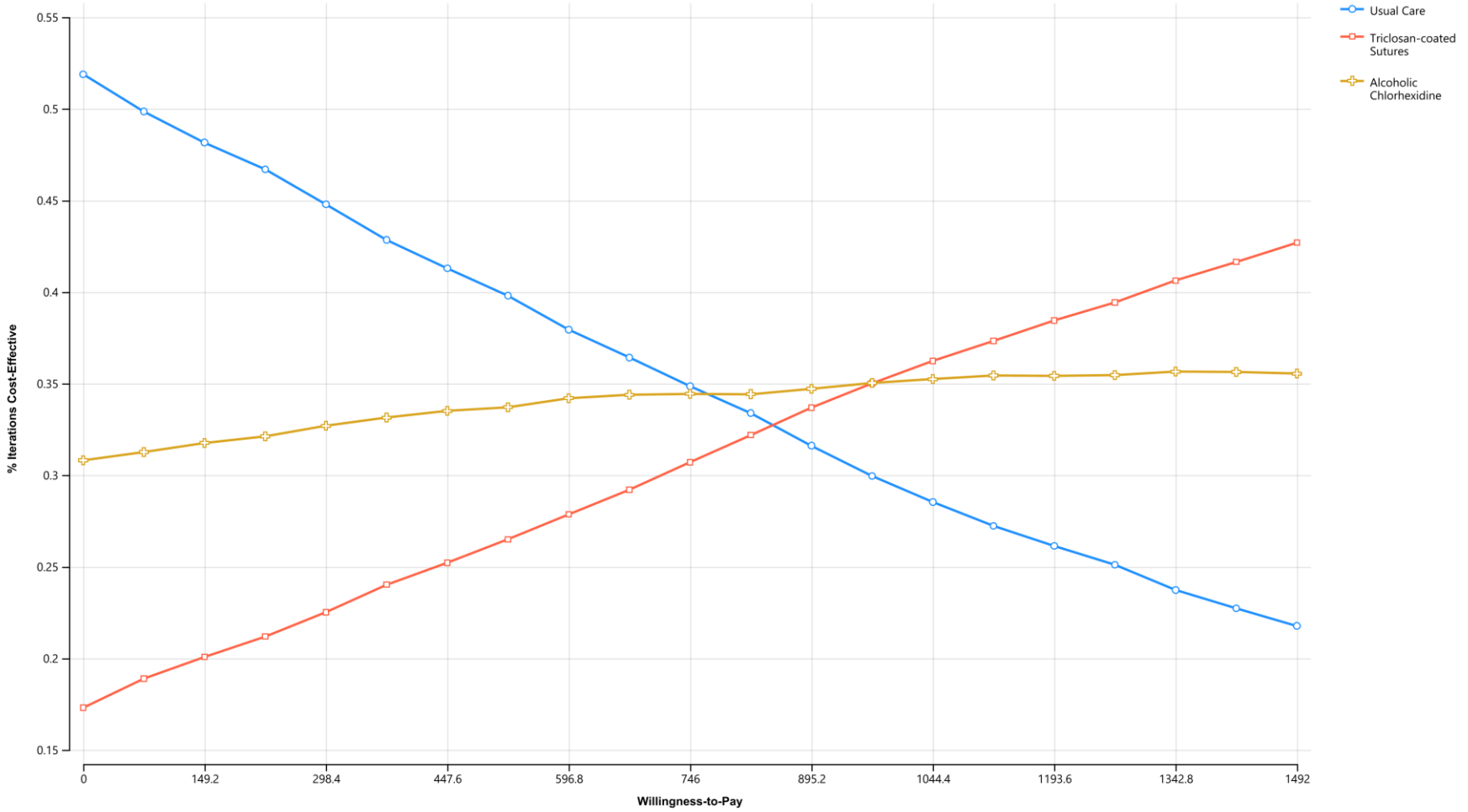


Figure 9.7 Cost-effectiveness acceptability curve Mexico Clean-Contaminated (Cost per DALY averted)



Ghana Contaminated-Dirty

For the Cost per QALY approach, the incremental iterations of Triclosan-coated Sutures versus Usual Care, Triclosan-coated Sutures versus Alcoholic Chlorhexidine, and Alcoholic Chlorhexidine versus Usual Care are shown in Appendix Figures A9.19- A9.21. In each scatterplot, the incremental iterations were mainly situated in the northwest or southeast quadrants. For Triclosan-coated Sutures versus Usual Care, more than half of the PSA iterations (57.41%) indicated that Triclosan-coated Sutures was the most cost-effective strategy. For Triclosan-coated Sutures versus Alcoholic Chlorhexidine, a minority of PSA iterations (17.56%) indicated that Triclosan-coated Sutures was the most cost-effective strategy. For Alcoholic Chlorhexidine versus Usual Care, the vast majority of the PSA iterations (91.85%) indicated that Alcoholic Chlorhexidine was the most cost-effective strategy.

For the Cost per DALY averted approach (Appendix Figure A9.22- A9.24), Alcoholic Chlorhexidine again had the most cost-effective iterations across the scatterplots. For Triclosan-coated Sutures versus Usual Care, 58.34% of the PSA iterations indicated that Triclosan-coated Sutures was the most cost-effective strategy. For Triclosan-coated Sutures versus Alcoholic Chlorhexidine, 18.21% of the PSA iterations indicated that Triclosan-coated Sutures was the most cost-effective strategy. For Alcoholic Chlorhexidine versus Usual Care, 92.33% of the PSA iterations indicated that Alcoholic Chlorhexidine was the most cost-effective strategy.

The CEAC for the Ghana Contaminated-Dirty surgical patients is shown in Figure 9.8 in the Cost per QALY approach. The percentage of cost-effective iterations from the Alcoholic Chlorhexidine strategy was high and did not noticeably change as the WTP threshold increased. Likewise, both Triclosan-coated Sutures and Usual Care also had flat curves that had little variation by WTP threshold. At a WTP threshold of $2043 per QALY, Alcoholic Chlorhexidine had the highest the proportion of iterations that were cost-effective (76.72%), followed by Triclosan-coated Sutures (19.73%) and Usual Care (3.55%).

The CEAC for the Ghana Contaminated-Dirty surgical patients in the Cost per DALY averted approach (Figure 9.9) chimes with the Cost per QALY approach. At a WTP threshold of $114 per DALY averted, Alcoholic Chlorhexidine had the highest the proportion of iterations that were cost-effective (77.40%), followed by Triclosan-coated Sutures (19.38%) and Usual Care (3.22%).

Table 9.11 summarises the CEAC information by displaying the percentage of PSA iterations that are most cost-effective from each strategy for each approach across settings at their specified thresholds.

Figure 9.8 Cost-effectiveness acceptability curve Ghana Contaminated-Dirty (Cost per QALY)

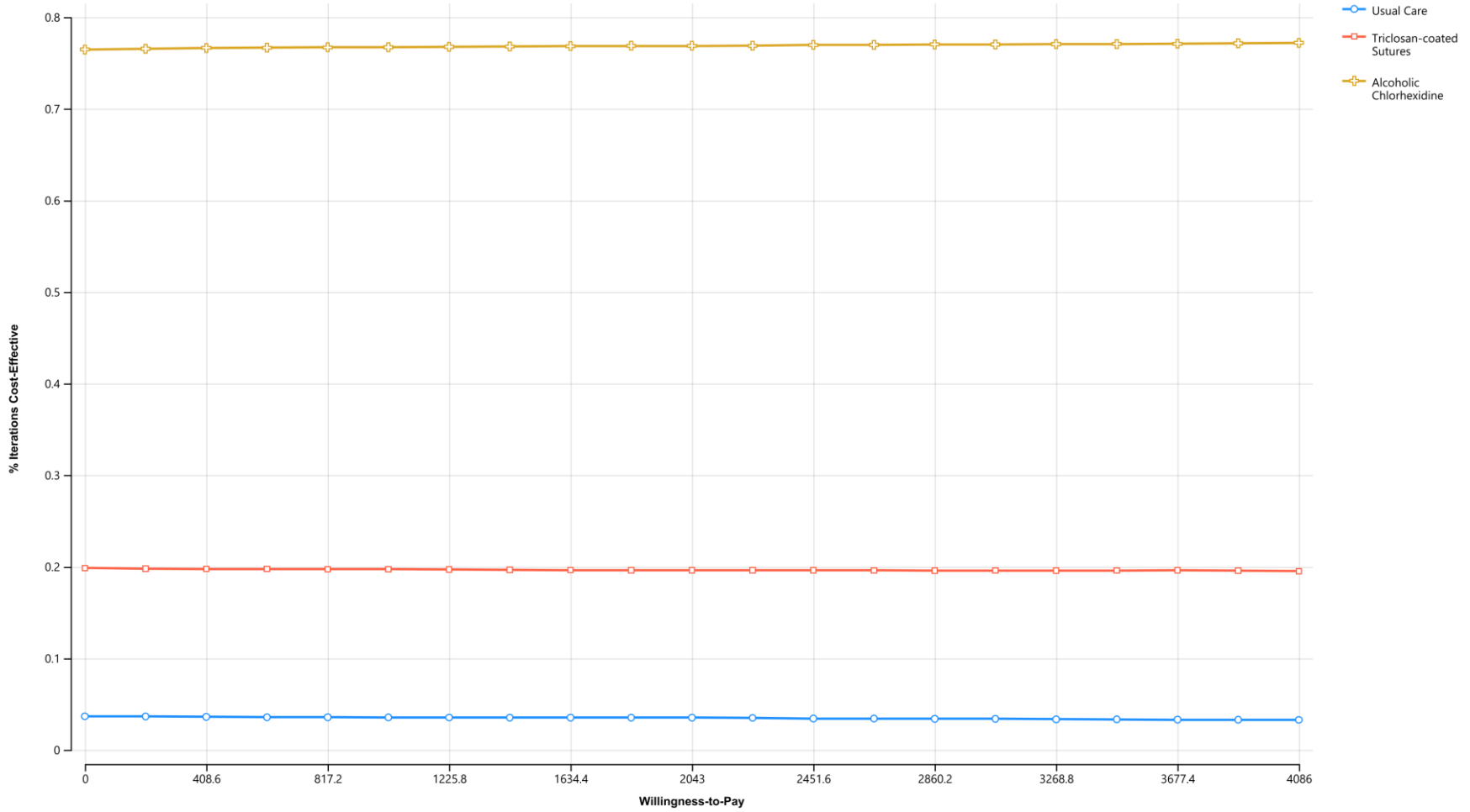


Figure 9.9 Cost-effectiveness acceptability curve Ghana Contaminated-Dirty (Cost per DALY averted)

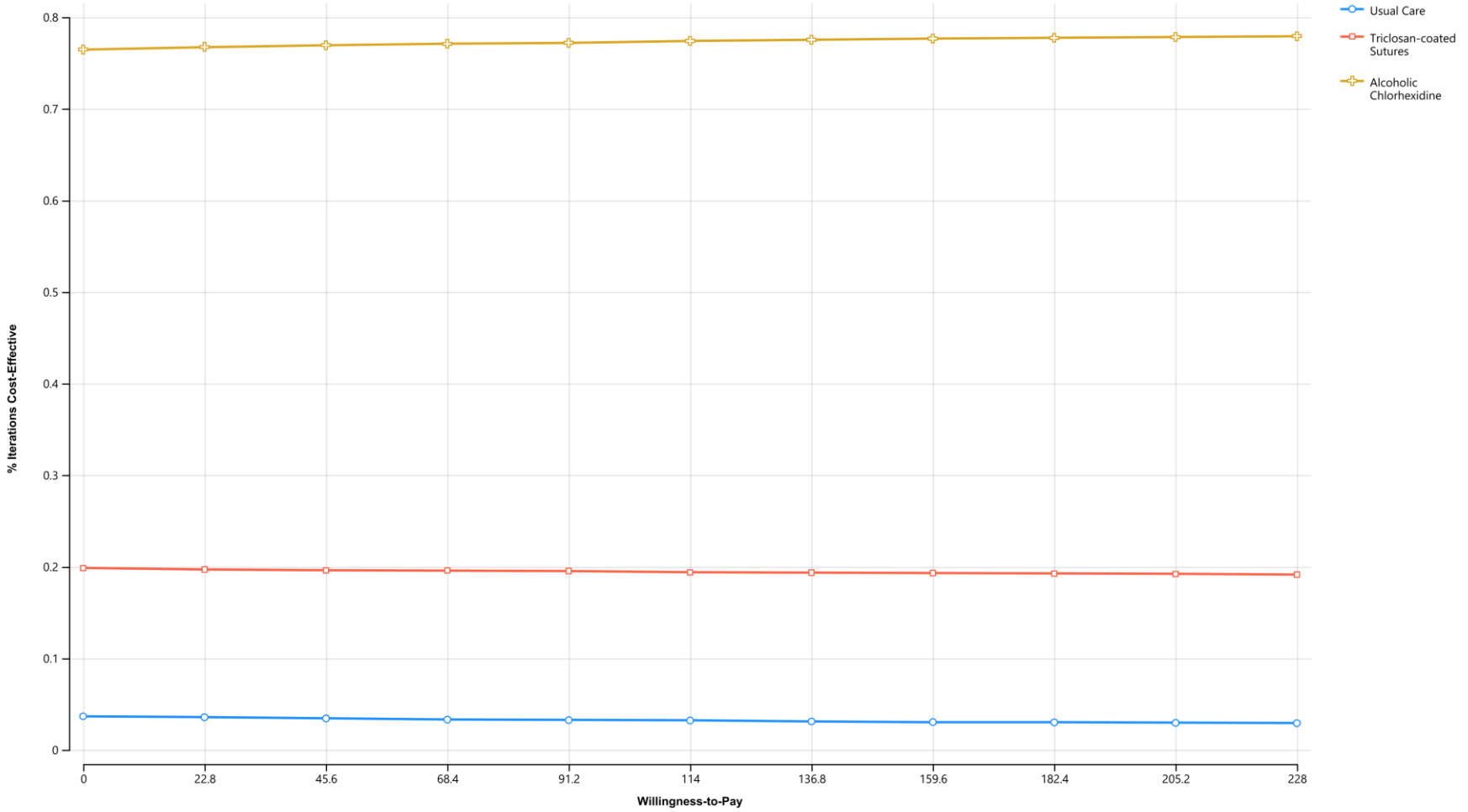


Table 9.11 Percentage of PSA iterations that are most cost-effective from each strategy

	Percentage of PSA iterations that are most cost-effective belonging to each strategy at country-specific cost-effectiveness threshold	
	Cost per QALY	Cost per DALY averted
India Clean-Contaminated		
Triclosan-coated Sutures	71.72%	72.31%
Alcoholic Chlorhexidine	19.55%	20.08%
Usual Care	8.73%	7.61%
India Contaminated-Dirty		
Alcoholic Chlorhexidine	49.61%	59.44%
Triclosan-coated Sutures	28.52%	26.15%
Usual Care	21.87%	14.41%
Mexico Clean-Contaminated		
Usual Care	47.54%	34.86%
Alcoholic Chlorhexidine	31.82%	34.44%
Triclosan-coated Sutures	20.64%	30.70%
Ghana Contaminated-Dirty		
Alcoholic Chlorhexidine	76.87%	77.40%
Triclosan-coated Sutures	19.61%	19.38%
Usual Care	3.52%	3.22%

9.3.3 Combined Treatment PSA scenario

The mean PSA iterations with the addition of a Combined Treatment strategy of Alcoholic Chlorhexidine and Triclosan-coated Sutures is shown in Table 9.12. The Combined Treatment was on average the most effective strategy across all settings. The Combined Treatment strategy had the highest QALYs and lowest DALYs on average across all settings The Combined Treatment had the highest QALY NMB in India. The Combined Treatment had the highest DALY NMB in all settings. The CEACs with the addition of a Combined Treatment strategy are shown in Appendix Figures A9.25-A9.30.

India Clean-Contaminated

For the Cost per QALY approach, Triclosan-coated Sutures has the highest proportion of cost-effective iterations across all the WTP thresholds for India Clean-Contaminated patients (Appendix Figure A9.25). At a WTP threshold of $2781 per QALY, Triclosan-coated Sutures had the highest the proportion of iterations that were cost-effective (45.51%), followed by Combined Treatment (36.13%), Usual Care (8.73%), and Alcoholic Chlorhexidine (7.63%). The CEAC for the India Clean-Contaminated surgical patients is shown in Appendix Figure A9.26 under the Cost per DALY averted approach. Triclosan-coated Sutures had the highest the proportion of iterations that were cost-effective (44.25%), followed by Combined Treatment (40.78%), Usual Care (7.61%), and Alcoholic Chlorhexidine (7.36%).

Table 9.12 Mean PSA results for Combined Treatment (International dollars, 2020)

Strategy	Healthcare Cost [Int$] (95% PI)	Societal Cost [Int$] (95% PI)	QALYs (95% PI)	QALY NMB [Int$] (95% PI)	DALYs (95% PI)	DALY NMB [Int$] (95% PI)
India Clean-Contaminated						
Usual Care	136 (136 to 137)	6.61 (6.34 to 6.88)	0.05842 (0.05838 to 0.05845)	26.3 (25.8 to 26.7)	0.1145 (0.114 to 0.1151)	-160.7 (-161.2 to -160.2)
Triclosan-coated Sutures	127 (127 to 128)	5.96 (5.72 to 6.21)	0.05863 (0.0586 to 0.05866)	35.7 (35.3 to 36.2)	0.1034 (0.1028 to 0.1039)	-149.4 (-149.9 to -149)
Alcoholic Chlorhexidine	137 (137 to 138)	6.44 (6.17 to 6.7)	0.05847 (0.05844 to 0.05851)	25.4 (25 to 25.9)	0.1115 (0.111 to 0.1121)	-161 (-161.5 to -160.6)
Combined Treatment	129 (128 to 129)	5.8 (5.57 to 6.04)	0.05868 (0.05865 to 0.05871)	34.6 (34.1 to 35.1)	0.1006 (0.1001 to 0.1011)	-150.1 (-150.6 to -149.6)
India Contaminated-Dirty						
Usual Care	105 (103 to 106)	18.38 (17.95 to 18.82)	0.05639 (0.05635 to 0.05642)	52.2 (50.8 to 53.6)	0.2214 (0.2204 to 0.2224)	-152 (-153.4 to -150.6)
Triclosan-coated Sutures	105 (104 to 106)	18.05 (17.62 to 18.48)	0.05646 (0.05643 to 0.05649)	52.1 (50.8 to 53.5)	0.2176 (0.2165 to 0.2186)	-151.4 (-152.8 to -150.1)
Alcoholic Chlorhexidine	102 (101 to 103)	16.76 (16.36 to 17.16)	0.05676 (0.05673 to 0.05679)	56.1 (54.8 to 57.3)	0.2018 (0.2009 to 0.2028)	-145 (-146.2 to -143.7)
Combined Treatment	102 (101 to 103)	16.46 (16.06 to 16.85)	0.05683 (0.05679 to 0.05686)	55.9 (54.6 to 57.1)	0.1984 (0.1974 to 0.1993)	-144.6 (-145.9 to -143.4)

Strategy	**Healthcare Cost [Int$] (95% PI)**	**Societal Cost [Int$] (95% PI)**	**QALYs (95% PI)**	**QALY NMB [Int$] (95% PI)**	**DALYs (95% PI)**	**DALY NMB [Int$] (95% PI)**
Mexico Clean-Contaminated						
Usual Care	113 (110 to 116)	6.66 (6 to 7.32)	0.05842 (0.05838 to 0.05845)	516.7 (514.1 to 519.4)	0.1292 (0.1286 to 0.1298)	-209.4 (-212.1 to -206.7)
Triclosan-coated Sutures	124 (121 to 126)	6.01 (5.41 to 6.61)	0.05863 (0.0586 to 0.05866)	508.5 (506 to 510.9)	0.1166 (0.116 to 0.1172)	-210.5 (-213 to -208.1)
Alcoholic Chlorhexidine	115 (112 to 117)	6.44 (5.8 to 7.09)	0.05847 (0.05844 to 0.05851)	515.6 (513 to 518.2)	0.1258 (0.1252 to 0.1264)	-208.6 (-211.2 to -205.9)
Combined Treatment	125 (123 to 128)	5.81 (5.23 to 6.4)	0.05868 (0.05865 to 0.05871)	507.1 (504.7 to 509.5)	0.1135 (0.1129 to 0.1141)	-210.2 (-212.6 to -207.7)
Ghana Contaminated-Dirty						
Usual Care	153 (152 to 153)	11.18 (10.26 to 12.1)	0.05639 (0.05635 to 0.05642)	-177.1 (-177.9 to -176.2)	0.215 (0.2141 to 0.216)	-177.1 (-177.9 to -176.2)
Triclosan-coated Sutures	151 (150 to 152)	11.01 (10.11 to 11.91)	0.05646 (0.05643 to 0.05649)	-174.9 (-175.7 to -174)	0.2113 (0.2103 to 0.2123)	-174.9 (-175.7 to -174)
Alcoholic Chlorhexidine	142 (141 to 142)	10.19 (9.35 to 11.03)	0.05676 (0.05673 to 0.05679)	-164.1 (-164.8 to -163.3)	0.1961 (0.1951 to 0.197)	-164.1 (-164.8 to -163.3)
Combined Treatment	140 (139 to 141)	10.04 (9.21 to 10.86)	0.05683 (0.05679 to 0.05686)	-162.1 (-162.9 to -161.3)	0.1927 (0.1918 to 0.1936)	-162.1 (-162.9 to -161.3)

Combined Treatment: Triclosan-coated Sutures and Alcoholic Chlorhexidine; DALY: Disability Adjusted Life Year; NMB: Net Monetary Benefit; PI: Prediction Interval; QALY: Quality Adjusted Life Year

India Contaminated-Dirty

For India Contaminated-Dirty surgical patients, the CEACs for the Cost per QALY approach and Cost per QALY approach are displayed in Appendix Figures A9.27- A9.28, respectively. For the Cost per QALY approach, Alcoholic Chlorhexidine narrowly missed out as the strategy with the highest proportion of cost-effective iterations across all the WTP thresholds (Appendix Figure A9.28). At a WTP threshold of $2,781 per QALY, Alcoholic Chlorhexidine had the highest the proportion of iterations that were cost-effective (31.51%), followed by the Combined Treatment (30.92%), Usual Care (21.87%), and Triclosan-coated Sutures (15.7%).

The CEAC for the India Clean-Contaminated surgical patients is shown in Appendix Figure A9.28 in the Cost per DALY averted approach. At a WTP threshold of $214 per DALY, the Combined Treatment had the highest the proportion of iterations that were cost-effective (37.87%), followed by Alcoholic Chlorhexidine (35.65%), Usual Care (14.4%), and Triclosan-coated Sutures (12.08%).

Mexico Clean-Contaminated

The CEAC for the Mexico Clean-Contaminated surgical patients is shown in Appendix Figure A9.29 in the Cost per QALY approach and Appendix Figure A9.30 in the Cost per DALY averted approach. At a WTP threshold of $10780 per QALY, Usual Care remained the strategy with the highest proportion of iterations that were cost-effective (47.54%), followed by Alcoholic Chlorhexidine (25.52%), Combined Treatment (13.71%), and Triclosan-coated Sutures (13.23%). At a WTP threshold of $746 per DALY, Usual Care had the highest the proportion of iterations that were cost-effective (34.86%), followed by Alcoholic Chlorhexidine (24.94%), Combined Treatment (21.3%), and Triclosan-coated Sutures (18.9%).

Ghana Contaminated-Dirty

The CEAC for the Ghana Contaminated-Dirty surgical patients is shown in Appendix Figure A9.31 in the Cost per QALY approach. At a WTP threshold of $2043 per QALY, Combined Treatment had the highest the proportion of iterations that were cost-effective (54.59%), followed by Alcoholic Chlorhexidine (37.5%), Triclosan-coated Sutures (4.63%), and Usual Care (3.28%). The CEAC for the Ghana Contaminated-Dirty surgical patients is shown in Appendix Figure A9.32 in the Cost per DALY averted approach. At a WTP threshold of $114 per DALY averted, Combined Treatment had the highest the proportion of iterations that were cost-effective (54.89%), followed by Alcoholic Chlorhexidine (37.37%), Triclosan-coated Sutures (4.52%), and Usual Care (3.22%).

9.3.4 Value of Information

The EVPI for each setting is shown in Appendix Table A9.28. It varied by setting and approach (cost per QALY and cost per DALY averted). For the country-specific WTP for an additional QALY, the per patient EVPI was $4.69, $1.86, $0.79, and $0.53 for the Mexico clean contaminated group, India contaminated dirty group, India clean-contaminated group, and Ghana contaminated dirty group, respectively. Across the examined threshold ranges, EVPI increased as the WTP increased in the India and Mexico clean contaminated groups , and the Ghana contaminated dirty group. EVPI decreased as the WTP increased in the India contaminated dirty group.

For the country-specific WTP for an additional DALY averted, the per patient EVPI was $7.32, $1.28, $0.87, and $0.57 for the Mexico clean contaminated group, India contaminated dirty group, India clean-contaminated group, and Ghana contaminated dirty group, respectively. Across the examined threshold ranges, EVPI rose with increases in the WTP in the India clean contaminated group, and the Ghana contaminated dirty group. As with the cost

per QALY approach, EVPI moved downward as the WTP increased in the India contaminated dirty group. For the Mexico clean-contaminated group, EVPI initially increases as the willingness to pay threshold increased, peaks at a WTP of $1044.4 per DALY averted (EVPI value of $8.80), and then begins to decrease for the subsequent WTP values.

The EVPPI results for each setting is shown in Appendix Tables A9.29-A9.31. Reducing decision uncertainty with treatment effectiveness constituted the largest EVPPI across the parameters examined in all settings and approaches except for Mexico. The EVPPI associated with treatment effectiveness increased with WTP across each setting and approach (Appendix Tables A9.29). For Mexico, the EVPPI was higher for the SSI healthcare cost (Appendix Tables A9.30) compared to the treatment effectiveness EVPPI. For the cost per QALY approach, there was no value in reducing decision uncertainty around the SSI healthcare cost model input in the contaminated dirty settings. For the cost per DALY averted approach, there was no value in reducing decision uncertainty around the SSI healthcare cost model input in the Ghana contaminated dirty and the India clean contaminated groups. The EVPPI for the SSI utility decrements were nil for all settings and approaches across the examined WTP ranges (Appendix Tables A9.31).

9.4 Discussion

9.4.1 Statement of principal findings

A model-based economic evaluation assessed the cost-effectiveness of the FALCON interventions to reduce SSI in abdominal surgery patients across Ghana, Mexico, and India. Using cost estimates from the KIWI sub study (Chapter 7) and utility estimates from the AVOCET study (Chapter 8), the preliminary model-based economic evaluation which was first developed in Chapter 5 was refined; the final model-based economic evaluation took both a Cost per QALY approach and Cost per DALY averted approach for the three middle-income countries. The base case deterministic results indicated that Triclosan-coated Sutures had the lowest healthcare costs and DALYs, and the highest QALYs in the Clean-Contaminated patient group in India. In contrast, Alcoholic Chlorhexidine dominated the other strategies in the Contaminated-Dirty settings (India and Ghana). These results were robust to extensive deterministic sensitivity analysis. For Mexico, Usual Care, and Alcoholic Chlorhexidine were the most cost-effective strategies under the Cost per QALY and Cost per DALY averted approaches, respectively. These results were robust to different cost and quality of life deterministic sensitivity analysis, and were sensitive to treatment effectiveness assumptions. Extending the time horizon to two months changed the most cost-effective option in Mexico from Usual Care to Alcoholic Chlorhexidine under the cost per QALY approach.

When a Combined Treatment of Triclosan-coated Sutures and Alcoholic Chlorhexidine was added as a strategy in the sensitivity analysis, the Combined Treatment was the most cost-effective strategy under the Cost per DALY averted approach at the assessed cost-effectiveness thresholds but did not change decision recommendations in the Cost per QALY approach in India and Mexico.

For the PSA, there were varying levels of parameter uncertainty across the settings. Triclosan-coated Sutures had the highest proportion of cost-effective iterations for Clean-Contaminated patients in India and it had more than double the proportion of cost-effective iterations of the Alcoholic Chlorhexidine strategy that had the second most cost-effective iterations. For Mexico, Usual Care and Triclosan-coated Sutures were again the most cost-effective option for Clean-Contaminated surgical patients under the Cost per QALY and Cost per DALY averted approaches, respectively. For the Contaminated-Dirty patients in India and Ghana, the Alcoholic Chlorhexidine strategy had the most cost-effective iterations under both the Cost per QALY approach and the Cost per DALY averted approach.

The VOI results indicate there is value with reducing decision uncertainty across settings and approaches even if the WTP is set to zero. EVPPI would prioritize reducing decision uncertainty associated with treatment effectiveness in India and Ghana while the additional healthcare costs of SSI took precedence in the Mexico clean-contaminated patient group.

9.4.2 Strengths and weaknesses

There are several strengths associated with the model-based economic evaluation. This represents the first cost-utility analysis of SSI prevention in Middle-Income Countries. The cost and treatment effectiveness data come from a large prospective multi-country randomised control trial that collected standardized patient data across several time-points in a 30 day postoperative follow up period. Within the trial, patients and wound assessors were both blinded to the allocated intervention [373]. Two types of cost-utility analysis were used that reported in different outcomes, namely QALYs and DALYs to cater for decision maker preference. Both deterministic and probabilistic sensitivity analysis techniques were used to assess the level of parameter uncertainty in the model across the two approaches.

There are some notable limitations associated with the model-based economic evaluation. The cost-effectiveness thresholds for the Cost per QALY and Cost per DALY averted analysis is based on historical healthcare expenditure which may not be representative of current healthcare expenditure in the different countries. However, this would only be an issue for the patient group in Mexico under the Cost per DALY averted approach where the most cost-effective strategy changed under the examined WTP thresholds. For other settings, the most cost-effective strategy did not change across a range of WTP thresholds. This implies that an updated cost-effectiveness threshold would not have altered the implication of which is the most cost-effective strategy under the cost-effectiveness threshold ranges examined.

The utility estimates come from a UK population where the transferability of whose preferences with respect to health to different income settings is unclear. As the vignettes were partly based on functional descriptions in the EQ-5D-5L, a comparison of EQ-5D-5L country value tariff sets can be informative here on country preferences with respect to health. India and Mexico both have EQ-5D-5L tariff value sets [481,482]. For the country tariff values, by ranking the order of importance of the EQ-5D-5L dimensions in each country assessed by the weight given by the most severe response level, Pain and discomfort ranked highest in Mexico, England, and India. Furthermore, Mexico and England both ranked Anxiety and Depression and the second most important dimension (India ranked mobility the 2nd highest). Thereafter all three diverge on the rankings of the rest of the dimensions. As pain and discomfort was an important attribute with an SSI, this suggests that the AVOCET utilities could have some transferability properties in both Mexico and India. Under the Cost per DALY averted approach, disability weights are not assumed to differ by country. However, a threshold analysis indicates that an SSI would have to increase quality of life, to an impossible amount in some settings, for decision recommendations to change.

The severity proportions of SSI come from High Income Countries in Europe and so this may not generalise to patients in a lower income setting. The overall mortality in the FALCON trial [373] was higher (5.5%) than modelled in the economic evaluation (1.9%) and differed by wound contamination strata (Clean-Contaminated: [2.3%] versus Contaminated-Dirty: [9.3%]). Relatively more deaths in patients with SSI would underestimate the cost-effectiveness of the Alcoholic Chlorhexidine and the Triclosan-coated Sutures strategies especially from the YLL in the Cost per DALY averted approach.

For Ghana, the intervention cost was inferred using a relative cost index of its nearest country in the current analysis to its GDP per capita. This was done as the requested intervention costs by the country has not arrived in time of PhD submission. The actual costs may not be reflective to the assumed costs in the analysis. The market basket approach has been successfully used in previous multi-country LMIC economic evaluations where missing costs are inferred using available cost estimates of another participating country [111,483].

Due to the one person with an SSI not having any post discharge travel costs or income loss in the Mexico Clean-Contaminated strata, the model produced results suggesting that an SSI decreased societal costs in this setting. In reality, this is likely a chance finding due to the low event rate and the decreased societal costs was not reflected in the other country settings. Lastly, the cost-effectiveness results relate to middle-income settings, and it is unknown if the results are transferable to low income settings.

9.4.3 Comparison with other studies

As mentioned previously, this represents the first cost-utility analysis of SSI prevention in Middle-Income Countries. In comparison with the preliminary model-based economic evaluation in Chapters 5 and 7, the SSI reducing interventions remained cheaper and more

effective than Usual Care in the Cost per QALY approach. In the current model-based economic evaluations, the total QALYs were higher, and the total costs were lower across all settings compared to both the preliminary model-based economic evaluations. Coated Sutures was the most cost-effective strategy in the preliminary model-based economic evaluation which was only the case in India Clean-Contaminated patients under the Cost per QALY approach. However, 2% Alcoholic Chlorhexidine was not assessed in the preliminary model so no comparison can be drawn here. In the literature, there are two model-based cost-effectiveness analyses looking at SSI prevention in one or more Middle-Income Country settings [484,485]. Both found interventions to reduce SSI were associated with lower costs and SSIs although the analyses were both limited by the lack of utility data to convey the health consequences of SSI.

9.4.4 Implication for practice

None of the FALCON trial interventions reached a statistically significant difference in effectiveness. The treatment effectiveness of coated sutures, derived from HIC trials, did not generalise to an LMIC setting. Yet for the model-based economic evaluation, one or more of these interventions in the FALCON trial had a higher probability of being cost-effective compared to Usual Care across most settings examined. This underlines the importance of undertaking an economic analysis even when the trial uncovers non-significant clinical findings. The most cost-effective interventions represent potential value for money compared with current practice and would likely result in decreased costs and less patient morbidity. Future research should consider embedding an economic evaluation alongside an LMIC randomised control trial to increase the sample size for the costs by SSI status and decrease the relative size of the associated standard errors of these cost calculations. Due to a lack of validated utility measures in many LMIC settings where a trial can be undertaken, the

economic evaluation can be limited to a cost-effectiveness analysis and future research could separately ascertain utilities in these country settings using direct health state valuation approaches to provide estimates for a cost-utility analysis.

9.4.5 Conclusion

The updated economic evaluation, incorporating cost and utility estimates from Chapters 8 and 9, performed the first model-based cost-utility analysis of SSI reducing interventions in LMIC settings. The FALCON interventions were considered cost-effective compared to Usual Care in all settings bar Mexico although the exact FALCON intervention considered most cost-effective varied by setting. The decision recommendation was the same for the Cost per QALY approach and the Cost per DALY averted approach except for Mexico where they diverged. This chapter concludes the empirical research phase of the thesis. The next Chapter contains the overall discussion and conclusion of the thesis.

Chapter 10:

Discussion and Conclusion

10.1 Introduction

The doctoral thesis set out to investigate the economic rationale for investing in safe surgery in Low- and Middle- Income Countries (LMIC) by using Surgical Site Infection (SSI) as a case study. Adopting an iterative economic modelling framework, the cost-effectiveness of SSI prevention was assessed and subsequently updated with more applicable data. This Chapter re-examines the objectives set out in Chapter 1 and summarises the main findings of the subsequent Chapters and their contribution to achieving these objectives. The main findings across the systematic reviews and empirical research are discussed, along with identified strengths and weaknesses pertinent to the interpretation of the results. The research findings are compared against the current literature to provide necessary context on the original contribution of the research within the thesis. The policy implications arising from the main findings are discussed with recommendations on specific areas for future research. Lastly, the Chapter finishes with an overall conclusion to the thesis.

The four objectives of the thesis outlined in Chapter 1 were to:

1. Ascertain the costs and quality of life implications of SSI from the best available estimates in secondary sources;
2. Build a decision analytic model populated with the best available estimates from secondary sources to preliminarily assess the economic rationale for investing in safe surgery;

3. Ascertain the costs and quality of life implications of SSI through primary research by generating health state valuations associated with SSI and collecting costs associated with SSI;
4. Update the decision analytic model with the primary research data to assess the economic rationale of interventions to reduce SSI in LMICs.

10.2 Summary of main findings' contribution to achievement of thesis objectives

The following section discusses the main findings from each of the research phases and how each thesis Objective was met.

10.2.1 Contribution of principal findings to meeting thesis objective 1

The first objective of the thesis related to the identification of the best available estimates from secondary sources on the financial and quality of life consequences associated with SSI. After a background on the relevant theories and concepts concerning SSI and economic evaluations was detailed in Chapter 2, two separate systematic reviews looked at the cost burden associated with SSI and the health state valuations associated with SSI, respectively.

Systematic review of SSI cost burden (Chapter 3)

A systematic review on the costs associated with SSI across LMIC settings was undertaken in Chapter 3 to address the first part of Objective 1. The inclusion of European studies in the systematic review provided a reference standard for the LMIC studies with a comparison of methodological approaches across income settings. The estimation of the additional costs of SSI was associated with methodological challenges. These included: competing definitions of SSI and severity levels of SSI; the length of time horizon required to detect both the onset and resolution of all types of SSI; the choice of comparator (patient without an SSI); and other

patient characteristics confounding the impact of SSI on costs, and analytic method to calculate the additional costs of SSI.

The studies included in the systematic review of the cost burden were critically appraised and subjected to a cost of illness checklist and quality assessment. The cost burden of SSI differed significantly between studies even with adjustment of the purchasing power of each country. The broad range of cost estimates in both settings reflected the difficulty associated with accurate estimation of the costs that are attributable to an SSI. The lack of transparency in reporting the breakdown of resource use and cost components for the patients with SSI and patients without SSI hindered meaningful explanations behind differences in findings across studies. For LMIC settings, the lack of follow-up post-discharge excluded detection of outpatient SSI and measurement of primary care healthcare resource use for patients discharged with an SSI. There was also an underrepresentation of studies from Low- and Lower Middle- Income countries within the systematic review. This made it difficult to ascertain the transferability of the reported SSI cost burden to these country settings.

Systematic review of health state valuations associated with SSI (Chapter 4)

The second part of Objective 1 required the procurement of the best available estimates from secondary sources on the quality of life consequences associated with SSI. A systematic review on the health state valuations associated with SSI was undertaken in Chapter 4 to help fulfil the second part of Objective 1. The purpose of the systematic review was to identify and critique the utility values on the impact of SSI that have either been previously used in model-based economic evaluations or had been generated from direct or indirect health state valuation approaches. With the existence of a systematic review previously published in the

area [210], the systematic review undertaken in Chapter 4 updated the search strategy to consider more recent studies published after the end search date of the original systematic review. A critique of the utility values identified in the previous review and an assessment of the quality of the utility values found in both reviews were also reported in the Chapter. This was to ensure the selection of the best available estimates for the preliminary model-based economic evaluation covered in Objective 2.

Quantifying appropriate utilities associated with SSI was beset with its own set of methodological challenges. These included different definitions on what constitutes an SSI diagnosis and the severity levels of an SSI, the choice of comparator, the other patient characteristics confounding the impact of SSI on quality of life, the need for repeated quality of life measurements to account for the variable impact on quality of life across the entire infection trajectory, the differential timing of SSI onset and resolution, and choice of the health state valuation method for utility elicitation.

SSI was found to have an adverse effect on quality of life across all studies in different surgical categories and countries in the updated systematic review. However, the review found questionable methodological quality in the selection of utilities in the reviewed model-based economic evaluations, including instances of utility values that did not correspond to descriptions of surgical patients; incorrectly sourced values; referenced values that could not be found in listed citation; and the use of health state valuation instruments for utility elicitation that are not recommended by national health technology assessment bodies [393]. Few patient-level studies had utility values that had adjusted for baseline imbalances between the SSI and no SSI patient groups. This meant that the cross-sectional SSI utility decrements could misrepresent the actual utility impact from an SSI where there were group differences in utilities before the onset of SSI in surgical patients. No studies reported utility estimates

from an LMIC setting, making it difficult to ascertain the transferability of the utility estimates to a different income setting. The lack of disability weights associated with SSI prevented Disability Adjusted Life Years (DALYs) to be estimated for economic evaluations alongside surgical trials.

ROSSINI re-analysis (Chapter 6)

This thesis has demonstrated that most of the previous research on the economic consequences of SSI is methodologically flawed. Most of literature assessed the economic burden of SSI in a single centre setting and coupled with a low sample size of SSIs made estimates prone to imprecision and not representative of the actual impact of SSI. Thus, a re-analysis derived from an economic evaluation alongside large Randomised Control Trial (RCT) was undertaken in Chapter 6 to develop more robust estimates on the costs and utility consequences associated with an SSI. Beyond the published economic evaluation [48], the original analysis also assessed unadjusted differences in costs and utilities by SSI status but reported this only in the linked doctoral dissertation [293]. As different analytic approaches will affect the calculation of the estimates, the re-analysis took the opportunity to compare three separate approaches to develop the SSI cost and quality of life estimates from the patient level data. In addition, sensitivity analyses were undertaken across the approaches to investigate the impact of different specifications and assumptions on the estimated additional economic burden of SSI.

The re-analysis confirmed in all three approaches that there was an additional statistically significant mean healthcare cost associated with an SSI, although the magnitude of difference varied by approach. For the same set of patients, adjusting for covariates in the Generalised Linear Model approach (£2,107) increased the size of the cost difference relative to the unadjusted cross comparison approach (£1,785). The Case Control approach used an

alternative way of covariate adjustment through patient matching where 1 patient with an SSI was matched to 2 patients without SSI. The additional healthcare costs associated with an SSI from Case Control 1:2 approach, calculated from the sum of the average paired differences in total costs between each case and control group, had the lowest cost of all three approaches (£1,555). The Case Control approach had fewer patients compared to the other approaches in the cost calculation due to non-matched patients being excluded from the cost calculation.

For the quality of life consequences of SSI, the re-analysis first reported a Cross-Comparison of the EQ-5D-3L scores for each of the three time points (pre-surgery baseline; 5-7 days post-surgery; 30-33 days post-surgery) by SSI status. Patients with SSI had lower utility values across all time points compared to patients without SSI, even preoperatively before the development of an SSI (-0.0675). The postoperative SSI utility decrements were all higher than the Quality Adjusted Life Month score (-0.0749) that combined the utility scores across the month using the area under the curve method and adjusted for baseline imbalances in the groups of patients with SSI and patients without SSI.

All the re-analysis approaches found that the presence of an SSI was associated with a quality of life decrement, even after accounting for lower preoperative scores of patients with SSI. The Cross-Comparison approach had the highest SSI Quality Adjusted Life Year (QALY) decrement (0.0062), and the Case Control approach had the lowest SSI QALY decrement (0.0035). However, the bootstrapped mean difference in QALYs from the Case Control approach was not statistically significant at the 5% level with the associated 95% level crossing zero. As with the Case Control approach for costs, the Case Control approach to estimate the QALY decrement used less patients than the other estimation approaches due to the matching criteria requirements. In contrast to the direction of movement observed with the cost results, the addition of adjusting for covariates in the Generalised Linear Model

decreased the size of the QALY decrement relative to the unadjusted cross comparison approach (0.0047 versus 0.0062).

Using the same dataset, a comparison of the original analysis and current re-analysis found markedly different cost and quality of life estimates. Explanations for the cost result differences included the data cleaning processes, the appropriateness of an inflation index in reflecting the current cost of healthcare items, different sourcing of the unit costs in some cases, the set of random numbers from the multiple imputation process, and the addition of bootstrapping for the mean difference in costs calculation. An examination of the original analysis code uncovered an error in the conversion of EQ-5D-3L responses into utilities, explaining some of the results discrepancy between the original analysis and re-analysis.

10.2.2 Contribution of principal findings to meeting thesis objective 2

Thesis Objective 2 was concerned with the building a decision analytic model populated with the best available estimates from secondary sources to preliminarily assess the economic rationale for investing in safe surgery.

Initial preliminary model-based economic evaluation (Chapter 5)

A preliminary model-based economic evaluation used cost and quality of life estimates from the systematic reviews. Both the cost and quality of life estimates within the respective systematic reviews were subjected to a quality assessment with a view to selecting the most suitable model inputs to support the decision analytic model Objective. The economic evaluation model took a UK separate and separate LMIC setting using rebased costs from the UK setting. The aim of the chapter was to assess the cost-effectiveness of measures to reduce SSI in general surgery patients. A decision tree model type represented the decision problem with exemplar interventions to reduce SSI. Antiseptic Wound Irrigation and Coated Sutures

were separately considered as exemplar interventions and applied at the perioperative stage to all patients undergoing surgery in their respective strategy. A Usual Care strategy of no antiseptic wound irrigation and uncoated sutures was included as a model comparator.

To account for the greater depths of infection being positively correlated (contributing to increased costs) with costs and negatively correlated with utilities (contributing to lower quality of life), severity levels of SSI were part of the postoperative patient pathway with SSI severity specific costs and utilities featuring in the base case analysis. After selection of the most suitable model inputs for the costs associated with SSI from a quality assessment (Chapter 3), a number of assumptions were still required to quantify the additional costs of SSI for the model population. After a quality assessment of studies with utility values was undertaken within the SSI health state valuations systematic review, information on the SSI decrements were chosen to be taken from the spine surgery health states from Matza et al. [236].

The base case results of the decision analytic model indicated that both exemplar interventions were cheaper and more effective than Usual Care. The Coated Sutures Intervention was considered the most cost-effective strategy as it was the cheapest and most effective strategy. This decision recommendation was robust to sensitivity analyses. Notably, the Wound Irrigation strategy had a much higher proportion of cost-effective strategies (as assessed by the net monetary benefit of each Probabilistic Sensitivity Analysis (PSA) iteration) than Usual Care despite the treatment effectiveness having a non-statistically significant confidence interval.

The value of information analysis (VOI) assessment suggested a high 1 year population expected value of perfect information given the large estimated size of the patient populations

in selected LMIC settings. However, the expected value of perfect parameter information (EVPPI) indicated that the value of future research was focused on reducing the parameter uncertainty treatment effectiveness between Wound Irrigation and Coated Suture, and not on the cost and utility estimates. Applying the results of the value of information analysis to LMIC settings carries an implicit assumption that the treatment effectiveness was generalizable across income settings. As the transferability of the treatment effectiveness of the SSI reducing interventions to LMIC settings was unknown, as highlighted in Chapter 5, it was unclear what the true value of further research was for LMIC settings. A PSA scenario with widened confidence intervals decreased the proportion of iterations that the Coated Sutures was the most cost-effective option, but it remained the strategy with the highest proportion of cost-effective iterations.

Preliminary model-based economic evaluation re-analysis (Chapter 6)

The preliminary model-based economic evaluation was revisited in Chapter 6 to assess the impact of using the ROSSINI re-analysis estimates. The cost and quality of life estimates from the Generalised Linear Model were used in the base case with the other approaches assessed in a deterministic sensitivity analysis. The cost and utility estimates were lower than the model inputs for the preliminary model-based economic evaluation in Chapter 5. Coated Sutures remained the dominant strategy and was cheaper and more effective than the Wound Irrigation and Usual Care strategies. Furthermore, Coated Sutures remained the most cost-effective strategy across a range of willingness to pay (WTP) thresholds in the PSA. There was still value associated with future research although per-patient expected value of perfect information (EVPI) with the ROSSINI re-analysis estimates.

10.2.3 Contribution of principal findings to meeting thesis objective 3

The third thesis objective was to ascertain the costs and quality of life implications of SSI from primary research by collecting costs associated with SSI in LMICs and generating health state valuations associated with SSI. The first part of Objective 3 was achieved in Chapter 7 with a cost sub-study within a LMIC SSI prevention RCT. The second part of objective 3 was achieved in Chapter 8 with a health valuation study on SSI using direct and indirect methods.

KIWI study (Chapter 7)

The KIWI study was carried out within the FALCON trial [280,373] in order to estimate the cost burden associated with SSI in LMIC settings. Two different strata of predicted wound contamination were separately powered for the FALCON trial (Clean-Contaminated, and Contaminated-Dirty). The cost sub-study aimed to estimate the both the overall cost burden associated with SSI and by predicted wound contaminated strata. Participating FALCON centres in India, Ghana, Nigeria, and Mexico were included in KIWI. Inpatient and post discharge resource use up to thirty days post-surgery was collected on FALCON trial patients participating in the sub-study. Resource use for SSI and no SSI patients was collected using additional Case Report Forms within the FALCON trial completed at hospital discharge and as close to 30 days post-surgery as possible.

One foreseen challenge with the cost sub-study was that the FALCON trial had already finished recruitment of predicted Clean-Contaminated cases by the time that prospective recruitment for KIWI had commenced. To collect information on the Clean-Contaminated cases, retrospective data collection via telephone interview was undertaken in India and Mexico.

As some SSIs may not be resolved within 30 days post-surgery, an aim of the cost sub-study was to explore the healthcare needs and resource use of patients with an unresolved SSI at 30 days and beyond. For patients with an unresolved SSI at 30 days post-surgery, additional telephone follow-up was carried at to collect resource use information related to their ongoing wound infection at postoperative day 45, and at postoperative day 60 where the wound infection was still unresolved at 45 days. Ethical approval for protocol amendments for extended follow up in participating countries was affected by the onset of COVID-19 and Ghana was the only participating KIWI sub study country that received ethical approval for the extended follow up of patients. Due to COVID-19, no prospective study enrolment of Contaminated-Dirty cases was possible in Mexico as the centres were closed for recruitment.

SSI was associated with additional postoperative costs in patients undergoing abdominal surgery across Ghana, Mexico, Nigeria, and India. The overall mean additional postoperative costs with SSI were higher in Clean-Contaminated cases compared to Contaminated-Dirty cases. Patients with an SSI had higher costs in both postoperative inpatient costs and post-discharge costs compared to patients without an SSI. The presence of an SSI was statistically significant predictor of total postoperative costs after covariate adjustment in a multilevel generalised linear model. The predicted cost of an SSI after covariate adjustment was lower than the overall unadjusted costs by wound contamination arm.

37.5% of prospective patients with an SSI were judged to have unresolved wound infection at 30 days post-surgery. An exploratory investigation in Ghana showed that the costs of unresolved wound infection in patients with an SSI persisted beyond 30 days with the 45- and 60- postoperative day post-discharge costs in addition to the 30 postoperative day post-discharge costs. However, fewer than half of patients with an ongoing wound infection at 30 days post-surgery were not followed up at the 45- day post-surgery time-point.

AVOCET study (Chapter 8)

The AVOCET Study was developed to elicit health state valuations associated with SSI. Specially constructed vignettes to describe different severity levels of SSI were valued with the general public remotely using different health state valuation techniques. A secondary aim assessed participants' willingness to view representative photos of the health state vignettes and whether the photos aligned with expectations of the health state based on the text descriptions.

The health state vignettes were developed through an iterative process from a variety of different sources. The vignette descriptions were deliberately constructed to be generic to different country settings and avoided references on how the healthcare was specifically delivered. Interviews were done on a 1:1 remote basis with interviewer and interviewee. Three different health valuation techniques were used to quantify the utility associated with SSI (EQ-5D-5L, Visual Analogue Scale, and Time-Trade Off).

The online mode of administration was feasible and had a high interview completion rate. Recruited participants identified mainly as female; young, and all were educated or were studying at a university degree level. Their self-health ratings were high with many participants reported no problems across the EQ-5D-5L domains. A range of utilities were obtained for each of the health states with more severe Health States having utilities that were statistically significant from the preceding health state across valuation techniques. Mean utility health states were highest for the Time Trade Off techniques while the lowest mean utility health states were from the EQ-5D-5L. Ordinary Least Square regression and subgroup analyses did not find an association between participant characteristics and the valuation scores. There was high acceptability of the SSI photographs with a large proportion of participants were willing to view photographs of the Health State.

10.2.4 Contribution of principal findings to meeting thesis objective 4

The final thesis objective was to update the decision analytic model with the primary research data to assess the economic rationale for interventions to reduce SSI in LMICs. This was accomplished in Chapter 9. Information from the KIWI and AVOCET studies were used as cost and utility model inputs, respectively. The updated model-based economic evaluation assessed the cost-effectiveness of the FALCON interventions by predicted contamination (Clean-Contaminated, Contaminated-Dirty) and setting (considering India, Ghana, and Mexico).

The base case deterministic results indicated that Triclosan-coated Sutures had the lowest healthcare costs and DALYs, and the highest QALYs in the India Clean-Contaminated strata settings ,while Alcoholic Chlorhexidine dominated the other strategies in the Contaminated-Dirty settings (India and Ghana). These results were robust to extensive deterministic sensitivity analysis. For the patient group in Mexico with Clean-Contaminated wounds, the results varied by approach with Alcoholic Chlorhexidine only being the most cost-effective strategy under the Cost per DALY averted approach and Usual Care being the most cost-effective strategy under the Cost per QALY approach. These results were sensitive to variations in treatment effectiveness.

The PSA supported the findings of the base case results. When a Combined Treatment of Triclosan-coated Sutures and Alcoholic Chlorhexidine was added as a strategy in the sensitivity analysis, the Combined Treatment was the most cost-effective strategy under the Cost per DALY averted approach at the assessed cost-effectiveness thresholds but failed to change decision recommendations under the Cost per QALY approach.

None of the FALCON trial interventions reached a statistically significant difference in effectiveness. The treatment effectiveness of Triclosan-coated sutures used in the preliminary model-based economic evaluation did not generalise to an LMIC setting. Yet for the updated model-based economic evaluation in Chapter 9, one or more of these interventions in the FALCON trial had a higher probability of being cost-effective compared to Usual Care across all settings examined in the Cost per QALY approach except for Mexico and in all settings examined in the Cost per DALY averted approach. The VOI analysis assessment suggested value in reducing overall decision uncertainty and focussing on reducing decision uncertainty in the additional SSI healthcare cost in Mexico and treatment effectiveness in the other settings.

10.3 Strengths of the thesis

This thesis has provided a comprehensive assessment of the economic rationale for safe surgery in LMIC settings. The existing literature on both the cost burden and quality of life consequences were systematically reviewed, and the methodological aspects critically appraised to obtain the best estimates currently available. The systematic review on the cost burden of SSI was the first to specifically investigate the economic impact of SSI in LMICs. By including a parallel review of SSI with High Income Countries in Europe, the review offers new insight into the methodological considerations and the potential data gaps in SSI cost studies from the contrasting settings. The SSI health state valuation systematic review builds upon a previous published systematic review and provides up-to date insight on the current evidence on the methodological quality of utility values pertaining to SSI.

The preliminary model-based economic evaluation benefitted from model inputs, taken from the two systematic reviews on the cost and utility estimates associated with SSI (referred to above), which had been subjected to quality assessment to ensure that the best available

estimates in the literature could be used. Furthermore, a value of information analysis to assess the benefit of future research on eliminating or reducing parameter uncertainty of all or some of the model inputs was also undertaken to inform the importance for further evidence generation.

Acknowledging the methodological issues surrounding the estimates taken from the systematic reviews, more robust cost and quality of life estimates were generated within this thesis that overcame many of the methodological weaknesses that were identified in the current available literature. A variety of different approaches were used which allowed for the comparison of estimates under different analytic assumptions. The Case Control approach to assess the SSI utility decrement is the first known study to examine QALY differences by this design. Estimates were taken from a prospective multicentre RCT (ROSSINI trial) which had standardized multiple data collection forms, blinding of wound assessors and patients to the treatment allocation, and post-discharge follow up data for a month post-surgery. The ROSSINI trial, characterized by a high SSI rate of approximately 25%, yielded valuable insights into the costs and quality of life challenges experienced by patients with SSI. In particular, the SSI utility decrement represented the first estimate in an abdominal population across multiple centres that accounted for baseline imbalances and patient covariates.

The KIWI study is the first multi-continental study to assess the postoperative costs associated with SSI. Resource use was collected in standardised forms within a trial setting, allowing comparability of findings across the countries. This study helps address literature gaps identified in the cost burden systematic review by providing cost information on outpatient SSI and cost information on surgical patients beyond discharge in low resource settings. Participating countries had more than one centre to increase generalisability of the findings.

The AVOCET study is the first direct health state valuation study for surgical site infection in abdominal surgery. It is also the first study to use photographs of a surgical health state to explore their use as a supplement to text based vignettes. The SSI health state vignettes followed best practice in the literature on the development and valuation of the vignette [385]. Three separate valuation techniques were used to derive utilities for the health states and allowed for an assessment on how valuations differed by method. Owing to the COVID-19 pandemic, the online mode of administration gave participants flexibility to engage as they were able to do the interview in the setting of their choosing and they did not suffer the inconvenience of having to be present at an interview venue in person and follow precautionary meeting procedures. The online design of the interview with the Redcap Survey Platform allowed for previous answers to be seamlessly displayed for participants at the health state photographs section to give context of how they had valued the health states using EQ-5D-5L and Time trade off (TTO).

The updated model-based economic evaluation is the first cost-utility analysis of SSI prevention in Middle-Income Countries. Both types of cost-utility approaches were used in the model to cater for decision maker preferences. The results were subject to extensive deterministic and probabilistic sensitivity analysis.

10.4 Limitations of the thesis

The systematic reviews were limited by an English language restriction for the article inclusion criteria. Within global health research, the exclusion of non-English language articles may have reduced the number of potentially relevant articles for both reviews. In addition, the broad definition of SSI included could affect the cross-study comparability of estimates as some of the observed differences between studies may be as a result of how each study categorised patients into SSI and no SSI groups.

For the preliminary model-based economic evaluation, the model inputs were not representative of LMIC settings, and it is unclear how transferable the decision recommendations were to a jurisdiction of a lower income setting. In addition, simplifying assumptions were needed on the impact of different types of SSI. The lack of reporting from studies on clinical parameters relevant to the SSI cost and quality of life estimation within the model has meant the use of assumptions and reliance on other studies to populate the model in their absence. Further, the externality cost of increased antibiotic resistance from treating SSI cases was not accounted for within the model.

For the ROSSINI re-analysis, information on wound dressings was not collected which would underestimate the costs of an SSI. The age of the trial may mean that the resource use from more than a decade ago may be less generalisable to current practice. The EQ-5D-3L outcome measure has now been updated with the newer EQ-5D-5L outcome measure and utility estimates may differ when using the more recent outcome measure and upcoming valuation set [486].

For the KIWI sub-study, the use of retrospective data collection for Clean-Contaminated cases may have affected the post-discharge healthcare estimates due to recall bias. The low sample size and event rate in Nigeria and Mexico respectively further limits the precision and the reliability of the estimates in these countries. The absence of any low-income countries meant that additional costs of SSI could not be generalised to these settings.

For the AVOCET study, a convenience population of participants with a university education was used. The young age and high educational attainment may have resulted in higher valuations than those from a UK general population and also it is unclear how transferable these preferences are to other country settings. As discussed in Chapter section 9.4.2, the

utilities may have some transferability properties in both Mexico and India based on the vignette content descriptions being partly derived from the EQ-5D-5L and a comparison of domain EQ-5D preferences within tariff sets between the UK, India, and Mexico.

The online mode of administration of the interviews may have also affected those who could take part as this excluded those who did not have access to a laptop or smartphone with video capabilities. The UK participants may have inferred that the healthcare would be applicable to the UK context when valuing the health states and valuations may have altered if they considered that the healthcare for the surgical patients was instead from an LMIC context. With the health state photographs, it was not possible to have a standardized patients with differences only in wound infection profile. Different shapes of the patient stomach and other aesthetic characteristics may have influenced participants expectation answers compared to the text vignettes alone.

For the updated model-based economic evaluation, the cost-effectiveness thresholds for the Cost per QALY and Cost per DALY analysis is based on historical healthcare expenditure which may not be representative of current healthcare expenditure in the different countries. Mortality by SSI status may overestimate the deaths caused by SSI as patients with SSI are typically in poorly preoperative health than patients without SSI [487].

10.5 Comparison with other studies

The empirical work developed cost and utility estimates from the ROSSINI re-analysis, KIWI sub-study, and AVOCET study.

For the ROSSINI re-analysis, other studies are compared to the value from the approach that was most aligned with their estimation method. The additional costs of SSI from the Cross-Comparison approaches were lower than the deep SSI costs and higher than the superficial

SSI costs in the only RCT designed study [174] included in the High Income Country European group in the cost burden of SSI systematic review. No weighted average was provided in their RCT on the overall costs of SSI. Other study aspects within the RCT also limited comparability including SSI definitions divergence and a time horizon being three times longer than ROSSINI. The highest scoring European study on the cost of illness checklist (Alfonso et al. [27]) within the cost burden systematic review had a higher additional healthcare cost of SSI compared to the ROSSINI re-analysis Case Control approach. Their nested case–control study of patients with and without SSI came from a single centre setting and the time horizon associated with the costs was not specified.

The additional cost of an SSI from the Jenks et al. [161] used in the preliminary model-based economic evaluation was higher than the equivalent estimate from the Case Control approach in the ROSSINI analysis. The comparison warrants caution as the SSIs in the Jenks et al. study [161] was skewed towards more severe SSIs, no primary care costs were included, and the 1 year time horizon in the single centre study was much longer than the 1 month ROSSINI time horizon.

For the utility estimates developed from the ROSSINI re-analysis, the SSI QALY decrement estimates with adjusted baseline results were compared to the two equivalent studies included in the Health State Valuation systematic review. Parker et al. [164] had a higher QALY decrement of 0.102 for deep SSI patients with an open lower limb fracture compared to the Generalised Linear Model estimate of 0.0047 from the ROSSINI re-analysis. However, the time horizon for the Parker et al. [164] study was over a longer time period of 1 year; assuming that the difference in quality of life scores by SSI status remained constant in ROSSINI from 1 month to 1 year (0.056) would still make the ROSSINI estimate much lower. Possible reasons for the difference could be the manifestation of an orthopaedic SSI

and the exclusion of Superficial SSIs in the Parker et al. [164] study. With the same ROSSINI time horizon, Totty et al. [238] had a higher SSI Quality Adjusted Life Month (QALM) decrement (0.156) in its pilot study of Clean-Contaminated vascular surgery patients. Reasons that could be driving the difference is the low number of patients with SSI (n=9) used in their QALM calculation and the omission of the 7 day EQ-5D-3L time point.

For the KIWI sub study, there were country specific costs from single centre settings in Mexico [189] and India [188] that were included in the cost burden systematic review ,and the study from Ghana [382] was published after the cost burden systematic review. The Porras-Hernandez et al. [189] study in Mexico which assessed the additional inpatient SSI costs in a paediatric surgical population, had much higher levels of length of stay by SSI status (median 13 days for patients with SSI versus 6 days for patients without SSI) compared to length of stay seen in KIWI patients in Mexico. The mean length of stay for clean-contamination Mexico patients with SSI and without SSI was 2.8 days and 2 days, respectively. For the Tiwari et al. [188] study in India, four patients with SSI had a much higher additional inpatient cost of SSI compared with India estimates from KIWI, although the time horizon for the costs was unstated. The Ghana study looked at both direct and indirect costs up to 30 days post-surgery in a teaching hospital and found similar additional cost of SSI in comparison to the Ghana cost estimates from KIWI.

For the AVOCET study, the time trade off SSI disutilities were much higher than the ROSSINI re-analysis estimates. The comparison with direct health state valuation orthopaedic SSI study was more mixed [236]. The mild and moderate SSI disutilities were higher and the severe disutility was similar to the AVOCET study. The differences in valuation scores apart from the different site of the infection may be from the use of path states.

10.6 Implications of the findings and future research recommendations

It is clear from the systematic reviews that SSI has both considerable cost and quality of life consequences. However, an indirect finding from the systematic screening of articles is that there is considerable existing research within the literature with the capacity to report on the cost and quality of life estimates of SSI, but studies only report by treatment group and not by SSI status. With appropriate presentation of results by SSI status, an additional 21 LMIC studies and 14 European studies would have been included in the SSI cost burden systematic review. This is also the case for many of the excluded 72 effectiveness studies in the health state valuation systematic review, where the SSI health utility decrement could not be calculated. Future research should consider the opportunities in the re-analysis of past research to minimise research waste and explore whether literature gaps can be first overcome with existing data. The ROSSINI re-analysis is an example of repurposing an existing dataset to develop robust cost and utility estimates that were lacking in the literature and would have otherwise required more funding to collect new data to generate these estimates.

From the ROSSINI re-analysis, there was a stark difference between the utility decrement and the QALY decrement with baseline adjustment. Future research should select outcome measures that are fit for purpose and can be repeated across multiple time points to create the longitudinal profile of the complication and be adjusted for baseline imbalances between groups to avoid misrepresenting the impact of an SSI on quality of life. In addition, future studies should include more subgroups on the severity levels of SSI to explore the quality of life impact from these complications. Further studies are needed to confirm whether adjusting for patient covariates increases the additional cost associated with SSI and decreases the SSI QALY decrement.

For the cost estimates developed in the KIWI study, there were limitations with retrospective data collection on Clean-Contaminated patients and low SSI event rates in Mexico. A planned cost study within another multinational RCT assessing interventions to reduce SSI [384] includes prospective data on Clean-Contaminated cases and the inclusion of Rwanda to explore the costs of SSI in a low income setting.

For the utility estimates developed in the AVOCET study, the results were derived from a UK population. Future research should explore health state preferences in different income settings with surgical photographs that are more reflective of different skin tones to show the impact of SSI across patients from different ethnicities. In addition, future research could explore the use of using the same actors with special effects makeup consistent with SSI to check if standardizing the patient across the health state photographs affect the valuations.

For the model-based economic evaluation, the main implication is that when interventions do not reach statistical significance, it does not necessarily follow that these interventions are not cost-effective. Future research should consider embedding an economic evaluation alongside an LMIC randomised control trial to increase the sample size for the costs by SSI status and decrease the relative size of the associated standard errors of these cost calculations.

While presenting a disaggregated societal perspective for the final model-based economic evaluation, analysis of cost-effectiveness was narrowed to health sector costs based on the source of the estimated cost-effectiveness thresholds. Productivity loss associated with the postoperative recovery may be significant and last longer than the 1 month SSI detection window. In the FALCON trial, 60% and 69% of patients in the clean-contaminated and contaminated-dirty arms did not return to normal activities by the 30 days after surgery, respectively [373]. Use of productivity loss predictions by health status (with UK data) was

incorporated into a sensitivity analysis but understanding the additional medium term productivity loss projections by SSI status due to delayed wound healing in LMIC settings could better complement and add weight to the interpretation of the cost-effectiveness evidence.

For LMIC decision-makers, there are competing demands on what healthcare interventions should be invested in with resource constraints on infrastructure, workforce, and funding. Investing in healthcare interventions that are more expensive within existing budgets can displace other healthcare expenditure that can improve healthcare outcomes. The results of the model-based economic evaluation suggest one or more of the SSI interventions are cost-effective in Ghana and India with many of PSA iterations indicating that the intervention dominates usual care. The likely healthcare cost savings with improved outcomes represents a strong case for investment in these interventions. With the considerable economic burden of SSI, investment in an SSI reducing prevention could also help these countries better achieve the WHO universal health coverage target in terms of improving financial risk protection from less postoperative surgical complications. One aspect that may complicate the adoption of the interventions shown likely to be cost saving and improving outcomes is the lack of statistically significant clinical results. This may be a barrier to implementation for decision makers and/or surgeons when trying to reconcile the statistical inference interpretation on the equivalence in treatment effectiveness and the economic evidence looking at the joint uncertainty of the costs and outcomes. Hesitancy in light of the uncertain clinical evidence can be alleviated with future research studies on treatment effectiveness to reduce decision uncertainty as indicated by the value of information analysis.

In general, there is need for multicentre studies with large number of SSI patients to capture relevant costs and consequences of the infection across income settings, especially low

income countries where there is a paucity of economic data. However, the endpoints for RCTs in SSI prevention may be insufficient to fully capture the costs and consequences of SSI. SSI prevention RCTs typically follow the CDC criteria of 30 days post-surgery for non-orthopaedic SSIs (although the criteria has changed in recent years so that some non-orthopaedic SSIs now have a 90 day detection window [488]). RCTs focused on the detection of SSI are not designed to capture the time period involved in the treatment and resolution of SSIs. Costs are known to persist beyond the 30 day period with morbidity consequences too. Extended follow up beyond the primary endpoint had mixed success in the KIWI sub-study. To capture all the relevant costs and consequences of an SSI with the advantages from multiple standardised data collection forms offered by an RCT, future research should specifically consider embedding economic evaluation into a platform RCT [489] designed with patients moving through multiple interventions that would include a preventative intervention at the beginning of the postoperative pathway and a treatment intervention for patients who suffer an SSI.

The feasibility of iterative economic modelling for safe surgery interventions in LMIC settings requires careful consideration with respect to the type of intervention to be evaluated. The nature of an intervention can affect the ease of undertaking a preliminary economic model and iteratively updating the economic model with additional evidence. While the effectiveness of the examined interventions (switching the type of sutures or skin preparation solution during a surgery) on SSI prevention can be done within the confines of an RCT, safe surgery interventions that necessitate service level changes face challenges on demonstrating effectiveness due to a complex interplay of system factors [127]. Evaluating a service level change could increase the complexity of model structure and model inputs required to accurately predict what happens to patients, and pose generalisability problems of

extrapolating findings implemented in one setting, evidence determined largely by contextual factors [127], beyond these settings. For complex interventions such as service level changes, guidance on realist economic evaluation is being developed to better contextualise and assess the benefits and costs of complex interventions [490]. In addition, the feasibility of iterative economic modelling for safe surgery interventions in LMIC settings requires careful consideration with respect to the limited resources available for decision makers to gather further evidence. The generation of further evidence in this thesis for the interventions to reduce SSI in LMIC settings was done by UK government funding.

Lastly, the focus of the thesis has been on postoperative complications of surgical patients. However, focusing on patients receiving surgery excludes patients who have an unmet surgical need due to capacity issues [43]. Looking at the implications of expanding surgical provision to help address unmet surgical need at the expense of an increased postoperative complication rate is an important future research area. Estimates from the current thesis can be incorporated into economic modelling of interventions to increase surgical volume such as surgical task-shifting [362]. A summary of the contributions to research presented in this thesis is shown in Table 10.1.

Table 10.1 Contributions of the research within this thesis

1. From the systematic reviews, trial re-analysis, and empirical work, it has been established that SSI is associated with an additional cost burden and quality of life decrement
2. Re-analysis of existing RCTs datasets is possible to generate economic estimates associated with postoperative complications and inform preliminary model-based economic evaluations
3. Cross-sectional SSI utility decrements without baseline adjustment should not be relied upon as model inputs as they can misrepresent the impact of an SSI on quality of life
4. A variety of cost and utility estimates for SSI across different calculation approaches were developed which can be used for future model-based economic evaluations
5. The additional cost of an SSI may be underestimated without patient covariate adjustment in the UK and overestimated without patient covariate adjustment in LMICs
6. The additional cost of an SSI may be overestimated without patient covariate adjustment in LMICs
7. The utility decrement of an SSI may be overestimated without patient covariate adjustment
8. The Case Control approach to assess the SSI utility decrement is the first known study to examine QALY differences by this design that specifically adjusts for baseline imbalances
9. SSI prevention RCTs have a time horizon that is too short to capture all the relevant costs and consequences associated with an SSI
10. Non-statistically significant treatment effectiveness does not rule out the cost-effectiveness of an SSI prevention intervention.
11. Cost sub-studies within multi-continental LMIC surgical trials are feasible during a global pandemic and under standardized data collection and RCT processes the cost of SSI was shown to vary between country setting and predicted wound contamination
12. Moving beyond considering SSI as a binary outcome and to a severity specific outcome can inform future trials on the heterogenous effects an SSI can have on a patient
13. Photographs associated with surgical health states have high acceptability for health state valuation
14. Health State Valuations can be feasibly obtained remotely during a pandemic

10.7 Conclusion

The thesis set out to make an assessment of the economic rationale for investing in safe surgery to reduce postoperative complications in LMICs with SSI as a case study. It has met this overall objective and, in so doing, the thesis makes a number of significant contributions which provide insight on the intricacies of working in this area (Table 10.1).

Ascertaining the additional costs and utility decrement associated with SSI had its own set of methodological challenges irrespective of income setting. Preliminary modelling of interventions to reduce SSI using literature estimates indicated a high probability of cost-effectiveness even with non-statistically significant treatment effectiveness. Updating the model-based economic evaluation with more robust estimates from an SSI RCT re-analysis did not change the decision recommendations.

Estimates of the costs associated with SSI were collected in a sub-study within a multicontinental LMIC SSI prevention trial, and estimates on the utilities associated with SSI were collected using direct health state valuation approaches with a UK general population. These primary research estimates were then incorporated in an updated model-based economic evaluation assessing the cost-effectiveness of the different FALCON trial interventions. From this updated model-based economic evaluation, there is evidence to suggest that one or more of the FALCON interventions are worthwhile investments to reduce SSI complications in Ghana and India. This is despite the lack of statistical significance associated with each of these treatments. There is an economic rationale to investing in safe surgery to reduce postoperative complications in LMICs.

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Appendices

Chapter 1 Appendix

Appendix Table A1.1 CDC SSI definition severity criteria

SUPERFICIAL INCISIONAL SURGICAL SITE INFECTION
Must meet the following criteria: Date of event occurs within 30 days following the National Healthcare Safety Network (NHSN) operative procedure (where day 1 = the procedure date) **AND** involves only skin and subcutaneous tissue of the incision **AND** patient has at least ***one*** of the following: a) purulent drainage from the superficial incision. b) organism(s) identified from an aseptically-obtained specimen from the superficial incision or subcutaneous tissue by a culture or non-culture based microbiologic testing method which is performed for purposes of clinical diagnosis or treatment (for example, not Active Surveillance Culture/Testing). c) a superficial incision that is deliberately opened by a surgeon, physician* or physician designee and culture or non-culture based testing of the superficial incision or subcutaneous tissue is not performed **AND** patient has at least one of the following signs or symptoms: localized pain or tenderness; localized swelling; erythema; or heat. d) diagnosis of a superficial incisional SSI by a physician* or physician designee.
Comments: There are two specific types of superficial incisional SSIs: 1. Superficial Incisional Primary– a superficial incisional SSI that is identified in the primary incision in a patient that has had an operation with one or more incisions (for example, caesarean section incision or chest incision for coronary artery bypass graft with both chest and donor site incisions) 2. Superficial Incisional Secondary– a superficial incisional SSI that is identified in the secondary incision in a patient that has had an operation with more than one incision (for example, donor site incision for coronary artery bypass graft with both chest and donor site incisions)
The following do not qualify as criteria for meeting the NHSN definition of superficial incisional SSI: • Diagnosis/treatment of cellulitis (redness/warmth/swelling), by itself, does not meet superficial incisional SSI criterion 'd'. • A stitch abscess alone (minimal inflammation and discharge confined to the points of suture penetration). • A localized stab wound or pin site infection; depending on the depth, these infections might be considered either a skin or soft tissue infection. **Note:** For an NHSN operative procedure, a laparoscopic trocar site is considered a surgical incision and not a stab wound. If a surgeon uses a laparoscopic trocar site to place a drain at the end of a procedure this is considered a surgical incision.

DEEP INCISIONAL SURGICAL SITE INFECTION

Must meet the following criteria:

Date of event occurs within 30[†] or 90[‡] days following the NHSN operative procedure (where day 1 = the procedure date)

AND

involves deep soft tissues of the incision (for example, fascial and muscle layers)

AND

patient has at least ***one*** of the following:

a) purulent drainage from the deep incision.

b) a deep incision that is deliberately opened or aspirated by a surgeon, physician* or physician designee or spontaneously dehisces

AND

organism(s) identified from the deep soft tissues of the incision by a culture or non-culture based microbiologic testing method which is performed for purposes of clinical diagnosis or treatment (for example, not Active Surveillance Culture/Testing) or culture or non-culture based microbiologic testing method is not performed. A culture or non-culture based test from the deep soft tissues of the incision that has a negative finding does not meet this criterion.

AND

patient has at least ***one*** of the following signs or symptoms: fever (>38°C); localized pain or tenderness.

c) an abscess or other evidence of infection involving the deep incision detected on gross anatomical exam, histopathologic exam, or imaging test.

Comments:

There are two specific types of deep incisional SSIs:

1. Deep Incisional Primary – a deep incisional SSI that is identified in the primary incision in a patient that has had an operation with one or more incisions (for example, caesarean section incision or chest incision for coronary artery bypass graft with both chest and donor site incisions)
2. Deep Incisional Secondary– a deep incisional SSI that is identified in the secondary incision in a patient that has had an operation with more than one incision (for example, donor site incision for coronary artery bypass graft with both chest and donor site incisions)

ORGAN/ SPACE SURGICAL SITE INFECTION

Must meet the following criteria:

Date of event occurs within 30* or 90[#] days following the NHSN operative procedure (where day 1 = the procedure date)

AND

involves any part of the body deeper than the fascial/muscle layers that is opened or manipulated during the operative procedure

AND

patient has at least ***one*** of the following:

a) purulent drainage from a drain placed into the organ/space (for example, closed suction drainage system, open drain, T-tube drain, computerised tomography-guided drainage).

b) organism(s) identified from fluid or tissue in the organ/space by a culture or non-culture based microbiologic testing method which is performed for purposes of clinical diagnosis or treatment (for example, not Active Surveillance Culture/Testing).
c) an abscess or other evidence of infection involving the organ/space detected on gross anatomical exam or histopathologic exam, or imaging test evidence definitive or equivocal for infection.

AND

meets at least one criterion for a specific organ/space infection site[§]

Footnotes

*The term physician for the purpose of application of the NHSN SSI criteria may be interpreted to mean a surgeon, infectious disease physician, emergency physician, other physician on the case, or physician's designee (nurse practitioner or physician's assistant).

[†]30 day surveillance applicable to the following operations: abdominal aortic aneurysm repair; limb amputation; appendix surgery; shunt for dialysis; bile duct liver or pancreatic surgery; carotid endarterectomy; gallbladder surgery; colon surgery; caesarean section; gastric surgery; heart transplant; abdominal hysterectomy; kidney transplant; laminectomy; liver transplant; neck surgery; kidney surgery; ovarian surgery; prostate surgery; rectal surgery; small bowel surgery; thoracic surgery; thyroid and/or parathyroid surgery; vaginal hysterectomy; and exploratory laparotomy

[‡]90 day surveillance applicable to the following operations: breast surgery; cardiac surgery; coronary artery bypass graft with both chest and donor site incisions; coronary artery bypass graft with chest incision only; craniotomy; spinal fusion; open reduction of fracture; herniorrhaphy; hip prosthesis; knee prosthesis; pacemaker surgery; peripheral vascular bypass surgery; and ventricular shunt

[§]Specific Sites of an Organ/Space SSI: osteomyelitis; breast abscess or mastitis; myocarditis or pericarditis; disc space infection; ear, mastoid infection; endometritis; endocarditis; gastrointestinal tract infection; intraabdominal infection, not specified elsewhere; intracranial infection; joint or bursa infection; other infection of the lower respiratory tract; mediastinitis; meningitis or ventriculitis; oral cavity infection (mouth, tongue, or gums); deep pelvic tissue infection or other infection of the male or female reproductive tract; periprosthetic joint infection; spinal abscess/infection; sinusitis; upper respiratory tract, pharyngitis, laryngitis, epiglottitis; urinary system infection; arterial or venous infection; and vaginal cuff infection

Adapted from CDC National Healthcare Safety Network Patient Safety Component Manual [488]

Chapter 3 Appendix

Appendix A3.1 Search strategies

LMIC Search strategy Medline

1. economics/ or cost of illness/ or exp "Costs and Cost Analysis"/ or exp health care costs/ or economic value of life/ or exp economics medical/ or exp economics hospital/ or economics pharmaceutical/ or exp "Fees and Charges"/ or (econom$ or cost or costs or costly or costing or price or pricing or pharmacoeconomic$).tw. or (expenditure$ not energy).tw. or (value adj1 money).tw. or budget$.tw.
2. exp Surgical Wound Infection/ or exp Wound Infection/ or Surgical wound$.tw. or Postoperative wound infection.tw. or Surgical wound infection.tw. or (wound infection adj8 surgery).tw. or Wound infec$.tw.
3. 1 and 2
4. Developing Countries.sh,kf. or ((developing or less* developed or under developed or underdeveloped or middle income or low* income or underserved or under served or deprived or poor*) adj (countr* or nation? or population? or world)).ti,ab. or ((developing or less* developed or under developed or underdeveloped or middle income or low* income) adj (economy or economies)).ti,ab. or (low* adj (gdp or gnp or gross domestic or gross national)).ti,ab. or (low adj3 middle adj3 countr*).ti,ab. or (lmic or lmics or third world or lami countr*).ti,ab. or transitional countr*.ti,ab.
5. (Africa or Asia or Caribbean or West Indies or South America or Latin America or Central America or (Afghanistan or Albania or Algeria or Angola or Antigua or Barbuda or Argentina or Armenia or Armenian or Aruba or Azerbaijan or Bahrain or Bangladesh or Barbados or Benin or Byelarus or Byelorussian or Belarus or Belorussian or Belorussia or Belize or Bhutan or Bolivia or Bosnia or Herzegovina or Hercegovina or Botswana or Brasil or Brazil or Bulgaria or Burkina Faso or Burkina Fasso or Upper Volta or Burundi or Urundi or Cambodia or Khmer Republic or Kampuchea or Cameroon or Cameroons or Cameron or Camerons or Cape Verde or Central African Republic or Chad or Chile or China or Colombia or Comoros or Comoro Islands or Comores or Mayotte or Congo or Zaire or Costa Rica or Cote d'Ivoire or Ivory Coast or Croatia or Cuba or Cyprus or Czechoslovakia or Czech Republic or Slovakia or Slovak Republic or Djibouti or French Somaliland or Dominica or Dominican Republic or East Timor or East Timur or Timor Leste or Ecuador or Egypt or United Arab Republic or El Salvador or Eritrea or Estonia or Ethiopia or Fiji or Gabon or Gabonese Republic or Gambia or Gaza or Georgia Republic or Georgian Republic or Ghana or Gold Coast or Greece or Grenada or Guatemala or Guinea or Guam or Guiana or Guyana or Haiti or Honduras or Hungary or India or Maldives or Indonesia or Iran or Iraq or Isle of Man or Jamaica or Jordan or Kazakhstan or Kazakh or Kenya or Kiribati or Korea or Kosovo or Kyrgyzstan or Kirghizia or Kyrgyz Republic or Kirghiz or Kirgizstan or Lao PDR or Laos or Latvia or Lebanon or Lesotho or Basutoland or Liberia or Libya or Lithuania or Macedonia or Madagascar or Malagasy Republic or Malaysia or Malaya or Malay or Sabah or Sarawak or Malawi or Nyasaland or Mali or Malta or Marshall Islands or Mauritania or Mauritius or Agalega Islands or Mexico or Micronesia or Middle East or Moldova or Moldovia or Moldovian or Mongolia or Montenegro or Morocco or Ifni or Mozambique or Myanmar or Myanma or Burma or Namibia or Nepal or Netherlands Antilles or New Caledonia or Nicaragua or Niger or Nigeria or Northern Mariana Islands or Oman or Muscat or Pakistan or Palau or Palestine or Panama or Paraguay or Peru or Philippines or Philipines or Phillipines or Phillippines or Poland or Portugal or Puerto Rico or Romania or Rumania or Roumania or Russia or Russian or Rwanda or Ruanda or Saint Kitts or St Kitts or Nevis or Saint Lucia or St Lucia or Saint Vincent or St Vincent or Grenadines or Samoa or Samoan Islands or Navigator Island or Navigator Islands or Sao Tome or Saudi Arabia or Senegal or Serbia or Montenegro or Seychelles or Sierra Leone or Slovenia or Sri Lanka or Ceylon or Solomon Islands or Somalia or South Africa or Sudan or Suriname or Surinam or Swaziland or Syria or Tajikistan or Tadzhikistan or Tadjikistan or Tadzhik or Tanzania or Thailand or Togo or Togolese Republic or Tonga or Trinidad or Tobago or Tunisia or Turkey or Turkmenistan or Turkmen or Uganda or Ukraine or Uruguay or USSR or Soviet Union or Union of Soviet Socialist Republics or Uzbekistan or Uzbek or Vanuatu or New Hebrides or Venezuela or Vietnam or Viet Nam or West Bank or Yemen or Yugoslavia or Zambia or Zimbabwe or Rhodesia)).hw,kf,ti,ab,cp.
6. 4 or 5
7. 3 and 6

LMIC Search strategy Embase

1. cost benefit analysis/
2. cost effectiveness analysis/
3. cost minimization analysis/
4. cost-utility analysis/
5. economic evaluation/
6. (cost or costs or costed or costly or costing).tw.
7. (economic$ or pharmacoeconomic$ or price$ or pricing).tw.
8. or/1-7
9. Exp Surgical Wound Infection/
10. Exp Wound Infection/
11. Exp Surgical wound/
12. Exp Surgical infection/
13. Surgical wound infection.tw.
14. (wound infection adj8 surgery).tw.
15. Wound infec$.tw
16. or/9-15
17. and/ 16,8
18. Developing Country.sh.
19. (Africa or Asia or Caribbean or West Indies or South America or Latin America or Central America).hw,ti,ab,cp.
20. (Afghanistan or Albania or Algeria or Angola or Antigua or Barbuda or Argentina or Armenia or Armenian or Aruba or Azerbaijan or Bahrain or Bangladesh or Barbados or Benin or Byelarus or Byelorussian or Belarus or Belorussian or Belorussia or Belize or Bhutan or Bolivia or Bosnia or Herzegovina or Hercegovina or Botswana or Brasil or Brazil or Bulgaria or Burkina Faso or Burkina Fasso or Upper Volta or Burundi or Urundi or Cambodia or Khmer Republic or Kampuchea or Cameroon or Cameroons or Cameron or Camerons or Cape Verde or Central African Republic or Chad or Chile or China or Colombia or Comoros or Comoro Islands or Comores or Mayotte or Congo or Zaire or Costa Rica or Cote d'Ivoire or Ivory Coast or Croatia or Cuba or Cyprus or Czechoslovakia or Czech Republic or Slovakia or Slovak Republic or Djibouti or French Somaliland or Dominica or Dominican Republic or East Timor or East Timur or Timor Leste or Ecuador or Egypt or United Arab Republic or El Salvador or Eritrea or Estonia or Ethiopia or Fiji or Gabon or Gabonese Republic or Gambia or Gaza or Georgia Republic or Georgian Republic or Ghana or Gold Coast or Greece or Grenada or Guatemala or Guinea or Guam or Guiana or Guyana or Haiti or Honduras or Hungary or India or Maldives or Indonesia or Iran or Iraq or Isle of Man or Jamaica or Jordan or Kazakhstan or Kazakh or Kenya or Kiribati or Korea or Kosovo or Kyrgyzstan or Kirghizia or Kyrgyz Republic or Kirghiz or Kirgizstan or Lao PDR or Laos or Latvia or Lebanon-or Lesotho or Basutoland or Liberia or Libya or Lithuania or Macedonia or Madagascar or Malagasy Republic or Malaysia or Malaya or Malay or Sabah or Sarawak or Malawi or Nyasaland or Mali or Malta or Marshall Islands or Mauritania or Mauritius or Agalega Islands or Mexico or Micronesia or Middle East or Moldova or Moldovia or Moldovian or Mongolia or Montenegro or Morocco or Ifni or Mozambique or Myanmar or Myanma or Burma or Namibia or Nepal or Netherlands Antilles or New Caledonia or Nicaragua or Niger or Nigeria or Northern Mariana Islands or Oman or Muscat or Pakistan or Palau or Palestine or Panama or Paraguay or Peru or Philippines or or Phillipines or Poland or Portugal or Puerto Rico or Romania or Rumania or Roumania or Russia or Russian or Rwanda or Ruanda or Saint Kitts or St Kitts or Nevis or Saint Lucia or St Lucia or Saint Vincent or St Vincent or Grenadines or Samoa or Samoan Islands or Navigator Island or Navigator Islands or Sao Tome or Saudi Arabia or Senegal or Serbia or Montenegro or Seychelles or Sierra Leone or Slovenia or Sri Lanka or Ceylon or Solomon Islands or Somalia or South Africa or Sudan or Suriname or Surinam or Swaziland or Syria or Tajikistan or Tadzhikistan or Tadjikistan or Tadzhik or Tanzania or Thailand or Togo or Togolese Republic or Tonga or Trinidad or Tobago or Tunisia or Turkey or Turkmenistan or Turkmen or Uganda or Ukraine or Uruguay or USSR or Soviet Union or Union of Soviet Socialist Republics or Uzbekistan or Uzbek or Vanuatu or New Hebrides or Venezuela or Vietnam or Viet Nam or West Bank or Yemen or Yugoslavia or Zambia or Zimbabwe or Rhodesia).hw,ti,ab,cp.
21. ((developing or less* developed or under developed or underdeveloped or middle income or low* income or underserved or under served or deprived or poor*) adj (countr* or nation? or population? or world)).ti,ab.
22. ((developing or less* developed or under developed or underdeveloped or middle income or low* income) adj (economy or economies)).ti,ab.
23. (low* adj (gdp or gnp or gross domestic or gross national)).ti,ab.
24. (low adj3 middle adj3 countr*).ti,ab.
25. (lmic or lmics or third world or lami countr*).ti,ab.
26. transitional countr*.ti,ab.

27. or/18-27
28. 23 and 13

Europe Search strategy Medline

1. economics/
2. cost of illness/
3. exp health care costs/
4. economic value of life/
5. exp economics medical/
6. exp economics hospital/
7. economics pharmaceutical/
8. exp fees/ and charges/
9. (econom$ or cost or costs or costly or costing or price or pricing or pharmacoeconomic$).tw.
10. (expenditure$ not energy).tw.
11. (value adj1 money).tw.
12. budget$.tw.
13. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12
14. (wound infection adj8 surgery).tw.
15. Wound infec$.tw.
16. exp Wound Infection/
17. Surgical wound infection.tw.
18. exp Surgical Wound Infection/
19. 14 or 15 or 16 or 17 or 18
20. 13 and 19
21. exp United Kingdom/ or exp iceland/ or exp switzerland/ or exp Austria/ or exp Wales/ or exp scotland/ or exp Northern Ireland/ or exp Norway/ or exp Belgium/ or exp sweden/ or exp Czech Republic/ or exp Estonia/ or exp Greece/ or exp Spain/ or exp England/ or exp France/ or exp Finland/ or exp Germany/ or exp Denmark/ or exp Italy/ or exp Hungary/ or exp Ireland/ or exp Latvia/ or exp lithuania/ or exp luxembourg/ or exp netherlands/ or exp poland/ or exp portugal/ or exp slovakia/ or exp slovenia/
22. 20 and 21

Europe Search strategy Embase

1. cost benefit analysis/
2. cost effectiveness analysis/
3. cost minimization analysis/
4. cost-utility analysis/
5. economic evaluation/
6. (cost or costs or costed or costly or costing).tw.
7. (economic$ or pharmacoeconomic$ or price$ or pricing).tw.
8. or/1-7
9. exp Surgical Wound Infection/
10. exp Wound Infection/
11. exp Surgical wound/
12. exp Surgical infection/
13. Surgical wound infection.tw.
14. (wound infection adj8 surgery).tw.
15. Wound infec$.tw.
16. or/9-15
17. and/8,16
18. exp United Kingdom/ or exp iceland/ or exp switzerland/ or exp Austria/ or exp Wales/ or exp scotland/ or exp Northern Ireland/ or exp Norway/ or exp Belgium/ or exp sweden/ or exp Czech Republic/ or exp Estonia/ or exp Greece/ or exp Spain/ or exp England/ or exp France/ or exp Finland/ or exp Germany/ or exp Denmark/ or exp Italy/ or exp Hungary/ or exp Ireland/ or exp Latvia/ or exp lithuania/ or exp luxembourg/ or exp netherlands/ or exp poland/ or exp portugal/ or exp slovakia/ or exp slovenia/
19. and/17-18

Appendix Table A3.1 Müller 2018 Cost of Illness checklist

Al-Zaru (2011)				
A	General aspects			Score
1	Illness and patient population	Was the illness defined?	Yes, CDC definition	1
2		Was the analysis limited to a defined patient population?	Yes, open heart surgery patients	1
3	Design	Was there a description of the setting in which the costs are incurred?	No, only that it was a teaching hospital	0
4		Was the data collection type described?	Yes, micro costing of retrospective data collection from the hospital IT department	1
5	Perspective	Was/were the perspective(s) stated?	No	0
6	Time period	Was the time period stated to which the costs refer to?	Yes, the time period of the study was between January 2005 and January 2008	1
B	Resource Identification			
1	Scope and type of resources	Was relevant resource use omitted with regard to the chosen perspective?	No perspective stated	0
2		Was there justification for omitting relevant resource use with regard to the chosen perspective?	No perspective stated	0
3		If indirect costs were included, were the costs of productivity loss clearly demarcated?	NA	0
C	Description and quantification of resource use			
1	Data Sources	Were the sources of the resource use specified?	Yes, Data was taken from patient medical records	1
2		Was resource use from overseas adjusted for the local country's context?	NA	0
3		Was there any analysis to account for missing data performed?	No	0
D	Resource Valuation			
1	Perspectives	Were the resources valued according to the chosen perspective?	No perspective stated	0
2	Data Sources	Were all data sources of the valuation of resource use specified?	Yes, provided by the hospital finance department	1
3	Productivity loss	Was the valuation method for productivity loss specified?	Not applicable	0
4	Discounting	Was discounting undertaken with a specified discount rate?	Not applicable	0
5	Inflation adjustment	Were cost data from different time periods adjusted for inflation with its method specified?	Unclear	0
6	Price and Price adjustment	Were all resources valued according to the specified cost year?	No cost year specified	0
7		Were price adjustments over time considered?	Unclear	0
8		Were prices from other countries used/applied?	Not applicable	0
E	Evaluation and presentation of results			
1	Evaluation methods	Were the data evaluation methods comprehensibly described?	Yes	0
2		Were subgroup analyses performed?	No	0
3		Were sensitivity analysis performed?	No	0
4		Were sensitivity analyses carried out on the resource use or costs?	No	0
5		Were parameters for estimating results uncertainty named?	Not applicable	0
6		Was modelling used to estimate costs?	No	0
7	Result presentation	Were the resource use category amounts separately listed?	No	0
8		Was the derivation of the calculations comprehensible?	No, how the cost results have been derived was not transparent	0

9		Were the cost categories separately listed?	No	0
F	Discussion and conclusion			
1	Conclusion	Were the conclusions comprehensible?	Yes, the authors discuss their costs of SSI results and the implications on patients and the hospital	1
2	Quality	Was the quality of the data source(s) discussed?	No	0
3	Comparison	Was there a comparison of the study findings with findings from other studies?	Yes	1
4	Limitations	Were limitations of the study stated?	No	0
5	Generalizability	Was the generalizability of the results discussed?	Yes	1
6	Future Research recommendations	Were future concrete research recommendations discussed?	Yes	1
7	Conflicts of interest	Was there a conflict of interest section?	No	0
	Score total			10
Coskun (2005)				
A	General aspects			
1	Illness and patient population	Was the illness defined?	Yes, CDC definition	1
2		Was the analysis limited to a defined patient population?	Yes, CABG patients	1
3	Design	Was there a description of the setting in which the costs are incurred?	Yes, a private medical hospital affiliated to a university with the annual number of cardiovascular and vascular operations undertaken was described	1
4		Was the data collection type described?	Yes, it was micro costing of retrospective data	1
5	Perspective	Was/were the perspective(s) stated?	No	0
6	Time period	Was the time period stated to which the costs refer to?	Yes the time period of the study was from January 1999 to December 2002	1
B	Resource Identification			
1	Scope and type of resources	Was relevant resource use omitted with regard to the chosen perspective?	No perspective stated.	0
2		Was there justification for omitting relevant resource use with regard to the chosen perspective?	No perspective stated.	0
3		If indirect costs were included, were the costs of productivity loss clearly demarcated?	NA	0
C	Description and quantification of resource use			
1	Data Sources	Were the sources of the resource use specified?	Yes, taken from patient medical records	1
2		Was resource use from overseas adjusted for the local country's context?	NA	0
3		Was there any analysis to account for missing data performed?	No	0
D	Resource Valuation			
1	Perspectives	Were the resources valued according to the chosen perspective?	No perspective stated	0
2	Data Sources	Were all data sources of the valuation of resource use specified?	Yes, provided by the hospital finance department	1

3	Productivity loss	Was the valuation method for productivity loss specified?	Not applicable	0
4	Discounting	Was discounting undertaken with a specified discount rate?	No	0
5	Inflation adjustment	Were cost data from different time periods adjusted for inflation with its method specified?	Unclear	0
6	Price and Price adjustment	Were all resources valued according to the specified cost year?	No specified cost year	0
7		Were price adjustments over time considered?	Unclear	0
8		Were prices from other countries used/applied?	Not applicable	0
E	Evaluation and presentation of results			
1	Evaluation methods	Were the data evaluation methods comprehensibly described?	Yes, the methods of obtaining the extra cost of SSI was described	0
2		Were subgroup analyses performed?	Yes, patients with deep sternal SSI and patients with superficial sternal SSI were assessed separately	0
3		Were sensitivity analysis performed?	No	0
4		Were sensitivity analyses carried out on the resource use or costs?	No	0
5		Were parameters for estimating results uncertainty named?	Not applicable	0
6		Was modelling used to estimate costs?	No	0
7	Result presentation	Were the resource use category amounts separately listed?	No	0
8		Was the derivation of the calculations comprehensible?	No, control group costs are not shown	0
9		Were the cost categories separately listed?	Yes	0
F	Discussion and conclusion			
1	Conclusion	Were the conclusions comprehensible?	Yes	1
2	Quality	Was the quality of the data source(s) discussed?	No	0
3	Comparison	Was there a comparison of the study findings with findings from other studies?	Yes	1
4	Limitations	Were limitations of the study stated?	No	0
5	Generalizability	Was the generalizability of the results discussed?	No	1
6	Future Research recommendations	Were future concrete research recommendations discussed?	No	1
7	Conflicts of interest	Was there a conflict of interest section?	No	0
	Score total			11
Dal-Paz (2010)				
A	General aspects			
1	Illness and patient population	Was the illness defined?	Yes, CDC definition	1
2		Was the analysis limited to a defined patient population?	Unclear, SSI patient population described but not the non SSI patient population	0
3	Design	Was there a description of the setting in which the costs are incurred?	Yes, there was a description of the teaching hospital with the bed capacity and typical number of operations and patient numbers	1
4		Was the data collection type described?	Yes, it was micro costing of retrospective data	1
5	Perspective	Was/were the perspective(s) stated?	No	0
6	Time period	Was the time period stated to which the costs refer to?	Yes, the time period of the study was between 2006 and 2007.	1
B	Resource Identification			
1	Scope and type of resources	Was relevant resource use omitted with regard to the chosen perspective?	No perspective stated	0

2		Was there justification for omitting relevant resource use with regard to the chosen perspective?	No perspective stated	0
3		If indirect costs were included, were the costs of productivity loss clearly demarcated?	NA	0
C	Description and quantification of resource use			
1	Data Sources	Were the sources of the resource use specified?	Yes, the hospital IT system identified the patients resource use from their medical records	1
2		Was resource use from overseas adjusted for the local country's context?	NA	0
3		Was there any analysis to account for missing data performed?	No	0
D	Resource Valuation			
1	Perspectives	Were the resources valued according to the chosen perspective?	No perspective stated	0
2	Data Sources	Were all data sources of the valuation of resource use specified?	Provided by the hospital finance department and the Brazilian Medical Association (estimated costs)	0
3	Productivity loss	Was the valuation method for productivity loss specified?	Not applicable	0
4	Discounting	Was discounting undertaken with a specified discount rate?	Not applicable	0
5	Inflation adjustment	Were cost data from different time periods adjusted for inflation with its method specified?	Unclear	0
6	Price and Price adjustment	Were all resources valued according to the specified cost year?	Yes, the cost year is 2008	1
7		Were price adjustments over time considered?	Unclear	0
8		Were prices from other countries used/applied?	Not applicable	0
E	Evaluation and presentation of results			
1	Evaluation methods	Were the data evaluation methods comprehensibly described?	No, the comparator group was not mentioned	0
2		Were subgroup analyses performed?	Not applicable	0
3		Were sensitivity analysis performed?	No	0
4		Were sensitivity analyses carried out on the resource use or costs?	No	0
5		Were parameters for estimating results uncertainty named?	Not applicable	0
6		Was modelling used to estimate costs?	No	0
7	Result presentation	Were the resource use category amounts separately listed?	Yes	1
8		Was the derivation of the calculations comprehensible?	No, the comparator group costs are not shown which is a part of the calculation of the additional cost of SSI	0
9		Were the cost categories separately listed?	Yes	1
F	Discussion and conclusion			
1	Conclusion	Were the conclusions comprehensible?	Yes	1
2	Quality	Was the quality of the data source(s) discussed?	No	0
3	Comparison	Was there a comparison of the study findings with findings from other studies?	Yes	1
4	Limitations	Were limitations of the study stated?	Yes, lack of inclusion of indirect costs, and the valuation of expenditure likely to be underestimate	1
5	Generalizability	Was the generalizability of the results discussed?	No	0

6	Future Research recommendations	Were future concrete research recommendations discussed?	No	0
7	Conflicts of interest	Was there a conflict of interest section?	No	0
	Score total			11
Dramowski (2016)				
A	General aspects			
1	Illness and patient population	Was the illness defined?	Yes, CDC definition	1
2		Was the analysis limited to a defined patient population?	Yes	1
3	Design	Was there a description of the setting in which the costs are incurred?	Yes, there is a whole subheading dedicated to describing the hospital setting	1
4		Was the data collection type described?	Yes, micro-costing from a prospective data collection	1
5	Perspective	Was/were the perspective(s) stated?	Yes, healthcare provider perspective	1
6	Time period	Was the time period stated to which the costs refer to?	Yes, the time period was between May 1st in 2014 and October 31st 2015	1
B	Resource Identification			
1	Scope and type of resources	Was relevant resource use omitted with regard to the chosen perspective?	Yes, there are resource use such as additional staffing and operations, that are not included	0
2		Was there justification for omitting relevant resource use with regard to the chosen perspective?	Yes due to lack of data availability	1
3		If indirect costs were included, were the costs of productivity loss clearly demarcated?	NA	0
C	Description and quantification of resource use			
1	Data Sources	Were the sources of the resource use specified?	Yes, taken as part of the prospective clinical surveillance	1
2		Was resource use from overseas adjusted for the local country's context?	NA	0
3		Was there any analysis to account for missing data performed?	No	0
D	Resource Valuation			
1	Perspectives	Were the resources valued according to the chosen perspective?	Yes	1
2	Data Sources	Were all data sources of the valuation of resource use specified?	None specified	0
3	Productivity loss	Was the valuation method for productivity loss specified?	Not applicable	0
4	Discounting	Was discounting undertaken with a specified discount rate?	No	0
5	Inflation adjustment	Were cost data from different time periods adjusted for inflation with its method specified?	Unclear	0
6	Price and Price adjustment	Were all resources valued according to the specified cost year?	Yes	1
7		Were price adjustments over time considered?	Unclear	0
8		Were prices from other countries used/applied?	Not applicable	0
E	Evaluation and presentation of results			
1	Evaluation methods	Were the data evaluation methods comprehensibly described?	No, the comparator group is not described	0
2		Were subgroup analyses performed?	No	0
3		Were sensitivity analysis performed?	No	0
4		Were sensitivity analyses carried out on the resource use or costs?	No	0
5		Were parameters for estimating results uncertainty named?	Not applicable	0
6		Was modelling used to estimate costs?	No	0
7	Result presentation	Were the resource use category amounts separately listed?	No	0

8		Was the derivation of the calculations comprehensible?	No, the extra costs associated with SSI did not describe the costs of patients without SSI	0
9		Were the cost categories separately listed?	No	0
F	Discussion and conclusion			
1	Conclusion	Were the conclusions comprehensible?	Yes	1
2	Quality	Was the quality of the data source(s) discussed?	Yes, they suspect SSI is underestimated owing to a lack of prospective follow-up	1
3	Comparison	Was there a comparison of the study findings with findings from other studies?	Yes	1
4	Limitations	Were limitations of the study stated?	Yes, they were unavailable to differentiate subcomponents of the direct costs	1
5	Generalizability	Was the generalizability of the results discussed?	Yes	1
6	Future Research recommendations	Were future concrete research recommendations discussed?	No	0
7	Conflicts of interest	Was there a conflict of interest section?	Yes	1
	Score total			16
Galal (2011)				
A	General aspects			
1	Illness and patient population	Was the illness defined?	Yes, CDC definition	1
2		Was the analysis limited to a defined patient population?	Yes, surgery patients	1
3	Design	Was there a description of the setting in which the costs are incurred?	No	0
4		Was the data collection type described?	Yes, micro costing of prospective data collection	1
5	Perspective	Was/were the perspective(s) stated?	No	0
6	Time period	Was the time period stated to which the costs refer to?	Not specified	0
B	Resource Identification			
1	Scope and type of resources	Was relevant resource use omitted with regard to the chosen perspective?	Yes, there was resource collected that could have been valued other than LOS	0
2		Was there justification for omitting relevant resource use with regard to the chosen perspective?	No	0
3		If indirect costs were included, were the costs of productivity loss clearly demarcated?	NA	0
C	Description and quantification of resource use			
1	Data Sources	Were the sources of the resource use specified?	Yes, taken as part of the trial	1
2		Was resource use from overseas adjusted for the local country's context?	NA	0
3		Was there any analysis to account for missing data performed?	No	0
D	Resource Valuation			
1	Perspectives	Were the resources valued according to the chosen perspective?	No perspective stated	0
2	Data Sources	Were all data sources of the valuation of resource use specified?	Not specified	0
3	Productivity loss	Was the valuation method for productivity loss specified?	Not applicable	0
4	Discounting	Was discounting undertaken with a specified discount rate?	Not applicable	0
5	Inflation adjustment	Were cost data from different time periods adjusted for inflation with its method specified?	Unclear	0
6	Price and Price adjustment	Were all resources valued according to the specified cost year?	Unclear	0
7		Were price adjustments over time considered?	Unclear	0
8		Were prices from other countries used/applied?	Not applicable	0
E	Evaluation and presentation of results			

1	Evaluation methods	Were the data evaluation methods comprehensibly described?	Yes	1
2		Were subgroup analyses performed?	Not applicable	0
3		Were sensitivity analysis performed?	No	0
4		Were sensitivity analyses carried out on the resource use or costs?	No	0
5		Were parameters for estimating results uncertainty named?	Not applicable	0
6		Was modelling used to estimate costs?	No	0
7	Result presentation	Were the resource use category amounts separately listed?	Not applicable	0
8		Was the derivation of the calculations comprehensible?	Yes	1
9		Were the cost categories separately listed?	Not applicable	0
F	Discussion and conclusion			
1	Conclusion	Were the conclusions comprehensible?	Yes	1
2	Quality	Was the quality of the data source(s) discussed?	No	0
3	Comparison	Was there a comparison of the study findings with findings from other studies?	Yes	1
4	Limitations	Were limitations of the study stated?	Yes	1
5	Generalizability	Was the generalizability of the results discussed?	No	0
6	Future Research recommendations	Were future concrete research recommendations discussed?	No	0
7	Conflicts of interest	Was there a conflict of interest section?	No	0
	Score total			9
Hweidi (2018)				
A	General aspects			
1	Illness and patient population	Was the illness defined?	Yes, based on culture from wound discharge or other signs and symptoms suggestive of SSI.	1
2		Was the analysis limited to a defined patient population?	Yes, adult patients who underwent nontraumatic craniotomy operations	1
3	Design	Was there a description of the setting in which the costs are incurred?	No	0
4		Was the data collection type described?	Yes, micro costing of retrospective data collection	1
5	Perspective	Was/were the perspective(s) stated?	No	0
6	Time period	Was the time period stated to which the costs refer to?	Yes, the time period was between May 2009 and March 2015	1
B	Resource Identification			
1	Scope and type of resources	Was relevant resource use omitted with regard to the chosen perspective?	No perspective stated	0
2		Was there justification for omitting relevant resource use with regard to the chosen perspective?	NA	0
3		If indirect costs were included, were the costs of productivity loss clearly demarcated?	NA	0
C	Description and quantification of resource use			
1	Data Sources	Were the sources of the resource use specified?	Yes, taken as part of the medical records	1
2		Was resource use from overseas adjusted for the local country's context?	NA	0
3		Was there any analysis to account for missing data performed?	No	0
D	Resource Valuation			
1	Perspectives	Were the resources valued according to the chosen perspective?	No perspective stated	0
2	Data Sources	Were all data sources of the valuation of resource use specified?	Yes, taken from the finance department in the hospital	1

3	Productivity loss	Was the valuation method for productivity loss specified?	Not applicable	0
4	Discounting	Was discounting undertaken with a specified discount rate?	Not applicable	0
5	Inflation adjustment	Were cost data from different time periods adjusted for inflation with its method specified?	Unclear	0
6	Price and Price adjustment	Were all resources valued according to the specified cost year?	Unclear	0
7		Were price adjustments over time considered?	Unclear	0
8		Were prices from other countries used/applied?	Not applicable	0
E	Evaluation and presentation of results			
1	Evaluation methods	Were the data evaluation methods comprehensibly described?	Yes	1
2		Were subgroup analyses performed?	Not applicable	0
3		Were sensitivity analysis performed?	No	0
4		Were sensitivity analyses carried out on the resource use or costs?	No	0
5		Were parameters for estimating results uncertainty named?	Not applicable	0
6		Was modelling used to estimate costs?	No	0
7	Result presentation	Were the resource use category amounts separately listed?	No	0
8		Was the derivation of the calculations comprehensible?	No	0
9		Were the cost categories separately listed?	No	0
F	Discussion and conclusion			
1	Conclusion	Were the conclusions comprehensible?	Yes	1
2	Quality	Was the quality of the data source(s) discussed?	No	0
3	Comparison	Was there a comparison of the study findings with findings from other studies?	Yes	1
4	Limitations	Were limitations of the study stated?	Yes	1
5	Generalizability	Was the generalizability of the results discussed?	Yes	1
6	Future Research recommendations	Were future concrete research recommendations discussed?	Yes	1
7	Conflicts of interest	Was there a conflict of interest section?	Yes	1
	Score total			13
Köşüş (2009)				
A	General aspects			
1	Illness and patient population	Was the illness defined?	Yes, CDC definition	1
2		Was the analysis limited to a defined patient population?	Yes, women who had caesarean surgery	1
3	Design	Was there a description of the setting in which the costs are incurred?	No	0
4		Was the data collection type described?	Yes, micro costing of prospective data collection	1
5	Perspective	Was/were the perspective(s) stated?	No	0
6	Time period	Was the time period stated to which the costs refer to?	Yes, the time period was between 2004 to 2007	1
B	Resource Identification			
1	Scope and type of resources	Was relevant resource use omitted with regard to the chosen perspective?	Yes, there was resource collected that could have been valued other than LOS	0
2		Was there justification for omitting relevant resource use with regard to the chosen perspective?	No	0
3		If indirect costs were included, were the costs of productivity loss clearly demarcated?	NA	0
C	Description and quantification of resource use			

1	Data Sources	Were the sources of the resource use specified?	Yes, taken as part of the trial	1
2		Was resource use from overseas adjusted for the local country's context?	NA	0
3		Was there any analysis to account for missing data performed?	No	0
D	Resource Valuation			
1	Perspectives	Were the resources valued according to the chosen perspective?	Unclear	0
2	Data Sources	Were all data sources of the valuation of resource use specified?	Not specified	0
3	Productivity loss	Was the valuation method for productivity loss specified?	Not applicable	0
4	Discounting	Was discounting undertaken with a specified discount rate?	Not applicable	0
5	Inflation adjustment	Were cost data from different time periods adjusted for inflation with its method specified?	Unclear	0
6	Price and Price adjustment	Were all resources valued according to the specified cost year?	Unclear	0
7		Were price adjustments over time considered?	Unclear	0
8		Were prices from other countries used/applied?	Not applicable	0
E	Evaluation and presentation of results			
1	Evaluation methods	Were the data evaluation methods comprehensibly described?	Yes	1
2		Were subgroup analyses performed?	Not applicable	0
3		Were sensitivity analysis performed?	No	0
4		Were sensitivity analyses carried out on the resource use or costs?	No	0
5		Were parameters for estimating results uncertainty named?	Not applicable	0
6		Was modelling used to estimate costs?	No	0
7	Result presentation	Were the resource use category amounts separately listed?	Yes	1
8		Was the derivation of the calculations comprehensible?	No, the total LOS for each group is not shown, just the additional LOS	0
9		Were the cost categories separately listed?	Yes	1
F	Discussion and conclusion			
1	Conclusion	Were the conclusions comprehensible?	Yes	1
2	Quality	Was the quality of the data source(s) discussed?	No	0
3	Comparison	Was there a comparison of the study findings with findings from other studies?	Yes	1
4	Limitations	Were limitations of the study stated?	Yes	1
5	Generalizability	Was the generalizability of the results discussed?	No	0
6	Future Research recommendations	Were future concrete research recommendations discussed?	No	0
7	Conflicts of interest	Was there a conflict of interest section?	No	0
	Score total			11
Liu (2018)				
A	General aspects			
1	Illness and patient population	Was the illness defined?	Yes, CDC definition	1
2		Was the analysis limited to a defined patient population?	Yes, colorectal patients	1
3	Design	Was there a description of the setting in which the costs are incurred?	No	0
4		Was the data collection type described?	Yes, micro costing of prospective data collection	1

5	Perspective	Was/were the perspective(s) stated?	No	0
6	Time period	Was the time period stated to which the costs refer to?	Time period of the study was 2015	1
B	Resource Identification			
1	Scope and type of resources	Was relevant resource use omitted with regard to the chosen perspective?	No perspective stated	0
2		Was there justification for omitting relevant resource use with regard to the chosen perspective?	No perspective stated	0
3		If indirect costs were included, were the costs of productivity loss clearly demarcated?	NA	0
C	Description and quantification of resource use			
1	Data Sources	Were the sources of the resource use specified?	Yes, taken from hospital records	1
2		Was resource use from overseas adjusted for the local country's context?	NA	0
3		Was there any analysis to account for missing data performed?	No	0
D	Resource Valuation			
1	Perspectives	Were the resources valued according to the chosen perspective?	Perspective not stated	0
2	Data Sources	Were all data sources of the valuation of resource use specified?	Yes, the valuation of resource use was hospital fees/charges	1
3	Productivity loss	Was the valuation method for productivity loss specified?	Not applicable	0
4	Discounting	Was discounting undertaken with a specified discount rate?	Not applicable	0
5	Inflation adjustment	Were cost data from different time periods adjusted for inflation with its method specified?	Not applicable	0
6	Price and Price adjustment	Were all resources valued according to the specified cost year?	Not applicable	0
7		Were price adjustments over time considered?	Not applicable	0
8		Were prices from other countries used/applied?	Not applicable	0
E	Evaluation and presentation of results			
1	Evaluation methods	Were the data evaluation methods comprehensibly described?	Yes	1
2		Were subgroup analyses performed?	Yes	1
3		Were sensitivity analysis performed?	No	0
4		Were sensitivity analyses carried out on the resource use or costs?	No	0
5		Were parameters for estimating results uncertainty named?	Not applicable	0
6		Was modelling used to estimate costs?	No	0
7	Result presentation	Were the resource use category amounts separately listed?	No	0
8		Was the derivation of the calculations comprehensible?	No, costs of no SSI groups not shown	0
9		Were the cost categories separately listed?	No	0
F	Discussion and conclusion			
1	Conclusion	Were the conclusions comprehensible?	Yes	1
2	Quality	Was the quality of the data source(s) discussed?	No	0
3	Comparison	Was there a comparison of the study findings with findings from other studies?	Yes	1
4	Limitations	Were limitations of the study stated?	Yes	1
5	Generalizability	Was the generalizability of the results discussed?	Yes	1
6	Future Research recommendations	Were future concrete research recommendations discussed?	Yes	1
7	Conflicts of interest	Was there a conflict of interest section?	Yes	1
	Score total			14

Özmen (2016)				
A	General aspects			
1	Illness and patient population	Was the illness defined?	Yes, CDC definition	1
2		Was the analysis limited to a defined patient population?	Yes, elective gastric cancer surgery	1
3	Design	Was there a description of the setting in which the costs are incurred?	Yes, it is a tertiary care centre with a description of the annual number of gastric cancer surgeries a year and a mention of a higher than literature reported average of SSI	1
4		Was the data collection type described?	Yes, micro costing of prospective data collection	1
5	Perspective	Was/were the perspective(s) stated?	No	0
6	Time period	Was the time period stated to which the costs refer to?	Time period of the study was June to December 2015	1
B	Resource Identification			
1	Scope and type of resources	Was relevant resource use omitted with regard to the chosen perspective?	No perspective stated. Unclear what resource use was included	0
2		Was there justification for omitting relevant resource use with regard to the chosen perspective?	No perspective stated.	0
3		If indirect costs were included, were the costs of productivity loss clearly demarcated?	NA	0
C	Description and quantification of resource use			
1	Data Sources	Were the sources of the resource use specified?	Unclear what resource use was included	1
2		Was resource use from overseas adjusted for the local country's context?	NA	0
3		Was there any analysis to account for missing data performed?	No	0
D	Resource Valuation			
1	Perspectives	Were the resources valued according to the chosen perspective?	Perspective not stated	0
2	Data Sources	Were all data sources of the valuation of resource use specified?	No	0
3	Productivity loss	Was the valuation method for productivity loss specified?	Not applicable	0
4	Discounting	Was discounting undertaken with a specified discount rate?	No	0
5	Inflation adjustment	Were cost data from different time periods adjusted for inflation with its method specified?	Unclear	0
6	Price and Price adjustment	Were all resources valued according to the specified cost year?	Not applicable	0
7		Were price adjustments over time considered?	Unclear	0
8		Were prices from other countries used/applied?	Not applicable	0
E	Evaluation and presentation of results			
1	Evaluation methods	Were the data evaluation methods comprehensibly described?	No	0
2		Were subgroup analyses performed?	No	0
3		Were sensitivity analysis performed?	No	0
4		Were sensitivity analyses carried out on the resource use or costs?	No	0
5		Were parameters for estimating results uncertainty named?	Not applicable	0
6		Was modelling used to estimate costs?	No	0

7	Result presentation	Were the resource use category amounts separately listed?	No	0
8		Was the derivation of the calculations comprehensible?	No	0
9		Were the cost categories separately listed?	No	0
F	Discussion and conclusion			
1	Conclusion	Were the conclusions comprehensible?	No	0
2	Quality	Was the quality of the data source(s) discussed?	No	0
3	Comparison	Was there a comparison of the study findings with findings from other studies?	No	0
4	Limitations	Were limitations of the study stated?	No	0
5	Generalizability	Was the generalizability of the results discussed?	No	0
6	Future Research recommendations	Were future concrete research recommendations discussed?	No	0
7	Conflicts of interest	Was there a conflict of interest section?	Yes	1
	Score total			7
Phothong (2015)				
A	General aspects			
1	Illness and patient population	Was the illness defined?	Not reported	0
2		Was the analysis limited to a defined patient population?	Yes, patients with sigmoid cancer	1
3	Design	Was there a description of the setting in which the costs are incurred?	No	0
4		Was the data collection type described?	Yes, micro costing of retrospective data collection	1
5	Perspective	Was/were the perspective(s) stated?	No	0
6	Time period	Was the time period stated to which the costs refer to?	Time period of the study was January 2008 to September 2013	1
B	Resource Identification			
1	Scope and type of resources	Was relevant resource use omitted with regard to the chosen perspective?	No perspective stated. No resource beyond discharge was considered	0
2		Was there justification for omitting relevant resource use with regard to the chosen perspective?	No perspective stated.	0
3		If indirect costs were included, were the costs of productivity loss clearly demarcated?	NA	0
C	Description and quantification of resource use			
1	Data Sources	Were the sources of the resource use specified?	Yes from the hospital records	1
2		Was resource use from overseas adjusted for the local country's context?	NA	0
3		Was there any analysis to account for missing data performed?	No	0
D	Resource Valuation			
1	Perspectives	Were the resources valued according to the chosen perspective?	Perspective not stated	0
2	Data Sources	Were all data sources of the valuation of resource use specified?	Yes, it was taken from the hospital	1
3	Productivity loss	Was the valuation method for productivity loss specified?	Not applicable	0
4	Discounting	Was discounting undertaken with a specified discount rate?	Not applicable	0
5	Inflation adjustment	Were cost data from different time periods adjusted for inflation with its method specified?	Unclear	0
6	Price and Price adjustment	Were all resources valued according to the specified cost year?	Not applicable	0
7		Were price adjustments over time considered?	Unclear	0
8		Were prices from other countries used/applied?	Not applicable	0
E	Evaluation and presentation of results			

1	Evaluation methods	Were the data evaluation methods comprehensibly described?	Yes	1
2		Were subgroup analyses performed?	No	0
3		Were sensitivity analysis performed?	No	0
4		Were sensitivity analyses carried out on the resource use or costs?	No	0
5		Were parameters for estimating results uncertainty named?	Not applicable	0
6		Was modelling used to estimate costs?	No	0
7	Result presentation	Were the resource use category amounts separately listed?	No	0
8		Was the derivation of the calculations comprehensible?	Yes	1
9		Were the cost categories separately listed?	Yes	1
F	Discussion and conclusion			
1	Conclusion	Were the conclusions comprehensible?	Yes	1
2	Quality	Was the quality of the data source(s) discussed?	No	0
3	Comparison	Was there a comparison of the study findings with findings from other studies?	Yes	1
4	Limitations	Were limitations of the study stated?	No	0
5	Generalizability	Was the generalizability of the results discussed?	No	0
6	Future Research recommendations	Were future concrete research recommendations discussed?	No	0
7	Conflicts of interest	Was there a conflict of interest section?	Yes	1
	Score total			11
Porras-Hernández (2003)				
A	General aspects			
1	Illness and patient population	Was the illness defined?	Not reported	0
2		Was the analysis limited to a defined patient population?	Yes, Surgery patients aged less than 18 years	1
3	Design	Was there a description of the setting in which the costs are incurred?	Yes, the patient profile, number of beds and number of operations are detailed.	1
4		Was the data collection type described?	Yes, micro costing of prospective data collection	1
5	Perspective	Was/were the perspective(s) stated?	No	0
6	Time period	Was the time period stated to which the costs refer to?	Time period of the study was August 1998 to January 1999	1
B	Resource Identification			
1	Scope and type of resources	Was relevant resource use omitted with regard to the chosen perspective?	No perspective stated. Only hospital LOS was valued so there was relevant resource use omitted	0
2		Was there justification for omitting relevant resource use with regard to the chosen perspective?	No perspective stated.	0
3		If indirect costs were included, were the costs of productivity loss clearly demarcated?	NA	0
C	Description and quantification of resource use			
1	Data Sources	Were the sources of the resource use specified?	Yes from the hospital records	1
2		Was resource use from overseas adjusted for the local country's context?	NA	0
3		Was there any analysis to account for missing data performed?	No	0
D	Resource Valuation			
1	Perspectives	Were the resources valued according to the chosen perspective?	Perspective not stated	0

2	Data Sources	Were all data sources of the valuation of resource use specified?	No	0
3	Productivity loss	Was the valuation method for productivity loss specified?	Not applicable	0
4	Discounting	Was discounting undertaken with a specified discount rate?	Not applicable	0
5	Inflation adjustment	Were cost data from different time periods adjusted for inflation with its method specified?	Not applicable	0
6	Price and Price adjustment	Were all resources valued according to the specified cost year?	Not applicable	0
7		Were price adjustments over time considered?	Not applicable	0
8		Were prices from other countries used/applied?	Not applicable	0
E	Evaluation and presentation of results			
1	Evaluation methods	Were the data evaluation methods comprehensibly described?	No	0
2		Were subgroup analyses performed?	No	0
3		Were sensitivity analysis performed?	No	0
4		Were sensitivity analyses carried out on the resource use or costs?	No	0
5		Were parameters for estimating results uncertainty named?	Not applicable	0
6		Was modelling used to estimate costs?	No	0
7	Result presentation	Were the resource use category amounts separately listed?	No	0
8		Was the derivation of the calculations comprehensible?	No	0
9		Were the cost categories separately listed?	Not applicable	0
F	Discussion and conclusion			
1	Conclusion	Were the conclusions comprehensible?	Yes	1
2	Quality	Was the quality of the data source(s) discussed?	No	0
3	Comparison	Was there a comparison of the study findings with findings from other studies?	No	0
4	Limitations	Were limitations of the study stated?	No	0
5	Generalizability	Was the generalizability of the results discussed?	No	0
6	Future Research recommendations	Were future concrete research recommendations discussed?	No	0
7	Conflicts of interest	Was there a conflict of interest section?	No	0
	Score total			6
	Silverstein (2016)			
A	General aspects			
1	Illness and patient population	Was the illness defined?	No	0
2		Was the analysis limited to a defined patient population?	Yes, Biliary disease surgery patients	1
3	Design	Was there a description of the setting in which the costs are incurred?	Yes, the hospital is described in terms of its patient mix and number of beds	1
4		Was the data collection type described?	Yes, micro costing of retrospective data	1
5	Perspective	Was/were the perspective(s) stated?	Yes, societal perspective	1
6	Time period	Was the time period stated to which the costs refer to?	No	0
B	Resource Identification			
1	Scope and type of resources	Was relevant resource use omitted with regard to the chosen perspective?	Unclear what resource use was in the calculation of an SSI	0
2		Was there justification for omitting relevant resource use with regard to the chosen perspective?	No	0
3		If indirect costs were included, were the costs of productivity loss clearly demarcated?	NA	0
C	Description and quantification of resource use			
1	Data Sources	Were the sources of the resource use specified?	Unclear what resource use was in SSI costs	0
2		Was resource use from overseas adjusted for the local country's context?	NA	0

3		Was there any analysis to account for missing data performed?	No	0
D	Resource Valuation			
1	Perspectives	Were the resources valued according to the chosen perspective?	Unclear	0
2	Data Sources	Were all data sources of the valuation of resource use specified?	Yes, Costs were taken from the hospital's electronic medical records	1
3	Productivity loss	Was the valuation method for productivity loss specified?	Not applicable	0
4	Discounting	Was discounting undertaken with a specified discount rate?	Yes	1
5	Inflation adjustment	Were cost data from different time periods adjusted for inflation with its method specified?	Unclear	0
6	Price and Price adjustment	Were all resources valued according to the specified cost year?	Yes, 2014 cost year	1
7		Were price adjustments over time considered?	Not applicable	0
8		Were prices from other countries used/applied?	Not applicable	0
E	Evaluation and presentation of results			
1	Evaluation methods	Were the data evaluation methods comprehensibly described?	No	0
2		Were subgroup analyses performed?	No	0
3		Were sensitivity analysis performed?	No	0
4		Were sensitivity analyses carried out on the resource use or costs?	Yes	1
5		Were parameters for estimating results uncertainty named?	Yes	1
6		Was modelling used to estimate costs?	Unclear	0
7	Result presentation	Were the resource use category amounts separately listed?	No	0
8		Was the derivation of the calculations comprehensible?	No	0
9		Were the cost categories separately listed?	No	0
F	Discussion and conclusion			
1	Conclusion	Were the conclusions comprehensible?	No	0
2	Quality	Was the quality of the data source(s) discussed?	Yes	1
3	Comparison	Was there a comparison of the study findings with findings from other studies?	No	0
4	Limitations	Were limitations of the study stated?	No	0
5	Generalizability	Was the generalizability of the results discussed?	No	0
6	Future Research recommendations	Were future concrete research recommendations discussed?	Yes	1
7	Conflicts of interest	Was there a conflict of interest section?	Yes	1
	Score total			12
Siribumrungwong (2015)				
A	General aspects			
1	Illness and patient population	Was the illness defined?	No	1
2		Was the analysis limited to a defined patient population?	Yes, varicose veins patients	1
3	Design	Was there a description of the setting in which the costs are incurred?	No	0
4		Was the data collection type described?	Yes, microcosting of prospective data collection	1
5	Perspective	Was/were the perspective(s) stated?	Yes, societal perspective	0
6	Time period	Was the time period stated to which the costs refer to?	Time period of the study was October 2011 to February 2013	0
B	Resource Identification			
1	Scope and type of resources	Was relevant resource use omitted with regard to the chosen perspective?	Unclear what resource use was included in SSI	0
2		Was there justification for omitting relevant resource use with regard to the chosen perspective?	No	0

3		If indirect costs were included, were the costs of productivity loss clearly demarcated?	NA	0
C	Description and quantification of resource use			
1	Data Sources	Were the sources of the resource use specified?	Unclear what resource use was included in SSI	1
2		Was resource use from overseas adjusted for the local country's context?	NA	0
3		Was there any analysis to account for missing data performed?	No	0
D	Resource Valuation			
1	Perspectives	Were the resources valued according to the chosen perspective?	Unclear what resource use was included in SSI	0
2	Data Sources	Were all data sources of the valuation of resource use specified?	Yes, hospital cost tables	0
3	Productivity loss	Was the valuation method for productivity loss specified?	Not applicable	0
4	Discounting	Was discounting undertaken with a specified discount rate?	Not applicable	0
5	Inflation adjustment	Were cost data from different time periods adjusted for inflation with its method specified?	Unclear, no cost year reported	0
6	Price and Price adjustment	Were all resources valued according to the specified cost year?	Unclear, no cost year reported	0
7		Were price adjustments over time considered?	Unclear, no cost year reported	0
8		Were prices from other countries used/applied?	Not applicable	0
E	Evaluation and presentation of results			
1	Evaluation methods	Were the data evaluation methods comprehensibly described?	No	1
2		Were subgroup analyses performed?	No	0
3		Were sensitivity analysis performed?	No	0
4		Were sensitivity analyses carried out on the resource use or costs?	No	0
5		Were parameters for estimating results uncertainty named?	Not applicable	0
6		Was modelling used to estimate costs?	No	0
7	Result presentation	Were the resource use category amounts separately listed?	No	0
8		Was the derivation of the calculations comprehensible?	No	1
9		Were the cost categories separately listed?	No	0
F	Discussion and conclusion			
1	Conclusion	Were the conclusions comprehensible?	No	1
2	Quality	Was the quality of the data source(s) discussed?	No	0
3	Comparison	Was there a comparison of the study findings with findings from other studies?	Yes	1
4	Limitations	Were limitations of the study stated?	Yes	1
5	Generalizability	Was the generalizability of the results discussed?	No	0
6	Future Research recommendations	Were future concrete research recommendations discussed?	Yes	0
7	Conflicts of interest	Was there a conflict of interest section?	Yes	0
	Score total			9
Tiwari (2013)				
A	General aspects			
1	Illness and patient population	Was the illness defined?		1
2		Was the analysis limited to a defined patient population?		1
3	Design	Was there a description of the setting in which the costs are incurred?	Yes, the number of beds, patient financing mix and annual number of admissions are detailed	1

4		Was the data collection type described?	Yes, micro costing of retrospective data	1
5	Perspective	Was/were the perspective(s) stated?	No perspective stated	0
6	Time period	Was the time period stated to which the costs refer to?	Yes, the time period of the study was from August 2008 to July 2009	1
B	Resource Identification			
1	Scope and type of resources	Was relevant resource use omitted with regard to the chosen perspective?	No perspective stated	0
2		Was there justification for omitting relevant resource use with regard to the chosen perspective?	No perspective stated	0
3		If indirect costs were included, were the costs of productivity loss clearly demarcated?	Not applicable	0
C	Description and quantification of resource use			
1	Data Sources	Were the sources of the resource use specified?	Yes, taken from patient medical records, and hospital databases	1
2		Was resource use from overseas adjusted for the local country's context?	NA	0
3		Was there any analysis to account for missing data performed?	No	0
D	Resource Valuation			
1	Perspectives	Were the resources valued according to the chosen perspective?	No perspective stated	0
2	Data Sources	Were all data sources of the valuation of resource use specified?	The costs were taken from the hospital	0
3	Productivity loss	Was the valuation method for productivity loss specified?	Not applicable	0
4	Discounting	Was discounting undertaken with a specified discount rate?	No	0
5	Inflation adjustment	Were cost data from different time periods adjusted for inflation with its method specified?	No	0
6	Price and Price adjustment	Were all resources valued according to the specified cost year?	No cost year specified	0
7		Were price adjustments over time considered?	Unclear	0
8		Were prices from other countries used/applied?	Not applicable	0
E	Evaluation and presentation of results			
1	Evaluation methods	Were the data evaluation methods comprehensibly described?	Yes	0
2		Were subgroup analyses performed?	No	0
3		Were sensitivity analysis performed?	No	0
4		Were sensitivity analyses carried out on the resource use or costs?	No	0
5		Were parameters for estimating results uncertainty named?	Not applicable	0
6		Was modelling used to estimate costs?	No	0
7	Result presentation	Were the resource use category amounts separately listed?	No	0
8		Was the derivation of the calculations comprehensible?	Yes	0
9		Were the cost categories separately listed?	Yes	0
F	Discussion and conclusion			
1	Conclusion	Were the conclusions comprehensible?	Yes	1
2	Quality	Was the quality of the data source(s) discussed?	Yes	1
3	Comparison	Was there a comparison of the study findings with findings from other studies?	Yes	1
4	Limitations	Were limitations of the study stated?	Yes	1
5	Generalizability	Was the generalizability of the results discussed?	Yes	1

6	Future Research recommendations	Were future concrete research recommendations discussed?	No	0
7	Conflicts of interest	Was there a conflict of interest section?	Yes	1
	Score total			12
Zhou (2015)				
A	General aspects			
1	Illness and patient population	Was the illness defined?	Yes, CDC definition	1
2		Was the analysis limited to a defined patient population?	Yes, craniocerebral patients	1
3	Design	Was there a description of the setting in which the costs are incurred?	No	0
4		Was the data collection type described?	Yes, micro costing of prospective surveillance collection	1
5	Perspective	Was/were the perspective(s) stated?	Yes, payer perspective	1
6	Time period	Was the time period stated to which the costs refer to?	Time period of the study was July 2009 and June 2012	1
B	Resource Identification			
1	Scope and type of resources	Was relevant resource use omitted with regard to the chosen perspective?	Yes, readmission costs relevant to the payer perspective was not considered	0
2		Was there justification for omitting relevant resource use with regard to the chosen perspective?	No	0
3		If indirect costs were included, were the costs of productivity loss clearly demarcated?	NA	0
C	Description and quantification of resource use			
1	Data Sources	Were the sources of the resource use specified?	Yes, the hospital data was manually collected due to a lack of a well-developed information system	1
2		Was resource use from overseas adjusted for the local country's context?	NA	0
3		Was there any analysis to account for missing data performed?	No	0
D	Resource Valuation			
1	Perspectives	Were the resources valued according to the chosen perspective?	Yes	1
2	Data Sources	Were all data sources of the valuation of resource use specified?	Yes	1
3	Productivity loss	Was the valuation method for productivity loss specified?	Not applicable	0
4	Discounting	Was discounting undertaken with a specified discount rate?	No but short time horizon so not necessary	0
5	Inflation adjustment	Were cost data from different time periods adjusted for inflation with its method specified?	Unclear, no cost year reported	0
6	Price and Price adjustment	Were all resources valued according to the specified cost year?	Unclear, no cost year reported	0
7		Were price adjustments over time considered?	Unclear, no cost year reported	0
8		Were prices from other countries used/applied?	Not applicable	0
E	Evaluation and presentation of results			
1	Evaluation methods	Were the data evaluation methods comprehensibly described?	Yes	1
2		Were subgroup analyses performed?	Yes, different types of SSI costs are shown.	1
3		Were sensitivity analysis performed?	No	0

4		Were sensitivity analyses carried out on the resource use or costs?	No	0
5		Were parameters for estimating results uncertainty named?	Not applicable	0
6		Was modelling used to estimate costs?	No	0
7	Result presentation	Were the resource use category amounts separately listed?	No	0
8		Was the derivation of the calculations comprehensible?	Yes	1
9		Were the cost categories separately listed?	Yes	1
F	Discussion and conclusion			
1	Conclusion	Were the conclusions comprehensible?	Yes	1
2	Quality	Was the quality of the data source(s) discussed?	No	0
3	Comparison	Was there a comparison of the study findings with findings from other studies?	No	1
4	Limitations	Were limitations of the study stated?	Yes	1
5	Generalizability	Was the generalizability of the results discussed?	Yes	1
6	Future Research recommendations	Were future concrete research recommendations discussed?	No	0
7	Conflicts of interest	Was there a conflict of interest section?	Yes	1
	Score total			17
Alfonso (2007)				
A	General aspects			
1	Illness and patient population	Was the illness defined?	Yes, CDC definition	1
2		Was the analysis limited to a defined patient population?	Yes, patients who had undergone major surgical treatment	1
3	Design	Was there a description of the setting in which the costs are incurred?	Yes, the setting is a public general hospital and the number of beds and annual number of patients treated is detailed.	1
4		Was the data collection type described?	Yes, micro costing of prospective surveillance data collection	1
5	Perspective	Was/were the perspective(s) stated?	Yes, societal perspective	1
6	Time period	Was the time period stated to which the costs refer to?	Time period of the study was from January 1, 2001 to June 30, 2005.	1
B	Resource Identification			
1	Scope and type of resources	Was relevant resource use omitted with regard to the chosen perspective?	Yes, travel costs.	0
2		Was there justification for omitting relevant resource use with regard to the chosen perspective?	No	0
3		If indirect costs were included, were the costs of productivity loss clearly demarcated?	Yes	1
C	Description and quantification of resource use			
1	Data Sources	Were the sources of the resource use specified?	Yes, the use of telephone survey, hospital database, patient interview	1
2		Was resource use from overseas adjusted for the local country's context?	NA	0
3		Was there any analysis to account for missing data performed?	No	0
D	Resource Valuation			
1	Perspectives	Were the resources valued according to the chosen perspective?	Yes	1
2	Data Sources	Were all data sources of the valuation of resource use specified?	Yes	1
3	Productivity loss	Was the valuation method for productivity loss specified?	Yes, the friction period method	1

4	Discounting	Was discounting undertaken with a specified discount rate?	Yes, 3% annual discount rate	1
5	Inflation adjustment	Were cost data from different time periods adjusted for inflation with its method specified?	NA	0
6	Price and Price adjustment	Were all resources valued according to the specified cost year?	Yes, 2006	1
7		Were price adjustments over time considered?	NA	0
8		Were prices from other countries used/applied?	NA	0
E	Evaluation and presentation of results			
1	Evaluation methods	Were the data evaluation methods comprehensibly described?	Yes	1
2		Were subgroup analyses performed?	Yes, different types of costs by age groups.	1
3		Were sensitivity analysis performed?	No	0
4		Were sensitivity analyses carried out on the resource use or costs?	No	0
5		Were parameters for estimating results uncertainty named?	NA	0
6		Was modelling used to estimate costs?	No	0
7	Result presentation	Were the resource use category amounts separately listed?	Yes	1
8		Was the derivation of the calculations comprehensible?	No, the no SSI group calculations are not shown	0
9		Were the cost categories separately listed?	Yes	0
F	Discussion and conclusion			
1	Conclusion	Were the conclusions comprehensible?	Yes	1
2	Quality	Was the quality of the data source(s) discussed?	No	0
3	Comparison	Was there a comparison of the study findings with findings from other studies?	Yes	1
4	Limitations	Were limitations of the study stated?	Yes	1
5	Generalizability	Was the generalizability of the results discussed?	Yes	1
6	Future Research recommendations	Were future concrete research recommendations discussed?	Yes	1
7	Conflicts of interest	Was there a conflict of interest section?	Yes	1
	Score total			21
Defez (2008)				
A	General aspects			
1	Illness and patient population	Was the illness defined?	Yes, CDC criteria	1
2		Was the analysis limited to a defined patient population?	Yes, patients in acute care and long-term care units.	1
3	Design	Was there a description of the setting in which the costs are incurred?	Yes, a description of the number of beds in each ward type is given along with the annual number of patients admitted to the hospital	1
4		Was the data collection type described?	Yes, micro costing of prospective data collection	1
5	Perspective	Was/were the perspective(s) stated?	Yes, the costs were from the point of view of the hospital	1
6	Time period	Was the time period stated to which the costs refer to?	Time period of the study was between May 2001 and January 2003	1
B	Resource Identification			
1	Scope and type of resources	Was relevant resource use omitted with regard to the chosen perspective?	Yes, readmission was not captured	0
2		Was there justification for omitting relevant resource use with regard to the chosen perspective?	No	0
3		If indirect costs were included, were the costs of productivity loss clearly demarcated?	NA	0
C	Description and quantification of resource use			
1	Data Sources	Were the sources of the resource use specified?	Yes	1

2		Was resource use from overseas adjusted for the local country's context?	NA	0
3		Was there any analysis to account for missing data performed?	No	0
D	Resource Valuation			
1	Perspectives	Were the resources valued according to the chosen perspective?	Yes, hospital costs were used	0
2	Data Sources	Were all data sources of the valuation of resource use specified?	Yes, the hospital	1
3	Productivity loss	Was the valuation method for productivity loss specified?	NA	0
4	Discounting	Was discounting undertaken with a specified discount rate?	NA	0
5	Inflation adjustment	Were cost data from different time periods adjusted for inflation with its method specified?	No	0
6	Price and Price adjustment	Were all resources valued according to the specified cost year?	No	0
7		Were price adjustments over time considered?	Unclear	0
8		Were prices from other countries used/applied?	NA	0
E	Evaluation and presentation of results			
1	Evaluation methods	Were the data evaluation methods comprehensibly described?	Yes	1
2		Were subgroup analyses performed?	No	0
3		Were sensitivity analysis performed?	No	0
4		Were sensitivity analyses carried out on the resource use or costs?	No	0
5		Were parameters for estimating results uncertainty named?	NA	0
6		Was modelling used to estimate costs?	No	0
7	Result presentation	Were the resource use category amounts separately listed?	No	0
8		Was the derivation of the calculations comprehensible?	No	0
9		Were the cost categories separately listed?	Yes	1
F	Discussion and conclusion			
1	Conclusion	Were the conclusions comprehensible?	Yes	1
2	Quality	Was the quality of the data source(s) discussed?	Yes	1
3	Comparison	Was there a comparison of the study findings with findings from other studies?	Yes	1
4	Limitations	Were limitations of the study stated?	Yes	1
5	Generalizability	Was the generalizability of the results discussed?	No	0
6	Future Research recommendations	Were future concrete research recommendations discussed?	No	0
7	Conflicts of interest	Was there a conflict of interest section?	Yes	1
	Score total			15
Edwards (2008)				
A	General aspects			
1	Illness and patient population	Was the illness defined?	Yes, patients on antibiotic treatment for wound problems	1
2		Was the analysis limited to a defined patient population?	Yes, acute care patients	1
3	Design	Was there a description of the setting in which the costs are incurred?	Yes, the teaching hospital catchment area is described	1
4		Was the data collection type described?	Yes, micro costing of retrospective audit data	1
5	Perspective	Was/were the perspective(s) stated?	No	0
6	Time period	Was the time period stated to which the costs refer to?	Time period of the study was between May 1999 and October 2004	1
B	Resource Identification			

1	Scope and type of resources	Was relevant resource use omitted with regard to the chosen perspective?	No perspective stated	0
2		Was there justification for omitting relevant resource use with regard to the chosen perspective?	No perspective stated	1
3		If indirect costs were included, were the costs of productivity loss clearly demarcated?	NA	0
C	Description and quantification of resource use			
1	Data Sources	Were the sources of the resource use specified?	Yes, from hospital audit data	1
2		Was resource use from overseas adjusted for the local country's context?	NA	0
3		Was there any analysis to account for missing data performed?	No	0
D	Resource Valuation			
1	Perspectives	Were the resources valued according to the chosen perspective?	No perspective stated	0
2	Data Sources	Were all data sources of the valuation of resource use specified?	Not specified	0
3	Productivity loss	Was the valuation method for productivity loss specified?	NA	0
4	Discounting	Was discounting undertaken with a specified discount rate?	NA	0
5	Inflation adjustment	Were cost data from different time periods adjusted for inflation with its method specified?	NA	0
6	Price and Price adjustment	Were all resources valued according to the specified cost year?	No cost year stated	0
7		Were price adjustments over time considered?	Yes	1
8		Were prices from other countries used/applied?	NA	0
E	Evaluation and presentation of results			
1	Evaluation methods	Were the data evaluation methods comprehensibly described?	Yes	1
2		Were subgroup analyses performed?	No	0
3		Were sensitivity analysis performed?	No	0
4		Were sensitivity analyses carried out on the resource use or costs?	No	0
5		Were parameters for estimating results uncertainty named?	NA	0
6		Was modelling used to estimate costs?	No	0
7	Result presentation	Were the resource use category amounts separately listed?	NA	0
8		Was the derivation of the calculations comprehensible?	Yes	1
9		Were the cost categories separately listed?	Yes	1
F	Discussion and conclusion			
1	Conclusion	Were the conclusions comprehensible?	Yes	1
2	Quality	Was the quality of the data source(s) discussed?	No	0
3	Comparison	Was there a comparison of the study findings with findings from other studies?	Yes	1
4	Limitations	Were limitations of the study stated?	No	0
5	Generalizability	Was the generalizability of the results discussed?	No	0
6	Future Research recommendations	Were future concrete research recommendations discussed?	No	0
7	Conflicts of interest	Was there a conflict of interest section?	Yes	1
	Score total			13

Graf (2010)				
A	General aspects			
1	Illness and patient population	Was the illness defined?	Yes, CDC criteria	1
2		Was the analysis limited to a defined patient population?	Yes, CABG patients	1
3	Design	Was there a description of the setting in which the costs are incurred?	Yes, the hospital is described with the number of patients treated in their department of cardiac, thoracic, transplantation and vascular surgery	1
4		Was the data collection type described?	Yes, micro costing of prospective data collection	1
5	Perspective	Was/were the perspective(s) stated?	No	0
6	Time period	Was the time period stated to which the costs refer to?	Time period of the study was January 2006 until March 2008	1
B	Resource Identification			
1	Scope and type of resources	Was relevant resource use omitted with regard to the chosen perspective?	No perspective stated	0
2		Was there justification for omitting relevant resource use with regard to the chosen perspective?	No perspective stated	0
3		If indirect costs were included, were the costs of productivity loss clearly demarcated?	NA	0
C	Description and quantification of resource use			
1	Data Sources	Were the sources of the resource use specified?	Yes, provided by the hospital finance department	1
2		Was resource use from overseas adjusted for the local country's context?	NA	0
3		Was there any analysis to account for missing data performed?	No	0
D	Resource Valuation			
1	Perspectives	Were the resources valued according to the chosen perspective?	No perspective stated	0
2	Data Sources	Were all data sources of the valuation of resource use specified?	Yes, provided by the hospital finance department	1
3	Productivity loss	Was the valuation method for productivity loss specified?	NA	0
4	Discounting	Was discounting undertaken with a specified discount rate?	NA	0
5	Inflation adjustment	Were cost data from different time periods adjusted for inflation with its method specified?	NA	0
6	Price and Price adjustment	Were all resources valued according to the specified cost year?	No cost year reported	0
7		Were price adjustments over time considered?	NA	0
8		Were prices from other countries used/applied?	NA	0
E	Evaluation and presentation of results			
1	Evaluation methods	Were the data evaluation methods comprehensibly described?	No unit costs provided.	0
2		Were subgroup analyses performed?	No	0
3		Were sensitivity analysis performed?	No	0
4		Were sensitivity analyses carried out on the resource use or costs?	No	0
5		Were parameters for estimating results uncertainty named?	NA	0
6		Was modelling used to estimate costs?	No	0
7	Result presentation	Were the resource use category amounts separately listed?	No	0
8		Was the derivation of the calculations comprehensible?	No	0
9		Were the cost categories separately listed?	No	0
F	Discussion and conclusion			
1	Conclusion	Were the conclusions comprehensible?	Yes	1
2	Quality	Was the quality of the data source(s) discussed?	Yes	1

3	Comparison	Was there a comparison of the study findings with findings from other studies?	No	0
4	Limitations	Were limitations of the study stated?	Yes	1
5	Generalizability	Was the generalizability of the results discussed?	Yes	1
6	Future Research recommendations	Were future concrete research recommendations discussed?	Yes	1
7	Conflicts of interest	Was there a conflict of interest section?	No	0
	Score Total			12
Hyldig (2018)				
A	General aspects			
1	Illness and patient population	Was the illness defined?	Yes, an infection at the surgical site requiring antibiotics within the first 30 days after caesarean section	1
2		Was the analysis limited to a defined patient population?	Yes, obese women after caesarean section	1
3	Design	Was there a description of the setting in which the costs are incurred?	No	0
4		Was the data collection type described?	Yes, micro costing of prospective data collection	1
5	Perspective	Was/were the perspective(s) stated?	Healthcare perspective	1
6	Time period	Was the time period stated to which the costs refer to?	Time period of the study was between 2013 to 2016	1
B	Resource Identification			
1	Scope and type of resources	Was relevant resource use omitted with regard to the chosen perspective?	No	1
2		Was there justification for omitting relevant resource use with regard to the chosen perspective?	No relevant resource use omitted	1
3		If indirect costs were included, were the costs of productivity loss clearly demarcated?	NA	0
C	Description and quantification of resource use			
1	Data Sources	Were the sources of the resource use specified?	Yes, the Danish National Databases	1
2		Was resource use from overseas adjusted for the local country's context?	NA	0
3		Was there any analysis to account for missing data performed?	Not for the SSI cost	0
D	Resource Valuation			
1	Perspectives	Were the resources valued according to the chosen perspective?	Yes	1
2	Data Sources	Were all data sources of the valuation of resource use specified?	Yes	1
3	Productivity loss	Was the valuation method for productivity loss specified?	NA	0
4	Discounting	Was discounting undertaken with a specified discount rate?	NA	0
5	Inflation adjustment	Were cost data from different time periods adjusted for inflation with its method specified?	Not mentioned	0
6	Price and Price adjustment	Were all resources valued according to the specified cost year?	Yes, 2015	1
7		Were price adjustments over time considered?	Unclear	0
8		Were prices from other countries used/applied?	NA	0
E	Evaluation and presentation of results			
1	Evaluation methods	Were the data evaluation methods comprehensibly described?	Yes	1
2		Were subgroup analyses performed?	Yes	1
3		Were sensitivity analysis performed?	Not for costs of SSI	0

4		Were sensitivity analyses carried out on the resource use or costs?	Not for costs of SSI	0
5		Were parameters for estimating results uncertainty named?	NA	0
6		Was modelling used to estimate costs?	No	0
7	Result presentation	Were the resource use category amounts separately listed?	No	0
8		Was the derivation of the calculations comprehensible?	No	0
9		Were the cost categories separately listed?	No	0
F	Discussion and conclusion			
1	Conclusion	Were the conclusions comprehensible?	Yes	1
2	Quality	Was the quality of the data source(s) discussed?	Yes	1
3	Comparison	Was there a comparison of the study findings with findings from other studies?	No	0
4	Limitations	Were limitations of the study stated?	Yes	1
5	Generalizability	Was the generalizability of the results discussed?	Yes	1
6	Future Research recommendations	Were future concrete research recommendations discussed?	No	0
7	Conflicts of interest	Was there a conflict of interest section?	Yes	1
	Score total			18
Jenks (2014)				
A	General aspects			
1	Illness and patient population	Was the illness defined?	Yes, CDC definition	1
2		Was the analysis limited to a defined patient population?	Yes, patient who underwent major surgical procedures	1
3	Design	Was there a description of the setting in which the costs are incurred?	Yes, the hospital is described with the number of beds, surgery specialist services, and number of surgeries performed	1
4		Was the data collection type described?	Yes, micro costing of prospective surveillance data collection	1
5	Perspective	Was/were the perspective(s) stated?	Yes, the hospitals perspective (including the revenue obtained to treat patients)	1
6	Time period	Was the time period stated to which the costs refer to?	Time period of the study was April 2010 – March 2012	1
B	Resource Identification			
1	Scope and type of resources	Was relevant resource use omitted with regard to the chosen perspective?	No	1
2		Was there justification for omitting relevant resource use with regard to the chosen perspective?	NA	0
3		If indirect costs were included, were the costs of productivity loss clearly demarcated?	NA	0
C	Description and quantification of resource use			
1	Data Sources	Were the sources of the resource use specified?	Yes	1
2		Was resource use from overseas adjusted for the local country's context?	NA	0
3		Was there any analysis to account for missing data performed?	NA	0
D	Resource Valuation			
1	Perspectives	Were the resources valued according to the chosen perspective?	Yes	1
2	Data Sources	Were all data sources of the valuation of resource use specified?	Yes	1
3	Productivity loss	Was the valuation method for productivity loss specified?	NA	0

4	Discounting	Was discounting undertaken with a specified discount rate?	NA	0
5	Inflation adjustment	Were cost data from different time periods adjusted for inflation with its method specified?	NA	0
6	Price and Price adjustment	Were all resources valued according to the specified cost year?	No cost year specified	0
7		Were price adjustments over time considered?	NA	0
8		Were prices from other countries used/applied?	NA	0
E	Evaluation and presentation of results			
1	Evaluation methods	Were the data evaluation methods comprehensibly described?	Yes	1
2		Were subgroup analyses performed?	Yes, different surgical operation types of SSI patients	1
3		Were sensitivity analysis performed?	No	0
4		Were sensitivity analyses carried out on the resource use or costs?	No	0
5		Were parameters for estimating results uncertainty named?	NA	0
6		Was modelling used to estimate costs?	No	0
7	Result presentation	Were the resource use category amounts separately listed?	No	0
8		Was the derivation of the calculations comprehensible?	No	0
9		Were the cost categories separately listed?	No	0
F	Discussion and conclusion			
1	Conclusion	Were the conclusions comprehensible?	Yes	1
2	Quality	Was the quality of the data source(s) discussed?	Yes	1
3	Comparison	Was there a comparison of the study findings with findings from other studies?	Yes	1
4	Limitations	Were limitations of the study stated?	Yes	1
5	Generalizability	Was the generalizability of the results discussed?	Yes	1
6	Future Research recommendations	Were future concrete research recommendations discussed?	No	0
7	Conflicts of interest	Was there a conflict of interest section?	Yes	1
	Score total			18
Lynch (1992)				
A	General aspects			
1	Illness and patient population	Was the illness defined?	Yes, ASEPSIS scoring system or wound pus discharge	1
2		Was the analysis limited to a defined patient population?	Yes, adult surgical patients	1
3	Design	Was there a description of the setting in which the costs are incurred?	No	0
4		Was the data collection type described?	Yes, micro costing of prospective surveillance data collection	1
5	Perspective	Was/were the perspective(s) stated?	Yes, costs faced by the hospital and community	1
6	Time period	Was the time period stated to which the costs refer to?	Time period of the study was 1987-1989	1
B	Resource Identification			
1	Scope and type of resources	Was relevant resource use omitted with regard to the chosen perspective?	Yes, indirect costs such as productivity loss	0
2		Was there justification for omitting relevant resource use with regard to the chosen perspective?	Yes, said they need separate studies in their own right.	1
3		If indirect costs were included, were the costs of productivity loss clearly demarcated?	NA	0
C	Description and quantification of resource use			
1	Data Sources	Were the sources of the resource use specified?	Yes, patient follow-up questionnaires, recorded patient	1

			information, timing of wound dressings by investigators	
2		Was resource use from overseas adjusted for the local country's context?	NA	0
3		Was there any analysis to account for missing data performed?	No	0
D	Resource Valuation			
1	Perspectives	Were the resources valued according to the chosen perspective?	Yes	1
2	Data Sources	Were all data sources of the valuation of resource use specified?	Yes and referenced	1
3	Productivity loss	Was the valuation method for productivity loss specified?	NA	0
4	Discounting	Was discounting undertaken with a specified discount rate?	NA	0
5	Inflation adjustment	Were cost data from different time periods adjusted for inflation with its method specified?	NA	0
6	Price and Price adjustment	Were all resources valued according to the specified cost year?	No cost year specified	0
7		Were price adjustments over time considered?	Unclear	0
8		Were prices from other countries used/applied?	NA	0
E	Evaluation and presentation of results			
1	Evaluation methods	Were the data evaluation methods comprehensibly described?	Yes	1
2		Were subgroup analyses performed?	Yes, different types of costs by inpatient SSI vs outpatient SSI	1
3		Were sensitivity analysis performed?	No	0
4		Were sensitivity analyses carried out on the resource use or costs?	No	0
5		Were parameters for estimating results uncertainty named?	NA	0
6		Was modelling used to estimate costs?	No	0
7	Result presentation	Were the resource use category amounts separately listed?	No	1
8		Was the derivation of the calculations comprehensible?	Yes	1
9		Were the cost categories separately listed?	Yes	1
F	Discussion and conclusion			
1	Conclusion	Were the conclusions comprehensible?	Yes	1
2	Quality	Was the quality of the data source(s) discussed?	Yes, study was an opportunistic valuation of an SSI clinical trial	1
3	Comparison	Was there a comparison of the study findings with findings from other studies?	Yes	1
4	Limitations	Were limitations of the study stated?	Yes	1
5	Generalizability	Was the generalizability of the results discussed?	No	0
6	Future Research recommendations	Were future concrete research recommendations discussed?	Yes	1
7	Conflicts of interest	Was there a conflict of interest section?	No	0
	Score total			19
Parker (2018)				
A	General aspects			
1	Illness and patient population	Was the illness defined?	Yes, CDC definition	1
2		Was the analysis limited to a defined patient population?	Yes, adult patients with lower limb open fractures	1
3	Design	Was there a description of the setting in which the costs are incurred?	No	0
4		Was the data collection type described?	Yes, microcosting of prospective data collection	1
5	Perspective	Was/were the perspective(s) stated?	NHS and personal social services (PSS) perspective	1

6	Time period	Was the time period stated to which the costs refer to?	Not stated	0
B	Resource Identification			
1	Scope and type of resources	Was relevant resource use omitted with regard to the chosen perspective?	No	1
2		Was there justification for omitting relevant resource use with regard to the chosen perspective?	No relevant resource use omitted	1
3		If indirect costs were included, were the costs of productivity loss clearly demarcated?	NA	0
C	Description and quantification of resource use			
1	Data Sources	Were the sources of the resource use specified?	Yes, taken from the trial	1
2		Was resource use from overseas adjusted for the local country's context?	NA	0
3		Was there any analysis to account for missing data performed?	Yes, multiple imputation was used	1
D	Resource Valuation			
1	Perspectives	Were the resources valued according to the chosen perspective?	Yes	1
2	Data Sources	Were all data sources of the valuation of resource use specified?	No	1
3	Productivity loss	Was the valuation method for productivity loss specified?	NA	0
4	Discounting	Was discounting undertaken with a specified discount rate?	NA	0
5	Inflation adjustment	Were cost data from different time periods adjusted for inflation with its method specified?	NA	0
6	Price and Price adjustment	Were all resources valued according to the specified cost year?	Yes, 2014/2015 prices	1
7		Were price adjustments over time considered?	NA	0
8		Were prices from other countries used/applied?	NA	0
E	Evaluation and presentation of results			
1	Evaluation methods	Were the data evaluation methods comprehensibly described?	Yes	1
2		Were subgroup analyses performed?	No	0
3		Were sensitivity analysis performed?	Yes	1
4		Were sensitivity analyses carried out on the resource use or costs?	No	0
5		Were parameters for estimating results uncertainty named?	NA	0
6		Was modelling used to estimate costs?	No	0
7	Result presentation	Were the resource use category amounts separately listed?	No	0
8		Was the derivation of the calculations comprehensible?	Yes	1
9		Were the cost categories separately listed?	Yes, in the supplementary tables	1
F	Discussion and conclusion			
1	Conclusion	Were the conclusions comprehensible?	Yes	1
2	Quality	Was the quality of the data source(s) discussed?	Yes	1
3	Comparison	Was there a comparison of the study findings with findings from other studies?	Yes	1
4	Limitations	Were limitations of the study stated?	Yes	1
5	Generalizability	Was the generalizability of the results discussed?	No	0
6	Future Research recommendations	Were future concrete research recommendations discussed?	No	0
7	Conflicts of interest	Was there a conflict of interest section?	Yes	1
	Score total			20

Pollard (2006)				
A	General aspects			
1	Illness and patient population	Was the illness defined?	Yes, SSI was defined as a microbiological confirmation	1
2		Was the analysis limited to a defined patient population?	Yes, proximal femoral fracture surgery patients over 65 years	1
3	Design	Was there a description of the setting in which the costs are incurred?	No	0
4		Was the data collection type described?	Yes, micro-costing of retrospective data	1
5	Perspective	Was/were the perspective(s) stated?	No	0
6	Time period	Was the time period stated to which the costs refer to?	Time period of the study was 1st January 1998 to 31 December 2003	1
B	Resource Identification			
1	Scope and type of resources	Was relevant resource use omitted with regard to the chosen perspective?	No perspective stated	0
2		Was there justification for omitting relevant resource use with regard to the chosen perspective?	No perspective stated	0
3		If indirect costs were included, were the costs of productivity loss clearly demarcated?	NA	0
C	Description and quantification of resource use			
1	Data Sources	Were the sources of the resource use specified?	Yes, hospital administration and microbiology databases, and operating theatre logs	1
2		Was resource use from overseas adjusted for the local country's context?	NA	0
3		Was there any analysis to account for missing data performed?	No	0
D	Resource Valuation			
1	Perspectives	Were the resources valued according to the chosen perspective?	No perspective stated	0
2	Data Sources	Were all data sources of the valuation of resource use specified?	Yes and referenced	1
3	Productivity loss	Was the valuation method for productivity loss specified?	NA	0
4	Discounting	Was discounting undertaken with a specified discount rate?	NA	0
5	Inflation adjustment	Were cost data from different time periods adjusted for inflation with its method specified?	NA	0
6	Price and Price adjustment	Were all resources valued according to the specified cost year?	Yes, 2003	1
7		Were price adjustments over time considered?	NA	0
8		Were prices from other countries used/applied?	NA	0
E	Evaluation and presentation of results			
1	Evaluation methods	Were the data evaluation methods comprehensibly described?	No, the costs of the comparator no SSI patients are not shown	0
2		Were subgroup analyses performed?	No	0
3		Were sensitivity analysis performed?	No	0
4		Were sensitivity analyses carried out on the resource use or costs?	No	0
5		Were parameters for estimating results uncertainty named?	NA	0
6		Was modelling used to estimate costs?	No	0
7	Result presentation	Were the resource use category amounts separately listed?	No	0
8		Was the derivation of the calculations comprehensible?	No	0
9		Were the cost categories separately listed?	No	0
F	Discussion and conclusion			
1	Conclusion	Were the conclusions comprehensible?	Yes	1

2	Quality	Was the quality of the data source(s) discussed?	No	0
3	Comparison	Was there a comparison of the study findings with findings from other studies?	Yes	1
4	Limitations	Were limitations of the study stated?	Yes	1
5	Generalizability	Was the generalizability of the results discussed?	No	0
6	Future Research recommendations	Were future concrete research recommendations discussed?	No	0
7	Conflicts of interest	Was there a conflict of interest section?	No	0
	Score total			10
Reilly (2001)				
A	General aspects			
1	Illness and patient population	Was the illness defined?	Yes, SSI was defined as either a purulent discharge in, or exuding from, the wound, or a painful erythema indicative of cellulitis	1
2		Was the analysis limited to a defined patient population?	Yes, clean elective surgery patients	1
3	Design	Was there a description of the setting in which the costs are incurred?	No	0
4		Was the data collection type described?	Yes, micro costing of prospective surveillance data collection	1
5	Perspective	Was/were the perspective(s) stated?	Yes, the hospital, patient and community perspective	1
6	Time period	Was the time period stated to which the costs refer to?	Time period of the study was November 1995 – March 1999	1
B	Resource Identification			
1	Scope and type of resources	Was relevant resource use omitted with regard to the chosen perspective?	Yes, indirect productivity costs	0
2		Was there justification for omitting relevant resource use with regard to the chosen perspective?	No	0
3		If indirect costs were included, were the costs of productivity loss clearly demarcated?	NA	0
C	Description and quantification of resource use			
1	Data Sources	Were the sources of the resource use specified?	Yes, patient records and interviews at outpatient wound clinics	1
2		Was resource use from overseas adjusted for the local country's context?	NA	0
3		Was there any analysis to account for missing data performed?	No	0
D	Resource Valuation			
1	Perspectives	Were the resources valued according to the chosen perspective?	Yes	1
2	Data Sources	Were all data sources of the valuation of resource use specified?	Yes and referenced	1
3	Productivity loss	Was the valuation method for productivity loss specified?	NA	0
4	Discounting	Was discounting undertaken with a specified discount rate?	NA	0
5	Inflation adjustment	Were cost data from different time periods adjusted for inflation with its method specified?	NA	0
6	Price and Price adjustment	Were all resources valued according to the specified cost year?	Yes, 1999	1
7		Were price adjustments over time considered?	NA	0
8		Were prices from other countries used/applied?	NA	0
E	Evaluation and presentation of results			
1	Evaluation methods	Were the data evaluation methods comprehensibly described?	No, the costs of the comparator no SSI patients are not shown	0

2		Were subgroup analyses performed?	Yes, different surgical operation types of SSI patients were presented	1
3		Were sensitivity analysis performed?	No	0
4		Were sensitivity analyses carried out on the resource use or costs?	No	0
5		Were parameters for estimating results uncertainty named?	NA	0
6		Was modelling used to estimate costs?	No	0
7	Result presentation	Were the resource use category amounts separately listed?	Yes, for SSI only	1
8		Was the derivation of the calculations comprehensible?	No	0
9		Were the cost categories separately listed?	Yes	1
F	Discussion and conclusion			
1	Conclusion	Were the conclusions comprehensible?	Yes	1
2	Quality	Was the quality of the data source(s) discussed?	No	0
3	Comparison	Was there a comparison of the study findings with findings from other studies?	No	0
4	Limitations	Were limitations of the study stated?	No	0
5	Generalizability	Was the generalizability of the results discussed?	No	0
6	Future Research recommendations	Were future concrete research recommendations discussed?	Yes	1
7	Conflicts of interest	Was there a conflict of interest section?	No	0
	Score total			14
Tanner (2009)				
A	General aspects			
1	Illness and patient population	Was the illness defined?	Yes, CDC criteria	1
2		Was the analysis limited to a defined patient population?	Yes, Adult colorectal patients	1
3	Design	Was there a description of the setting in which the costs are incurred?	No	0
4		Was the data collection type described?	Yes, micro-costing of prospective data collection	1
5	Perspective	Was/were the perspective(s) stated?	No	0
6	Time period	Was the time period stated to which the costs refer to?	Time period of the study was January 2006 until March 2008	1
B	Resource Identification			
1	Scope and type of resources	Was relevant resource use omitted with regard to the chosen perspective?	No perspective stated	0
2		Was there justification for omitting relevant resource use with regard to the chosen perspective?	No perspective stated	0
3		If indirect costs were included, were the costs of productivity loss clearly demarcated?	NA	0
C	Description and quantification of resource use			
1	Data Sources	Were the sources of the resource use specified?	Yes, a nurse collected resource use information from each patient.	1
2		Was resource use from overseas adjusted for the local country's context?	NA	0
3		Was there any analysis to account for missing data performed?	No	0
D	Resource Valuation			
1	Perspectives	Were the resources valued according to the chosen perspective?	No perspective stated	0
2	Data Sources	Were all data sources of the valuation of resource use specified?	Yes	1

3	Productivity loss	Was the valuation method for productivity loss specified?	NA	0
4	Discounting	Was discounting undertaken with a specified discount rate?	NA	0
5	Inflation adjustment	Were cost data from different time periods adjusted for inflation with its method specified?	NA	0
6	Price and Price adjustment	Were all resources valued according to the specified cost year?	Yes, 2008	1
7		Were price adjustments over time considered?	NA	0
8		Were prices from other countries used/applied?	NA	0
E	Evaluation and presentation of results			
1	Evaluation methods	Were the data evaluation methods comprehensibly described?	Yes	1
2		Were subgroup analyses performed?	No	0
3		Were sensitivity analysis performed?	No	0
4		Were sensitivity analyses carried out on the resource use or costs?	No	0
5		Were parameters for estimating results uncertainty named?	NA	0
6		Was modelling used to estimate costs?	No	0
7	Result presentation	Were the resource use category amounts separately listed?	Yes (for SSI patients only)	1
8		Was the derivation of the calculations comprehensible?	Yes	1
9		Were the cost categories separately listed?	Yes	1
F	Discussion and conclusion			
1	Conclusion	Were the conclusions comprehensible?	Yes	1
2	Quality	Was the quality of the data source(s) discussed?	Yes	1
3	Comparison	Was there a comparison of the study findings with findings from other studies?	Yes	1
4	Limitations	Were limitations of the study stated?	No	0
5	Generalizability	Was the generalizability of the results discussed?	No	0
6	Future Research recommendations	Were future concrete research recommendations discussed?	No	0
7	Conflicts of interest	Was there a conflict of interest section?	Yes	1
	Score total			15
Thakar (2010)				
A	General aspects			
1	Illness and patient population	Was the illness defined?	Partial, deep SSI infection defined, superficial was not	0
2		Was the analysis limited to a defined patient population?	Yes, proximal femoral Fracture patients after initial surgery with complications who needed further surgery	1
3	Design	Was there a description of the setting in which the costs are incurred?	No	0
4		Was the data collection type described?	Yes, microcosting of prospective data collection	1
5	Perspective	Was/were the perspective(s) stated?	No perspective stated	0
6	Time period	Was the time period stated to which the costs refer to?	Time period of the study was between March 2003 and February 2008	1
B	Resource Identification			
1	Scope and type of resources	Was relevant resource use omitted with regard to the chosen perspective?	No perspective stated	0
2		Was there justification for omitting relevant resource use with regard to the chosen perspective?	No perspective stated	0
3		If indirect costs were included, were the costs of productivity loss clearly demarcated?	NA	0
C	Description and quantification of resource use			

1	Data Sources	Were the sources of the resource use specified?	Yes	1
2		Was resource use from overseas adjusted for the local country's context?	NA	0
3		Was there any analysis to account for missing data performed?	No	0
D	Resource Valuation			
1	Perspectives	Were the resources valued according to the chosen perspective?	No perspective stated	0
2	Data Sources	Were all data sources of the valuation of resource use specified?	Yes, the finance department at the hospital	1
3	Productivity loss	Was the valuation method for productivity loss specified?	NA	0
4	Discounting	Was discounting undertaken with a specified discount rate?	NA	0
5	Inflation adjustment	Were cost data from different time periods adjusted for inflation with its method specified?	Not applicable	0
6	Price and Price adjustment	Were all resources valued according to the specified cost year?	Yes, 2008/2009 cost year	1
7		Were price adjustments over time considered?	They used unit costs from one year	1
8		Were prices from other countries used/applied?	NA	0
E	Evaluation and presentation of results			
1	Evaluation methods	Were the data evaluation methods comprehensibly described?	Yes	1
2		Were subgroup analyses performed?	Yes	1
3		Were sensitivity analysis performed?	No	0
4		Were sensitivity analyses carried out on the resource use or costs?	No	0
5		Were parameters for estimating results uncertainty named?	NA	0
6		Was modelling used to estimate costs?	No	0
7	Result presentation	Were the resource use category amounts separately listed?	No	0
8		Was the derivation of the calculations comprehensible?	No	0
9		Were the cost categories separately listed?	No	0
F	Discussion and conclusion			
1	Conclusion	Were the conclusions comprehensible?	Yes	1
2	Quality	Was the quality of the data source(s) discussed?	Yes	1
3	Comparison	Was there a comparison of the study findings with findings from other studies?	Yes	1
4	Limitations	Were limitations of the study stated?	Yes	1
5	Generalizability	Was the generalizability of the results discussed?	No	0
6	Future Research recommendations	Were future concrete research recommendations discussed?	No	0
7	Conflicts of interest	Was there a conflict of interest section?	Yes	1
	Score total			14
Turtiainen (2010)				
A	General aspects			
1	Illness and patient population	Was the illness defined?	Yes, CDC criteria	1
2		Was the analysis limited to a defined patient population?	Yes, Vascular surgery patients	1
3	Design	Was there a description of the setting in which the costs are incurred?	No	0

4		Was the data collection type described?	Yes, micro costing of prospective data collection	1
5	Perspective	Was/were the perspective(s) stated?	No	0
6	Time period	Was the time period stated to which the costs refer to?	Time period of the study was between June 2007 and January 2008	1
B	Resource Identification			
1	Scope and type of resources	Was relevant resource use omitted with regard to the chosen perspective?	No perspective stated	0
2		Was there justification for omitting relevant resource use with regard to the chosen perspective?	No perspective stated	0
3		If indirect costs were included, were the costs of productivity loss clearly demarcated?	NA	0
C	Description and quantification of resource use			
1	Data Sources	Were the sources of the resource use specified?	Yes	1
2		Was resource use from overseas adjusted for the local country's context?	NA	0
3		Was there any analysis to account for missing data performed?	No	0
D	Resource Valuation			
1	Perspectives	Were the resources valued according to the chosen perspective?	No perspective stated	0
2	Data Sources	Were all data sources of the valuation of resource use specified?	Yes, the hospital accounting system	1
3	Productivity loss	Was the valuation method for productivity loss specified?	NA	0
4	Discounting	Was discounting undertaken with a specified discount rate?	NA	0
5	Inflation adjustment	Were cost data from different time periods adjusted for inflation with its method specified?	NA	0
6	Price and Price adjustment	Were all resources valued according to the specified cost year?	Cost year not reported	0
7		Were price adjustments over time considered?	NA	0
8		Were prices from other countries used/applied?	NA	0
E	Evaluation and presentation of results			
1	Evaluation methods	Were the data evaluation methods comprehensibly described?	No	0
2		Were subgroup analyses performed?	No	0
3		Were sensitivity analysis performed?	No	0
4		Were sensitivity analyses carried out on the resource use or costs?	No	0
5		Were parameters for estimating results uncertainty named?	NA	0
6		Was modelling used to estimate costs?	No	0
7	Result presentation	Were the resource use category amounts separately listed?	No	0
8		Was the derivation of the calculations comprehensible?	No	0
9		Were the cost categories separately listed?	No	0
F	Discussion and conclusion			
1	Conclusion	Were the conclusions comprehensible?	Yes	1
2	Quality	Was the quality of the data source(s) discussed?	Yes	1
3	Comparison	Was there a comparison of the study findings with findings from other studies?	Yes	1
4	Limitations	Were limitations of the study stated?	Yes	1
5	Generalizability	Was the generalizability of the results discussed?	No	0
6	Future Research recommendations	Were future concrete research recommendations discussed?	No	0
7	Conflicts of interest	Was there a conflict of interest section?	Yes	1
	Score total			11

Vegas (1993)				
A	General aspects			
1	Illness and patient population	Was the illness defined?	Yes, CDC definition	1
2		Was the analysis limited to a defined patient population?	Yes, the general and digestive surgical patients	1
3	Design	Was there a description of the setting in which the costs are incurred?	No	0
4		Was the data collection type described?	Yes, micro costing of prospective surveillance data collection	1
5	Perspective	Was/were the perspective(s) stated?	No	0
6	Time period	Was the time period stated to which the costs refer to?	Time period of the study was the first seven months of 1990	1
B	Resource Identification			
1	Scope and type of resources	Was relevant resource use omitted with regard to the chosen perspective?	No perspective chosen	0
2		Was there justification for omitting relevant resource use with regard to the chosen perspective?	No	0
3		If indirect costs were included, were the costs of productivity loss clearly demarcated?	NA	0
C	Description and quantification of resource use			
1	Data Sources	Were the sources of the resource use specified?	Yes, a nurse recorded all demographic, clinical and laboratory data of the hospitalized patients.	1
2		Was resource use from overseas adjusted for the local country's context?	NA	0
3		Was there any analysis to account for missing data performed?	No	0
D	Resource Valuation			
1	Perspectives	Were the resources valued according to the chosen perspective?	NA	0
2	Data Sources	Were all data sources of the valuation of resource use specified?	Yes, and referenced	1
3	Productivity loss	Was the valuation method for productivity loss specified?	NA	0
4	Discounting	Was discounting undertaken with a specified discount rate?	NA	0
5	Inflation adjustment	Were cost data from different time periods adjusted for inflation with its method specified?	NA	0
6	Price and Price adjustment	Were all resources valued according to the specified cost year?	Yes, 1990	1
7		Were price adjustments over time considered?	NA	0
8		Were prices from other countries used/applied?	NA	0
E	Evaluation and presentation of results			
1	Evaluation methods	Were the data evaluation methods comprehensibly described?	No, the control group's Length of stay was not described	0
2		Were subgroup analyses performed?	Yes, different types of costs by age groups.	1
3		Were sensitivity analysis performed?	No	0
4		Were sensitivity analyses carried out on the resource use or costs?	No	0
5		Were parameters for estimating results uncertainty named?	NA	0
6		Was modelling used to estimate costs?	No	0
7	Result presentation	Were the resource use category amounts separately listed?	Yes	1
8		Was the derivation of the calculations comprehensible?	No	0
9		Were the cost categories separately listed?	NA	0
F	Discussion and conclusion			
1	Conclusion	Were the conclusions comprehensible?	Yes	1

2	Quality	Was the quality of the data source(s) discussed?	No	0
3	Comparison	Was there a comparison of the study findings with findings from other studies?	Yes	1
4	Limitations	Were limitations of the study stated?	Yes	1
5	Generalizability	Was the generalizability of the results discussed?	No	0
6	Future Research recommendations	Were future concrete research recommendations discussed?	Yes	1
7	Conflicts of interest	Was there a conflict of interest section?	No	0
	Score total			13
Weber (2008)				
A	General aspects			
1	Illness and patient population	Was the illness defined?	Yes, CDC criteria	1
2		Was the analysis limited to a defined patient population?	Yes, surgery patients from the visceral, vascular and traumatology hospital departments. The surgeries had to be incisional and the postoperative length of stay had to be greater than 1 day	1
3	Design	Was there a description of the setting in which the costs are incurred?	No	0
4		Was the data collection type described?	Yes, microcosting of prospective data collection	1
5	Perspective	Was/were the perspective(s) stated?	No	0
6	Time period	Was the time period stated to which the costs refer to?	Time period of the study was between January 2000 and December 2001	1
B	Resource Identification			
1	Scope and type of resources	Was relevant resource use omitted with regard to the chosen perspective?	No perspective stated	0
2		Was there justification for omitting relevant resource use with regard to the chosen perspective?	No perspective stated	0
3		If indirect costs were included, were the costs of productivity loss clearly demarcated?	NA	0
C	Description and quantification of resource use			
1	Data Sources	Were the sources of the resource use specified?	Yes	1
2		Was resource use from overseas adjusted for the local country's context?	NA	0
3		Was there any analysis to account for missing data performed?	No	0
D	Resource Valuation			
1	Perspectives	Were the resources valued according to the chosen perspective?	No perspective stated	0
2	Data Sources	Were all data sources of the valuation of resource use specified?	Yes, the hospital accounting system	1
3	Productivity loss	Was the valuation method for productivity loss specified?	NA	0
4	Discounting	Was discounting undertaken with a specified discount rate?	NA	0
5	Inflation adjustment	Were cost data from different time periods adjusted for inflation with its method specified?	No	0
6	Price and Price adjustment	Were all resources valued according to the specified cost year?	Resource use was valued by the year it occurred (either 2000 or 2001)	1

7		Were price adjustments over time considered?	Yes	1
8		Were prices from other countries used/applied?	NA	0
E	Evaluation and presentation of results			
1	Evaluation methods	Were the data evaluation methods comprehensibly described?	Yes	1
2		Were subgroup analyses performed?	Yes, by surgery division	1
3		Were sensitivity analysis performed?	No	0
4		Were sensitivity analyses carried out on the resource use or costs?	No	0
5		Were parameters for estimating results uncertainty named?	NA	0
6		Was modelling used to estimate costs?	No	0
7	Result presentation	Were the resource use category amounts separately listed?	No	0
8		Was the derivation of the calculations comprehensible?	No	0
9		Were the cost categories separately listed?	No	0
F	Discussion and conclusion			
1	Conclusion	Were the conclusions comprehensible?	Yes	1
2	Quality	Was the quality of the data source(s) discussed?	Yes	1
3	Comparison	Was there a comparison of the study findings with findings from other studies?	Yes	1
4	Limitations	Were limitations of the study stated?	Yes	1
5	Generalizability	Was the generalizability of the results discussed?	Yes	1
6	Future Research recommendations	Were future concrete research recommendations discussed?	No	0
7	Conflicts of interest	Was there a conflict of interest section?	Yes	1
	Score total			16
Vrijens (2012)				
A	General aspects			
1	Illness and patient population	Was the illness defined?	Yes, CDC criteria	1
2		Was the analysis limited to a defined patient population?	Yes, acute care patients	1
3	Design	Was there a description of the setting in which the costs are incurred?	No	0
4		Was the data collection type described?	Yes, as part of a prevalence survey	1
5	Perspective	Was/were the perspective(s) stated?	Public Healthcare provider	1
6	Time period	Was the time period stated to which the costs refer to?	Time period of the study was 2007	1
B	Resource Identification			
1	Scope and type of resources	Was relevant resource use omitted with regard to the chosen perspective?	Yes, other healthcare costs such as medication, treatment, overheads, hospital readmission.	0
2		Was there justification for omitting relevant resource use with regard to the chosen perspective?	It was beyond the scope of the project	1
3		If indirect costs were included, were the costs of productivity loss clearly demarcated?	NA	0
C	Description and quantification of resource use			
1	Data Sources	Were the sources of the resource use specified?	Yes, the administrative hospital discharge data	1
2		Was resource use from overseas adjusted for the local country's context?	NA	0

3		Was there any analysis to account for missing data performed?	No	0
D	Resource Valuation			
1	Perspectives	Were the resources valued according to the chosen perspective?	Yes	1
2	Data Sources	Were all data sources of the valuation of resource use specified?	Yes	1
3	Productivity loss	Was the valuation method for productivity loss specified?	NA	0
4	Discounting	Was discounting undertaken with a specified discount rate?	NA	0
5	Inflation adjustment	Were cost data from different time periods adjusted for inflation with its method specified?	NA	0
6	Price and Price adjustment	Were all resources valued according to the specified cost year?	Yes, 2008	1
7		Were price adjustments over time considered?	NA	0
8		Were prices from other countries used/applied?	NA	0
E	Evaluation and presentation of results			
1	Evaluation methods	Were the data evaluation methods comprehensibly described?	Yes	1
2		Were subgroup analyses performed?	No	0
3		Were sensitivity analysis performed?	No	0
4		Were sensitivity analyses carried out on the resource use or costs?	No	0
5		Were parameters for estimating results uncertainty named?	NA	0
6		Was modelling used to estimate costs?	No	0
7	Result presentation	Were the resource use category amounts separately listed?	NA	0
8		Was the derivation of the calculations comprehensible?	Yes	1
9		Were the cost categories separately listed?	NA	0
F	Discussion and conclusion			
1	Conclusion	Were the conclusions comprehensible?	Yes	1
2	Quality	Was the quality of the data source(s) discussed?	Yes	1
3	Comparison	Was there a comparison of the study findings with findings from other studies?	Yes	1
4	Limitations	Were limitations of the study stated?	Yes	1
5	Generalizability	Was the generalizability of the results discussed?	No	0
6	Future Research recommendations	Were future concrete research recommendations discussed?	No	0
7	Conflicts of interest	Was there a conflict of interest section?	Yes	1
	Score total			17
Reporting Score: 1 Yes; 0 No , Not specified, Not Applicable or Unclear				

Chapter 4 Appendix

Appendix A4.1 Study categorisations from Gheorghe et al. [210] review

Original Stage 1 categorisation

A. The study mainly reports primary data on SSI utility or quality of life
B. The study contains useful primary or secondary SSI quality of life or utility data
C. The study may have useful economic information on aspects of SSI care, but does not fall into A or B
D. The study discusses aspects related to SSI care but neither A, B or C
E. The study has no relevance to SSI

Original Stage 2 categorisation

1. Economic evaluation (cost-minimization, cost-effectiveness , cost-utility, cost-benefit)
2. Cost study
3. Effectiveness study with SSI quality of life or health utility data relevant AND an SSI –free control group
4. Effectiveness study other than 3
5. Methodological study on aspects of economic assessment of SSI
6. Review of medical or economic information
7. Other study, for example purely clinical content , survey of resources and facilities, survey of utilization, estimate of economic burden, health policy and financing
8. Foreign language, to be translated

Appendix Table A4.1 Descriptions of SSI and no SSI in economic evaluations

Lead Author (Year)	Source description of SSI health state	Source description of non SSI health state
General Surgery		
Chatterjee (2015) [219]	Wound complications requiring debridement	Successful reconstruction
Chopra (2016) [221]	Surgical Site Infection	Successful surgery
Colorectal surgery		
Chomsky-Higgins (2019) [220]	SSI utility value	No SSI utility value
Lee (2014) [233]	Unclear	Unclear
Vicentini (2021)[239]	SSI utility value	No SSI utility value
Multiple surgeries		
Conway (2019)[234]	Unclear	Adult general population in Queensland, Australia
Cardiac Surgery		
Hawkins (2019)[222]	Assumption	Assumption
Hong (2018) [223]	Unclear	Unclear
Gastrointestinal surgery		
Morrell (2022)[226]	Wound infection	Patient undergoing transoral robotic surgery and adjuvant external radiotherapy or patient undergoing transoral robotic surgery and adjuvant chemoradiotherapy.
Oncology surgery		
Mericli (2019)[225]	Infection	Successful procedure
Sekigami (2021)[228]	Infection	Successful surgery without complications

Lead Author (Year)	Source description of SSI health state	Source description of non SSI health state
Orthopaedic surgery		
Bydon (2015) [218]	Fortnight Hospital confinement	Person not affected by any of 28 health conditions in the past year
Graves (2016) [235]	Patients with periprosthetic infection after total joint replacement	Primary THA patients at 12 months
Nherera (2017) [237]	Orthopaedic Surgical Site Infection	Matched control of patients undergoing orthopaedic surgery who did not have an SSI
Shearer (2015) [229]	Chronically infected THA	Assumption
Obstetrics and Gynaecology surgery		
Skeith (2017) [231]	Included sepsis or uterine, urinary, pulmonary, or wound infection	Assumption
Siedhoff (2015) [230]	Wound infection	Successful surgery
Spinal surgery		
Zhuang (2020) [232]	Deep infection	Single-level decompression and instrumented posterolateral fusion adult patients without infection
Vascular surgery		
Bloom (2022) [217]	Wound complications requiring debridement	Successful reconstruction

SSI: Surgical Site Infection; THA: Total hip arthroplasty; TTO: Time trade off

Appendix A4.2 Search strategy for the systematic review of SSI utility values

OVID MEDLINE and MEDLINE-In-Process

1 exp Quality of Life/
2 Quality of life.tw.
3 Life quality.tw.
4 Hrql.tw.
5 Hrqol.tw.
6 Hql.tw.
7 Qol.tw.
8 Ql.tw.
9 Sf$.tw.
10 Short form.tw.
11 Shortform.tw.
12 Euroqol.tw.
13 Eq 5d.tw.
14 EQ-5D.tw.

15 Qaly$.tw.
16 Quality adjusted life year$.tw.
17 Hye.tw.
18 Daly$.
19 Disability weight$.tw
20 Health utilit$.tw.
21 Hui$.tw.
22 Quality of wellbeing.tw.
23 Quality of well being.tw.
24 Qwb$.tw.
25 General health questionnaire$.tw.
26 Ghq.tw.
27 Nottingham health profile.tw.
28 Nhp.tw.
29 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28
30 Exp Surgical Wound Infection/
31 Exp Wound Infection/
32 Surgical wound$.tw.
33 Postoperative wound infection.tw.
34 Surgical wound infection.tw.
35 (wound infection adj8 surgery).tw.
36 Wound infec$.tw.
37 30 or 31 or 32 or 33 or 34 or 35 or 36
38 29 and 37

OVID EMBASE

1 exp Quality of Life/
2 Quality of life.tw.
3 Life quality.tw.
4 Hrql.tw.
5 Hrqol.tw.
6 Hql.tw.
7 Qol.tw.
8 Ql.tw.
9 Sf$.tw.
10 Short form.tw.
11 Shortform.tw.
12 Euroqol.tw.
13 Eq 5d.tw.
14 EQ-5D.tw.
15 Qaly$.tw.
16 Quality adjusted life year$.tw.
17 Hye.tw.
18 Health utilit$.tw.
19 Hui$.tw.
20 Quality of wellbeing.tw.
21 Quality of well being.tw.
22 Qwb$.tw.
23 Nottingham health profile.tw.
24 Nhp.tw.
25 Daly$.tw.
26 Disability weight$.tw
27 Disability adjusted life year$.tw.

28 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27
29 Exp Surgical Wound Infection/
30 Exp Wound Infection/
31 Exp Surgical wound/
32 Exp Surgical infection/
33 Surgical wound infection.tw.
34 (wound infection adj8 surgery).tw.
35 Wound infec$.tw.
36 29 or 30 or 31 or 32 or 33 or 34 or 35
37 28 and 36

ISI Web of Science

1 TS=(euroqol or euro qol or EQ-5D or eq 5d or eq-5d)
2 TS=(hui or hui1 or hui2 or hui3)
3 TS=(sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six)
4 TS=(sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six)
5 TS=(sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve)
6 TS=(sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen)
7 TS=(sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty)
8 TS= (Nottingham health profile or nhp)
9 TS=(quality of wellbeing or qwb)
10 TS=(quality adjusted life or qaly$)
11 TS= (Disability adjusted life or Daly$ or disability weight$)
12 #11 OR #10 OR #9 OR #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1
13 TS=(cost effective* or cost-effective or cost-utility or cost-utility or cost-benefit or cost benefit or economic evaluation*)
14 #12 or #13
15 TS=(surgical site infection*)
16 TS=(surgical infection*)
17 TS=(wound infection*)
18 TS=(surgical wound infection*)
19 TS=(wound infection NEAR/8 surgery)
20 TS=(surgical wound*)
21 #15 or #16 or #17 or #18 or #19 or #20
22 #14 and #21

NHS Economic Evaluation Database (NHS EED)

1 Surgical site infect*
2 Surgical wound infect*
3 Surg* infect*
4 Wound infect*
5 SSI
6 1 or 2 or 3 or 4 or 5

Tuft Cost effectiveness Registry Utility search

1 Surgical site infection [abstract]
2 Surgical site infections [abstract]
3 Surgery infection [abstract]
4 Surgery infections [abstract]
5 Wound infection [abstract]
6 Wound infections [abstract]
7 SSI [abstract]
8 1 or 2 or 3 or 4 or 5 or 6 or 7

Chapter 5 Appendix

Appendix Table A5.1 Univariate and multivariate deterministic sensitivity analysis results (UK costs)

Strategy	Cost	Incremental Costs	QALY	Incremental QALY	ICER
DSA1: Proportion of inpatient SSIs changed to 37.5%					
Coated Sutures	£655		0.04409		Dominant
Wound Irrigation	£765	£110	0.04395	-0.000144	Dominated
Usual Care	£873	£218	0.0438	-0.000294	Dominated
DSA2: 30 day postoperative SSI probability changed to 11%					
Coated Sutures	£724		0.04418		Dominant
Wound irrigation	£849	£125	0.04405	-0.000132	Dominated
Usual Care	£969	£245	0.04391	-0.000266	Dominated
DSA3: SSI primary care costs as a % of total costs parameter changed to 10.83%					
Coated Sutures	£774		0.04409		Dominant
Wound irrigation	£903	£130	0.04395	-0.000144	Dominated
Usual Care	£1,032	£258	0.0438	-0.000294	Dominated
DSA4: Outpatient SSI costs as a percentage of Inpatient SSI costs parameter was doubled to 52%					
Coated Sutures	£953		0.04409		Dominant
Wound irrigation	£1,112	£160	0.04395	-0.000144	Dominated
Usual Care	£1,272	£319	0.0438	-0.000294	Dominated
DSA5: Outpatient SSI costs as a percentage of Inpatient SSI costs parameter was halved to 13%					
Coated Sutures	£739		0.04409		Dominant
Wound irrigation	£863	£124	0.04395	-0.000144	Dominated
Usual Care	£985	£246	0.0438	-0.000294	Dominated
DSA6: Overall additional cost of SSI reduced by 50% (from £11,895 to £5,948)					
Coated Sutures	£407		0.04409		Dominant
Wound irrigation	£476	£69	0.04395	-0.000144	Dominated
Usual Care	£540	£133	0.0438	-0.000294	Dominated

Strategy	Cost	Incremental Costs	QALY	Incremental QALY	ICER
DSA7: additional cost of an SSI changed to £163					
Usual Care	£13	£0	0.043796	0.000000	
Coated Sutures	£14	£1	0.044089	0.000294	£3,344
Wound irrigation	£17	£3	0.043946	-0.000144	Dominated
DSA8: Additional cost of Superficial, Deep Incisional, and Deep Organ SSI assumed to be £371, £2,753, and £19,725, respectively					
Coated Sutures	£401		0.04409		Dominant
Wound irrigation	£469	£68	0.04395	-0.000144	Dominated
Usual Care	£532	£131	0.0438	-0.000294	Dominated
DSA9: additional cost of an SSI changed to £1,048 for to all SSI health states					
Coated Sutures	£100		0.04409		Dominant
Wound irrigation	£117	£17	0.04395	-0.000144	Dominated
Usual Care	£128	£28	0.0438	-0.000294	Dominated
DSA10: SSI utility decrements were each decreased by 25%					
Coated Sutures	£810		0.0449		Dominant
Wound irrigation	£946	£136	0.04489	-0.000008	Dominated
Usual Care	£1,080	£270	0.04489	-0.000016	Dominated
DSA11: SSI utility decrements were each increased by 25%					
Coated Sutures	£810		0.04328		Dominant
Wound irrigation	£946	£136	0.043	-0.000279	Dominated
Usual Care	£1,080	£270	0.04271	-0.000571	Dominated
DSA12: An SSI decrement of 0.156 was used for all the SSI health severity states					
Coated Sutures	£810		0.04372		Dominant
Wound irrigation	£946	£136	0.04352	-0.000205	Dominated
Usual Care	£1,080	£270	0.0433	-0.000419	Dominated
DSA13: Two month time horizon					
Coated Sutures	£810		0.0878		Dominant
Wound irrigation	£946	£136	0.0875	-0.000294	Dominated
Usual Care	£1,080	£270	0.0872	-0.000601	Dominated
ICER: Incremental cost effectiveness ratio; QALY: Quality Adjusted Life Year					

Appendix Table A5.2 Univariate and multivariate deterministic sensitivity analysis results (International dollars)

Strategy	Cost (Int$)	Incremental Costs (Int$)	QALY	Incremental QALY	ICER
DSA1: Proportion of inpatient SSIs changed to 37.5%					
Coated Sutures	$1,016		0.04418		Dominant
Wound Irrigation	$1,187	$171	0.04405	-0.000132	Dominated
Usual Care	$1,354	$338	0.04391	-0.000266	Dominated
DSA2: 30 day postoperative SSI probability changed to 11%					
Coated Sutures	$1,123		0.04409		Dominant
Wound irrigation	$1,316	$193	0.04395	-0.000144	Dominated
Usual Care	$1,503	$380	0.0438	-0.000294	Dominated
DSA3: SSI primary care costs as a % of total costs parameter changed to 10.83%					
Coated Sutures	$1,200		0.04409		Dominant
Wound irrigation	$1,401	$201	0.04395	-0.000144	Dominated
Usual Care	$1,600	$400	0.0438	-0.000294	Dominated
DSA4: Outpatient SSI costs as a percentage of Inpatient SSI costs parameter was doubled to 52%					
Coated Sutures	$1,477		0.04409		Dominant
Wound irrigation	$1,725	$248	0.04395	-0.000144	Dominated
Usual Care	$1,972	$495	0.0438	-0.000294	Dominated
DSA5: Outpatient SSI costs as a percentage of Inpatient SSI costs parameter was halved to 13%					
Coated Sutures	$1,146		0.04409		Dominant
Wound irrigation	$1,338	192	0.04395	-0.000144	Dominated
Usual Care	$1,527	382	0.0438	-0.000294	Dominated
DSA6: Overall additional cost of SSI reduced by 50%					
Coated Sutures	$631		0.04409		Dominant
Wound irrigation	$738	$106	0.04395	-0.000144	Dominated
Usual Care	$838	$206	0.0438	-0.000294	Dominated
DSA7: additional cost of an SSI changed to £163					
Usual Care	$21		0.043796		
Coated Sutures	$22	$2	0.044089	0.000294	$5187
Wound irrigation	$27	$5	0.043946	-0.000144	Dominated

Strategy	Cost (Int$)	Incremental Costs (Int$)	QALY	Incremental QALY	ICER
DSA8: Additional cost of Superficial, Deep Incisional, and Deep Organ SSI assumed to be £371, £2,753, and £19,725, respectively					
Coated Sutures	$622		0.04409		Dominant
Wound irrigation	$727	$105	0.04395	-0.000144	Dominated
Usual Care	$826	$203	0.0438	-0.000294	Dominated
DSA9: additional cost of an SSI changed to £1,048 for to all SSI health states					
Coated Sutures	$155		0.04409		Dominant
Wound irrigation	$182	$27	0.04395	-0.000144	Dominated
Usual Care	$199	$44	0.0438	-0.000294	Dominated
DSA10: SSI utility decrements were each decreased by 25%					
Coated Sutures	$1,256		0.0449		Dominant
Wound irrigation	$1,467	$211	0.04489	-0.000008	Dominated
Usual Care	$1,676	$419	0.04489	-0.000016	Dominated
DSA11: SSI utility decrements were each increased by 25%					
Coated Sutures	$1,256		0.04328		Dominant
Wound irrigation	$1,467	$211	0.043	-0.000279	Dominated
Usual Care	$1,676	$419	0.04271	-0.000571	Dominated
DSA12: An SSI decrement of 0.156 was used for all the SSI health severity states					
Coated Sutures	$1,256		0.04372		Dominant
Wound irrigation	$1,467	$211	0.04352	-0.000205	Dominated
Usual Care	$1,676	$419	0.0433	-0.000419	Dominated
DSA13: Two month time horizon					
Coated Sutures	$1,256	0	0.0878		Dominant
Wound irrigation	$1,467	$211	0.0875	-0.000294	Dominated
Usual Care	$1,676	$419	0.0872	-0.000601	Dominated
ICER: Incremental cost effectiveness ratio; QALY: Quality Adjusted Life Year					

Appendix Table A5.3 Incremental cost-effectiveness report

Comparison					Country			
Coated Sutures versus Usual Care incremental cost-effectiveness					UK	Ghana	India	Mexico
COMPONENT	QUADRANT	INCREFF	INCRCOST	INCRCE	Proportion	Proportion	Proportion	Proportion
C1	IV	IE>0	IC<0	Superior	74.3%	74.3%	74.3%	74.3%
C2	I	IE>0	IC>0	<threshold	0.1%	0.0%	0.0%	0.1%
C3	III	IE<0	IC<0	ICER> threshold	23.8%	25.3%	25.3%	24.8%
C4	I	IE>0	IC>0	ICER> threshold	0.1%	0.2%	0.2%	0.1%
C5	III	IE<0	IC<0	ICER<threshold	1.6%	0.1%	0.1%	0.7%
C6	II	IE<0	IC>0	Inferior	0.1%	0.1%	0.1%	0.1%
Coated Sutures versus Wound Irrigation incremental cost-effectiveness								
C1	IV	IE>0	IC<0	Superior	63.1%	63.1%	63.1%	63.1%
C2	I	IE>0	IC>0	ICER<threshold	0.3%	0.0%	0.0%	0.1%
C3	III	IE<0	IC<0	ICER> threshold	20.6%	21.9%	21.9%	21.5%
C4	I	IE>0	IC>0	ICER> threshold	3.7%	3.9%	3.9%	3.8%
C5	III	IE<0	IC<0	ICER<threshold	1.3%	0.0%	0.1%	0.5%
C6	II	IE<0	IC>0	Inferior	11.1%	11.1%	11.1%	11.1%
Wound Irrigation versus Usual Care incremental cost-effectiveness								
C1	IV	IE>0	IC<0	Superior	62.3%	62.3%	62.3%	62.3%
C2	I	IE>0	IC>0	ICER<threshold	0.6%	0.0%	0.1%	0.2%
C3	III	IE<0	IC<0	ICER> threshold	19.4%	21.0%	20.9%	20.4%
C4	I	IE>0	IC>0	ICER> threshold	5.2%	5.8%	5.7%	5.6%
C5	III	IE<0	IC<0	ICER<threshold	1.6%	0.1%	0.2%	0.7%
C6	II	IE<0	IC>0	Inferior	10.9%	10.9%	10.9%	10.9%
INCREFF: Incremental effectiveness; INCRCOST: Incremental cost; INCRCE: Incremental cost-effectiveness; ICER: Incremental Cost-effectiveness ratio								

Chapter 6 Appendix

Appendix Table A6.1 ROSSINI participating hospitals

Hospital Name	NHS Hospital type
Hope Hospital Manchester	Teaching hospital
Derriford Hospital, Plymouth	Teaching hospital
Good Hope Hospital, Sutton Coldfield	Teaching hospital
Heartlands Hospital, Birmingham	Teaching hospital
Leighton Hospital, Crewe	General hospital
Maidstone Hospital, Kent	General hospital
Medway Maritime Hospital, Kent	General hospital
New Cross Hospital , Wolverhampton	General hospital
Northwick Park Hospital, London	Teaching hospital
Queens Medical Centre, Nottingham	Teaching hospital
Royal Derby Hospital, Derby	Teaching hospital
Royal Devon and Exeter Hospital, Exeter	Teaching hospital
Russells Hall Hospital, Dudley	General hospital
Sandwell Hospital	Teaching hospital
Tameside General Hospital, Ashton-under-Lyne	General hospital
Torbay Hospital, Torquay	General hospital
University Hospital Birmingham	Teaching hospital
University Hospital North Staffordshire	Teaching hospital
Walsall Manor Hospital	General hospital
Warwick Hospital	Teaching hospital
Wrightington, Wigan and Leigh	Teaching hospital

Appendix A6.1 Reproduction of original analysis methods

Resource use and cost methods

Hospital length of stay was calculated as the difference between the surgery date and the discharge date. Similarly, hospital readmission length of stay was calculated as the difference between the readmission date and the readmission discharge date.

The original analysis took a bottom-up costing approach where resource use was multiplied by national unit cost sources to obtain postoperative costs associated with the patient population. A cost year of 2011 was selected for the analysis. The cost of a hospital bed day on a hospital general ward was taken from NHS Reference Costs 2010/2011 [491]. The unit cost of an outpatient clinic visit was sourced from NHS 2010/2011 reference costs [491] although no detail was provided on the specific unit cost(s) used. The cost of a bed day in ITU and HDU was taken from NHS reference costs 2007/2008 [492] and inflated to the 2011 cost year using the hospital and community health services pay and price inflation index [312]. An earlier NHS reference cost publication was used because it was the last available year that these unit costs were provided.

Medication costs were taken from the British National Formulary (BNF) 2011 [313]. The unit costs of primary care visits were taken from Personal Social Services Research Unit (PSSRU) costs [312]. In the absence of reported information, the following assumptions from the original analysis were inferred based on cross-checking the data sources with the unit costs displayed in the doctoral thesis. The cost of GP visit was assumed to be a clinic consultation and included direct care staff costs and a contribution to GP training qualification costs [312]. The cost of a practice nurse visit was assumed to be equivalent to 20 minutes of Band 7 Nurse's time and included a contribution to training qualification costs [312]. In the original

analysis, it was assumed that the district nurse visit took 1 hour and the cost of the visit was taken from the PSSRU Unit costs 2011 [312].

The time horizon for the original analysis was thirty days after surgery in accordance with the trial data. Due to the short time horizon of 1 month, no discounting of costs or utilities was performed.

Quality of life methods

In the original analysis, the EQ-5D-3L data was converted to utility data using UK population norms [314]. For the utility decrement associated with SSI, these were shown as cross-sectional points, and no calculation of Quality Adjusted Life Years (QALY) by SSI status was undertaken.

Data cleaning

The following data cleaning was inferred from the SAS code from the original analysis. Where BMI was missing, BMI was calculated using height and weight values. For the hospital length of stay calculation where surgery date was missing, the date of entry into the trial was used as the surgery date. For patients who were readmitted where the readmission date was beyond thirty days postoperatively, their length of stay was not included in accordance with the time horizon. The combined length of stay of readmission and index length of stay was censored to thirty days after surgery. For patients readmitted within the 30-day postoperative period and not yet discharged by the thirty days, their readmission length of stay valuation was censored to thirty days after surgery.

For patients with no recorded ITU days but they had recorded days of ventilation, these days of ventilation were assumed to be ITU days. Where CRFs had been returned but there was no completion of resource use items, the resource use was assumed to be zero. Patients who died

within the first seven days were assigned an EQ-5D-3L score of zero at the five to seven day timepoint. Patients who died within the thirty days were assigned a utility score of zero at the thirty postoperative day follow up.

Imputation

Multiple imputation was undertaken to account for missing cost data and quality of life data. This was done using the Multiple Imputation by Chained Equations (MICE) technique [315]. In the original analysis, item level imputation was undertaken for missing values relating to the baseline demographics, surgical procedure, and cost items. The items were imputed using predictive mean matching [315] to the nearest observation. Age and SSI status variables were used to predict the missing cost and demographic values. Twenty imputation datasets were generated for each missing item with the mean values and their standard errors were pooled across the imputed datasets using Rubin's Rule [316]. The MICE technique relies on a Missing at Random assumption which was assessed to be valid in the original analysis [48].

Partial completion of EQ-5D-3L was considered fully missing, and index score level imputation was undertaken. The original analysis imputed utility scores using MICE and predictive mean matching the nearest observation with age, and SSI status variables used to predict the EQ-5D-3L scores at baseline. For the 30 to 33 days postoperative EQ-5D-3L timepoint, the utility value was imputed using MICE and predictive mean matching the nearest observation with age, SSI status, and the addition of the 5 to 7 days postoperative EQ-5D-3L scores.

Appendix A6.2 Re-analysis data cleaning

Data cleaning was undertaken to prepare the data for the re-analysis. As the original analysis was undertaken in SAS software, the data and commands were adapted to work for analysis in STATA 17. For the re-analysis, any observations in the accessed dataset with a missing consent form response or who did not consent to the study were excluded. Where BMI was missing, BMI was calculated using height and weight values as per the original analysis. For the re-analysis, for primary care visits where it has been indicated that there was a healthcare visit and the number of visits was missing, a conservative estimate of 1 visit was assumed for these patients. It is unclear how the original analysis dealt with the above situation and whether the number of visits was treated as missing for these patients. For the hospital length of stay calculation where surgery date was missing, the date of entry into the trial was used as the surgery date as per the original analysis. Where the discharge date was recorded as before the surgery, the length of stay was treated as missing for the re-analysis. In accordance with the original analysis, patients who were still an inpatient at thirty days postoperatively had their length of stay was truncated to thirty days.

In both analyses (the original and the re-analysis), for patients who were readmitted where the readmission date was beyond thirty days postoperatively, their length of stay was not included in the analysis in accordance with the time horizon. For patients readmitted within the 30-day postoperative period and not yet discharged by the thirty days, their readmission length of stay valuation was censored to thirty days after surgery.

In common with the original analysis, for patients with no recorded ITU days but recorded days of ventilation, these days of ventilation were assumed to be ITU days. For the re-analysis, any ITU and HDU days greater than thirty days were first censored to thirty days. As ITU days and HDU days are recorded separately from the hospital length of stay, instances

where the sum of ITU and HDU days were greater than the reported hospital length of stay during the month were adjusted to fit within calculated hospital length of stay for the re-analysis. In these instances of requiring ITU and HDU days to be scaled back to accommodate the reported length of stay, ITU days took precedence and HDU days were first to be trimmed where applicable. For example, if the calculated hospital length of stay for a patient was seven days with five ITU days and four HDU days also reported, the patient would be assumed to have five ITU days, two HDU days and zero general ward days.

Where CRFs had been returned but there was no completion of resource use items, the resource use was assumed to be zero as per the original analysis. For the re-analysis, patients who died within the first seven days were assigned an EQ-5D-3L score of zero at the five to seven day timepoint. In the original analysis and re-analysis, patients who died within the thirty days were assigned a utility score of zero at the thirty postoperative day follow up.

Appendix Table A6.2 Case Control characteristics by imputed datasets for cost analysis

m	1		2		3		4		5	
Variable	No SSI (n=226)	SSI (n= 113)	No SSI (n=228)	SSI (n= 114)	No SSI (n=226)	SSI (n= 113)	No SSI (n=226)	SSI (n= 113)	No SSI (n=220)	SSI (n= 110)
Mean Age in years (SE)	63.56 (0.73)	63.6 (1.04)	63.42 (0.75)	63.39 (1.05)	63.45 (0.75)	63.41 (1.06)	63.28 (0.74)	63.27 (1.05)	63.61 (0.77)	63.23 (1.08)
Females	39.82%	39.82%	40.35%	40.35%	38.94%	38.94%	39.82%	39.82%	40.00%	40.00%
Mean BMI (SE)	26.29 (0.33)	27.55 (0.47)	26.56 (0.34)	27.83 (0.49)	26.25 (0.33)	27.73 (0.47)	26.14 (0.35)	27.99 (0.5)	26.48 (0.34)	27.9 (0.48)
Diabetics	11.50%	11.50%	10.53%	10.53%	11.50%	11.50%	11.50%	11.50%	11.82%	11.82%
Clean-Contaminated Surgeries	88.50%	88.50%	88.60%	88.60%	89.38%	89.38%	89.38%	89.38%	90.91%	90.91%
Planned Stoma	11.50%	11.50%	11.40%	11.40%	10.62%	10.62%	8.85%	8.85%	10.00%	10.00%
Elective Surgeries	46.02%	46.02%	46.49%	46.49%	46.02%	46.02%	46.02%	46.02%	45.45%	45.45%
Current Smoker	10.62%	10.62%	11.40%	11.40%	10.62%	10.62%	11.50%	11.50%	10.91%	10.91%
Mean Surgery duration in minutes (SE)	176.08 (6.42)	204.31 (11.48)	179.28 (6.6)	199.59 (11.37)	187.98 (6.74)	205.49 (11.74)	187.02 (6.57)	205.5 (11.5)	184.36 (6.46)	204.66 (11.64)

M	6		7		8		9		10	
Variable	No SSI (n=224)	SSI (n= 112)	No SSI (n=220)	SSI (n= 110)	No SSI (n=224)	SSI (n= 112)	No SSI (n=224)	SSI (n= 112)	No SSI (n=222)	SSI (n= 111)
Mean Age in years (SE)	63.77 (0.76)	63.45 (1.06)	63.45 (0.76)	63.6 (1.06)	64.18 (0.78)	63.41 (1.08)	63.89 (0.75)	63.4 (1.06)	63.84 (0.76)	63.43 (1.09)
Females	40.18%	40.18%	39.09%	39.09%	39.29%	39.29%	39.29%	39.29%	39.64%	39.64%
Mean BMI (SE)	26.59 (0.35)	27.73 (0.46)	26.35 (0.36)	27.71 (0.46)	26.52 (0.35)	27.81 (0.47)	26.47 (0.38)	27.61 (0.46)	26.28 (0.35)	27.55 (0.46)
Diabetics	10.71%	10.71%	10.91%	10.91%	11.61%	11.61%	11.61%	11.61%	10.81%	10.81%
Clean-Contaminated Surgeries	89.29%	89.29%	90.00%	90.00%	89.29%	89.29%	90.18%	90.18%	90.09%	90.09%
Planned Stoma	11.61%	11.61%	10.00%	10.00%	10.71%	10.71%	10.71%	10.71%	10.81%	10.81%
Elective Surgeries	47.32%	47.32%	46.36%	46.36%	46.43%	46.43%	46.43%	46.43%	46.85%	46.85%
Current Smoker	10.71%	10.71%	11.82%	11.82%	10.71%	10.71%	10.71%	10.71%	10.81%	10.81%
Mean Surgery duration in minutes (SE)	178.11 (6.01)	203.92 (11.6)	181.22 (6.42)	204.95 (11.7)	187.44 (6.61)	208.26 (11.71)	188.52 (6.73)	203.65 (11.75)	179.59 (6.41)	205.22 (11.75)

m	11		12		13		14		15	
Variable	No SSI (n=222)	SSI (n= 111)	No SSI (n=224)	SSI (n= 112)	No SSI (n=222)	SSI (n= 111)	No SSI (n=222)	SSI (n= 111)	No SSI (n=226)	SSI (n= 113)
Mean Age in years (SE)	63.59 (0.78)	63.31 (1.08)	63.48 (0.78)	63.25 (1.08)	63.61 (0.75)	63.36 (1.08)	63.57 (0.77)	63.37 (1.07)	63.38 (0.77)	63.34 (1.06)
Females	40.54%	40.54%	39.29%	39.29%	39.64%	39.64%	39.64%	39.64%	40.71%	40.71%
Mean BMI (SE)	26.26 (0.33)	27.58 (0.45)	26.43 (0.35)	27.84 (0.49)	26.59 (0.34)	28.04 (0.48)	26.3 (0.33)	27.8 (0.51)	25.8 (0.33)	27.94 (0.47)
Diabetics	10.81%	10.81%	10.71%	10.71%	10.81%	10.81%	11.71%	11.71%	11.50%	11.50%
Clean-Contaminated Surgeries	90.99%	90.99%	89.29%	89.29%	89.19%	89.19%	90.09%	90.09%	88.50%	88.50%
Planned Stoma	10.81%	10.81%	8.93%	8.93%	9.01%	9.01%	9.91%	9.91%	10.62%	10.62%
Elective Surgeries	47.75%	47.75%	46.43%	46.43%	45.05%	45.05%	45.95%	45.95%	46.02%	46.02%
Current Smoker	10.81%	10.81%	11.61%	11.61%	11.71%	11.71%	10.81%	10.81%	10.62%	10.62%
Mean Surgery duration in minutes (SE)	181.4 (6.22)	204.26 (11.75)	184.21 (6.36)	202.17 (11.43)	183.59 (6.66)	207.87 (11.84)	187.95 (6.76)	211.61 (11.81)	181.73 (6.33)	203.97 (11.61)

m	16		17		18		19		20	
Variable	No SSI (n=220)	SSI (n= 110)	No SSI (n=226)	SSI (n= 113)	No SSI (n=226)	SSI (n= 113)	No SSI (n=222)	SSI (n= 111)	No SSI (n=216)	SSI (n= 108)
Mean Age in years (SE)	63.86 (0.78)	63.33 (1.09)	63.62 (0.74)	63.37 (1.05)	63.67 (0.74)	63.57 (1.05)	63.41 (0.76)	63.54 (1.08)	63.41 (0.76)	63.73 (1.08)
Females	40.00%	40.00%	39.82%	39.82%	38.94%	38.94%	40.54%	40.54%	39.81%	39.81%
Mean BMI (SE)	26.06 (0.35)	27.67 (0.49)	25.93 (0.32)	27.81 (0.48)	26.68 (0.33)	27.74 (0.47)	26.35 (0.35)	27.93 (0.5)	26.45 (0.33)	27.39 (0.46)
Diabetics	10.91%	10.91%	11.50%	11.50%	11.50%	11.50%	10.81%	10.81%	10.19%	10.19%
Clean-Contaminated Surgeries	90.00%	90.00%	89.38%	89.38%	89.38%	89.38%	90.09%	90.09%	88.89%	88.89%
Planned Stoma	9.09%	9.09%	10.62%	10.62%	10.62%	10.62%	10.81%	10.81%	10.19%	10.19%
Elective Surgeries	47.27%	47.27%	46.02%	46.02%	46.02%	46.02%	46.85%	46.85%	46.30%	46.30%
Current Smoker	10.91%	10.91%	10.62%	10.62%	10.62%	10.62%	10.81%	10.81%	11.11%	11.11%
Mean Surgery duration in minutes (SE)	183.99 (6.89)	202.88 (11.69)	180.26 (6.47)	201.04 (11.47)	182.45 (6.51)	205.57 (11.4)	171.95 (5.99)	205.63 (11.7)	184.31 (6.93)	206.63 (11.95)

Appendix Table A6.3 Case Control characteristics by imputed datasets for quality of life analysis

m	1		2		3		4		5	
Variable	No SSI (n= 94)	SSI (n=47)	No SSI (n= 98)	SSI (n=49)	No SSI (n= 94)	SSI (n=47)	No SSI (n= 98)	SSI (n=49)	No SSI (n= 96)	SSI (n=48)
Mean Age in years (SE)	64.32 (0.98)	64.49 (1.38)	64.38 (0.97)	64.18 (1.36)	64.06 (0.95)	64.4 (1.33)	64.35 (0.94)	64.67 (1.34)	64.43 (0.94)	64.35 (1.38)
Females	29.79%	29.79%	30.61%	30.61%	29.79%	29.79%	28.57%	28.57%	29.17%	29.17%
Mean BMI (SE)	25.84 (0.49)	26.84 (0.62)	25.58 (0.47)	27 (0.6)	25.55 (0.48)	27.01 (0.62)	25.42 (0.47)	27.29 (0.62)	25.64 (0.51)	27.06 (0.61)
Diabetics	4.26%	4.26%	4.08%	4.08%	4.26%	4.26%	4.08%	4.08%	4.17%	4.17%
Clean-Contaminated Surgeries	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%
Planned Stoma	6.38%	6.38%	6.12%	6.12%	6.38%	6.38%	6.12%	6.12%	6.25%	6.25%
Elective Surgeries	51.06%	51.06%	48.98%	48.98%	48.94%	48.94%	51.02%	51.02%	50.00%	50.00%
Current Smoker	10.64%	10.64%	10.20%	10.20%	8.51%	8.51%	10.20%	10.20%	10.42%	10.42%
Mean Surgery duration in minutes (SE)	205.91 (11.11)	210.85 (19.76)	205.48 (10.69)	217.63 (19.32)	212.79 (11.53)	228.09 (20.45)	206.93 (10.81)	202.84 (10.48)	208.03 (10.72)	213.21 (19.35)

m	6		7		8		9		10	
Variable	No SSI (n= 96)	SSI (n=48)	No SSI (n= 98)	SSI (n=49)	No SSI (n= 96)	SSI (n=48)	No SSI (n= 90)	SSI (n=45)	No SSI (n= 96)	SSI (n=48)
Mean Age in years (SE)	64.54 (0.94)	64.6 (1.33)	64.92 (0.96)	64.78 (1.31)	64.46 (0.95)	64.02 (1.33)	64.23 (1)	64.31 (1.41)	64.39 (0.96)	64.48 (1.35)
Females	29.17%	29.17%	30.61%	30.61%	31.25%	31.25%	31.11%	31.11%	29.17%	29.17%
Mean BMI (SE)	26.02 (0.53)	26.93 (0.6)	25.8 (0.52)	26.9 (0.59)	25.56 (0.48)	26.93 (0.61)	25.69 (0.5)	27 (0.64)	25.67 (0.47)	26.93 (0.6)
Diabetics	4.17%	4.17%	4.08%	4.08%	4.17%	4.17%	4.44%	4.44%	4.17%	4.17%
Clean-Contaminated Surgeries	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%
Planned Stoma	6.25%	6.25%	6.12%	6.12%	6.25%	6.25%	6.67%	6.67%	6.25%	6.25%
Elective Surgeries	50.00%	50.00%	48.98%	48.98%	47.92%	47.92%	51.11%	51.11%	50.00%	50.00%
Current Smoker	10.42%	10.42%	10.20%	10.20%	10.42%	10.42%	8.89%	8.89%	10.42%	10.42%
Mean Surgery duration in minutes (SE)	202.27 (10.87)	221.25 (20.19)	205.72 (10.77)	198.88 (10.67)	203.09 (10.32)	215.83 (19.85)	209.07 (10.96)	199.09 (9.99)	203.05 (10.43)	212.6 (19.38)

m	11		12		13		14		15	
Variable	No SSI (n= 94)	SSI (n=47)	No SSI (n= 96)	SSI (n=48)	No SSI (n= 96)	SSI (n=48)	No SSI (n= 96)	SSI (n=48)	No SSI (n= 94)	SSI (n=47)
Mean Age in years (SE)	64.65 (0.96)	65.04 (1.33)	64.11 (0.94)	64.35 (1.34)	64.3 (0.95)	64.35 (1.38)	64.17 (0.95)	64.35 (1.38)	64.73 (0.96)	64.91 (1.32)
Females	29.79%	29.79%	31.25%	31.25%	29.17%	29.17%	29.17%	29.17%	29.79%	29.79%
Mean BMI (SE)	26.33 (0.54)	27.06 (0.61)	25.93 (0.5)	27.05 (0.61)	25.98 (0.53)	27 (0.61)	26.1 (0.53)	27.49 (0.73)	26 (0.46)	26.99 (0.62)
Diabetics	4.26%	4.26%	4.17%	4.17%	4.17%	4.17%	4.17%	4.17%	4.26%	4.26%
Clean-Contaminated Surgeries	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%
Planned Stoma	6.38%	6.38%	6.25%	6.25%	6.25%	6.25%	6.25%	6.25%	6.38%	6.38%
Elective Surgeries	51.06%	51.06%	45.83%	45.83%	50.00%	50.00%	50.00%	50.00%	51.06%	51.06%
Current Smoker	8.51%	8.51%	10.42%	10.42%	10.42%	10.42%	10.42%	10.42%	10.64%	10.64%
Mean Surgery duration in minutes (SE)	205.65 (10.96)	209.68 (11.75)	207.98 (11.03)	218.23 (19.66)	199.17 (10.84)	213.83 (19.44)	205.54 (9.59)	221.33 (19.7)	192.19 (10.13)	199.57 (11.03)

m	16		17		18		19		20	
Variable	No SSI (n= 96)	SSI (n=48)	No SSI (n= 96)	SSI (n=48)	No SSI (n= 96)	SSI (n=48)	No SSI (n= 92)	SSI (n=46)	No SSI (n=98)	SSI (n= 49)
Mean Age in years (SE)	63.92 (0.91)	63.92 (1.36)	64.25 (0.96)	64.48 (1.35)	64.1 (0.98)	63.85 (1.35)	64.59 (0.97)	64.63 (1.32)	64.83 (0.97)	64.67 (1.34)
Females	29.17%	29.17%	29.17%	29.17%	31.25%	31.25%	30.43%	30.43%	28.57%	28.57%
Mean BMI (SE)	26.36 (0.52)	27.66 (0.79)	25.67 (0.5)	26.93 (0.6)	25.94 (0.52)	26.94 (0.61)	25.77 (0.52)	26.91 (0.62)	25.94 (0.5)	26.95 (0.61)
Diabetics	4.17%	4.17%	4.17%	4.17%	4.17%	4.17%	4.35%	4.35%	4.08%	4.08%
Clean-Contaminated Surgeries	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%
Planned Stoma	6.25%	6.25%	6.25%	6.25%	6.25%	6.25%	6.52%	6.52%	6.12%	6.12%
Elective Surgeries	50.00%	50.00%	50.00%	50.00%	47.92%	47.92%	50.00%	50.00%	51.02%	51.02%
Current Smoker	10.42%	10.42%	10.42%	10.42%	10.42%	10.42%	10.87%	10.87%	10.20%	10.20%
Mean Surgery duration in minutes (SE)	201.2 (10.61)	218.83 (19.81)	207.98 (10.97)	213.13 (19.37)	210.95 (10.71)	219.35 (19.68)	206.53 (10.59)	198.26 (11.27)	206.19 (10.46)	202.12 (10.42)

Appendix Table A6.4 GLM Modified Parker tests diagnostics

	Total Costs		**QALY decrement**	
Family	Chi2	P-value	Chi2	P-value
Poisson:	0.0517	0.8201	1.7516	0.1857
Gamma:	4.2113	0.0402	25.3469	0
Gaussian	6.2852	0.0122	5.7008	0.017
Inverse Gaussian	18.7639	0	76.4869	0

Appendix Table A6.5 GLM link function diagnostics

	Total Costs		**QALY decrement**	
Base Case or Sensitivity Analysis	Base case	Sensitivity analysis	Base case	Sensitivity analysis
Family Distribution	Poisson	Gamma	Poisson	Gaussian
Link function	-0.5	-0.4	1.4	-0.7
	P-value (except Akaike information criterion)			
Pearson Correlation Test	0.9982	0.7298	0.4887	0.5843
Pregibon Link Test	0.9922	0.409	0.0624	0.0699
Modified Hosmer and Lemeshow	0.1922	0.5283	0.758	0.1367
Akaike information criterion	2767.086	19.5399	0.2924	-5.0064

Appendix Table A6.6 Complete Case Cross-Comparison of costs by SSI status

Cost Variable	No SSI Mean (SE)	SSI Mean (SE)	Bootstrapped Mean difference (95% Confidence Interval)
GP visits	£16 (£1)	£32 (£4)	£15.85 (£8.49 to £23.61)
Practice Nurse Visits	£4 (£1)	£6 (£2)	£2.38 (-£0.45 to £5.67)
District Nurse Visits	£236 (£25)	£614 (£60)	£378.34 (£262 to £518.17)
Outpatient clinic visits	£53 (£5)	£86 (£16)	£32.29 (£1.49 to £70.41)
Hospital day on ward	£3,833 (£121)	£4,836 (£247)	£1,002.75 (£444.19 to £1,508.72)
Hospital day in ITU	£1,661 (£230)	£2,036 (£511)	£375.19 (-£618.56 to £1501.38)
Hospital day in HDU	£707 (£82)	£729 (£154)	£21.62 (-£328.9 to £347.7)
Antibiotics	£0.11 (£0.03)	£2.10 (£0.94)	£2.00 (£0.76 to £4.13)
Painkiller medication	£0.49 (£0.10)	£0.80 (£0.14)	£0.30 (-£0.03 to £0.66)
Total Health Care Cost	£6,202 (£207)	£7,409 (£392)	£1,208 (£299 to £2,093)
GP: General Practitioner; HDU: High Dependency Unit; ITU: Intensive Therapy Unit			

Appendix Table A6.7 Complete Case Generalised Linear Model SSI Cost Predictions

Variable	No SSI	SSI	Marginal effect
	Mean (SE)	Mean (SE)	(95% Confidence Interval)
Total Health Care Cost	£6,157 (£211)	£7,517 (£414)	£1,360 (£429 to £2,291)

Appendix Table A6.8 Complete Case Generalised Linear Model for total costs

Variables	Coefficient	Standard Error	P-value
Age	-0.0000598	0.0000140	0.0000
Female Sex	0.0004794	0.0003581	0.1810
Male Sex (reference category)	-	-	-
Planned Stoma	-0.0011530	0.0004718	0.0150
No Planned Stoma (reference category)	-	-	-
Current Smoker	-0.0001311	0.0005114	0.7980
Not current smoker (reference category)	-	-	-
Diabetic	-0.0008485	0.0004778	0.0760
Not Diabetic (reference category)	-	-	-
Body Mass Index	0.0000056	0.0000332	0.8670
Elective Surgery	0.0013532	0.0003849	0.0000
Emergency Surgery (reference category)	-	-	-
Surgical Site Infection	-0.0011919	0.0003890	0.0020
No Surgical Site Infection (reference category)	-	-	-
Contaminated-Dirty Surgery	-0.0004363	0.0004439	0.3260
Clean-Contaminated Surgery (reference category)	-	-	-
Intercept	0.0160727	0.0015729	0.0000

Appendix Table A6.9 Case Control Approach Costs by SSI status Complete Case

Variable	SSI (n=95) Mean (SE)	No SSI (n=190) Mean (SE)	Bootstrapped mean difference (95% Confidence Interval)
Total Health Care Cost	£5,942 (£309)	£6,951 (£444)	£1,009 (£162 to £1,831)

Appendix Table A6.10 Complete Case EQ-5D-3L scores by SSI status

Variable	SSI Mean (SE)	No SSI Mean (SE)	Bootstrapped Mean difference (95% Confidence Interval)
EQ-5D-3L baseline (SSI: n= 169; No SSI: n=525)	0.7077 (0.0262)	0.7662 (0.0121)	-0.0585 (-0.1191 to -0.005)
EQ-5D-3L 5-7 days (SSI: n= 161; no SSI: n=489)	0.447 (0.0265)	0.5211 (0.0151)	-0.0741 (-0.1344 to -0.0155)
EQ-5D-3L 30 days (SSI: n= 163; No SSI: n=492)	0.5972 (0.0257)	0.7202 (0.0126)	-0.123 (-0.1836 to -0.0714)
Quality Adjusted Life Year	0.0455 (0.0019)	0.0522 (0.001)	-0.0052 (-0.0089 to -0.0013)
Quality Adjusted Life Month	0.5465 (0.023)	0.6268 (0.0117)	-0.062 (-0.108 to -0.018)

Appendix Table A6.11 Complete Case Generalised Linear Model SSI Decrement predictions

	No SSI	SSI	
	Mean (SE)	Mean (SE)	Decrement marginal effect (95% Confidence Interval)
Quality Adjusted Life Year	0.0517 (0.0009)	0.0472 (0.0017)	0.0045 (0.0007 to 0.0083)
Quality Adjusted Life Month	0.6203 (0.0112)	0.5664 (0.0207)	0.0539 (0.0079 to 0.0999)

Appendix Table A6.12 Complete Case Generalised Linear Model for QALY decrements

Variables	Coefficient	Standard Error	P-value
Age	-0.0000177	0.0000219	0.417
Female Sex	0.000764	0.000605	0.207
Male Sex (reference category)	-	-	-
Planned Stoma	0.000799	0.0007441	0.283
No Planned Stoma (reference category)	-	-	-
Current Smoker	-0.0000979	0.0007893	0.901
Not current smoker (reference category)	-	-	-
Diabetic	0.0011577	0.0007576	0.126
Not Diabetic (reference category)	-	-	-
Elective Surgery	0.0002703	0.0006053	0.655
Emergency Surgery (reference category)	-	-	-
Body Mass Index	-0.0000927	0.0000375	0.013
Surgical Site Infection	0.0015962	0.0007072	0.024
No Surgical Site Infection (reference category)	-	-	-
Contaminated-Dirty Surgery	0.0012115	0.0007845	0.123
Clean-Contaminated Surgery (reference category)	-	-	-
Baseline EQ-5D-3L	-0.0109545	0.0014116	0
Intercept	0.0191108	0.0022412	0

Appendix Table A6.13 Case Control Approach QALY by SSI Status Complete Case

Variable	No SSI	SSI	Bootstrapped mean difference
	Mean (SE)	Mean (SE)	(95% Confidence Interval)
Quality Adjusted Life Year	0.0597 (0.0022)	0.0536 (0.0033)	-0.006 (-0.0115 to -0.0002)
Quality Adjusted Life Month	0.7158 (0.0269)	0.6435 (0.0395)	-0.0724 (-0.1376 to -0.0028)

Appendix Table A6.14 Generalised Linear Model SSI total health care cost predictions (Gamma family distribution and power link function of -0.4)

	SSI	No SSI	Marginal effect
	Mean (Pooled SE)	Mean (Pooled SE)	(95% Confidence Interval)
Total Health Care Cost	£8,562 (£571)	£6,492 (£249)	£2,071 (£861 to £3,280)

Appendix Table A6.15 Generalised Linear Model for total healthcare costs (Gamma family distribution and power link function of -0.4)

Variables	Coefficient	Standard Error	P-value
Age	-0.0001217	0.0000264	0
Female Sex	0.0011838	0.0007409	0.11
Male Sex (reference category)	-	-	-
Planned Stoma	-0.0024959	0.0009749	0.01
No Planned Stoma (reference category)	-	-	-
Current Smoker	-0.0001381	0.0011435	0.904
Not current smoker (reference category)	-	-	-
Diabetic	-0.0004738	0.0008933	0.596
Not Diabetic (reference category)	-	-	-
Elective Surgery	0.0030931	0.0007983	0
Emergency Surgery (reference category)	-	-	-
Body Mass Index	0.0000243	0.0000625	0.698
Surgical Site Infection	-0.0030866	0.0008223	0
No Surgical Site Infection (reference category)	-	-	-
Contaminated-Dirty Surgery	-0.0005057	0.0008763	0.564
Clean-Contaminated Surgery (reference category)	-	-	-
Intercept	0.0358531	0.0028771	0

Appendix Table A6.16 Generalised Linear Model with Gaussian distribution predictions of QALY and QALM by SSI status

Variable	SSI Mean (Pooled SE)	No SSI Mean (Pooled SE)	Marginal Effect Decrement (95% Confidence Interval)
Quality Adjusted Life Year	0.0368 (0.0016)	0.032 (0.0009)	0.0048 (0.0013 to 0.0083)
Quality Adjusted Life Month	0.5581 (0.0189)	0.6158 (0.0107)	0.0578 (0.0158 to 0.0997)

Appendix Table A6.17 Generalised Linear Model for QALY decrements

Variables	Coefficient	Pooled Standard Error	P-value
Age	-0.014574	0.011842	0.219
Female Sex	-0.2778	0.308372	0.368
Male Sex (reference category)	-	-	-
Planned Stoma	-0.5958465	0.3620124	0.1
No Planned Stoma (reference category)	-	-	-
Current Smoker	0.0157054	0.4301861	0.971
Not current smoker (reference category)	-	-	-
Diabetic	-0.8209732	0.3859489	0.034
Not Diabetic (reference category)	-	-	-
Elective Surgery	0.0776151	0.3803269	0.838
Emergency Surgery (reference category)	-	-	-
Body Mass Index	-0.0042218	0.0215979	0.845
Surgical Site Infection	-1.150746	0.3405314	0.001
No Surgical Site Infection (reference category)	-	-	-
Contaminated-Dirty Surgery	-0.8209378	0.37201	0.027
Clean-Contaminated Surgery (reference category)	-	-	-
Baseline EQ-5D-3L	3.680118	0.4059389	0
Intercept	10.12087	1.21478	0

Appendix Table A6.18 Case Control Analysis (1:1) by SSI status

Variables	SSI	No SSI	Bootstrapped Mean difference (95% Confidence Interval)
	Mean (Pooled SE)	Mean (Pooled SE)	
Total Health Care Cost	£8,454 (£684)	£6,252 (£632)	£2,121 (£345 to £3,935)
Quality Adjusted Life Year	0.0530 (0.0024)	0.0584 (0.0032)	-0.0029 (-0.0127 to 0.0025)
Quality Adjusted Life Month	0.6366 (0.0293)	0.701 (0.0379)	-0.0349 (-0.152 to 0.0295)

Appendix Table A6.19 Model parameters

Variable	Deterministic Value	PSA Distribution	PSA parameters	Value Updated?	Source
Costs					
Cost of Wound Irrigation Intervention	£5.83	Gamma	α=44.44; λ=7.623	×	Tables 2 & 3; NICE Guideline, No. 157. Evidence review H [286]
Cost of Antimicrobial-coated Sutures Intervention	£4.37	Gamma	α=44.44; λ =10.17	×	Table 7 NICE medical technology consultation MT507 supporting documentation [287]
Additional Cost of SSI	£2,107	Normal	α = 8.766; λ = 0.0042	✓	Chapter 6 Generalised Linear Model Approach
Clinical parameters					
Wound irrigation Intervention Relative Risk	0.87 (95% CI 0.68 to 1.11)	Log-Normal	μ= -0.1393; σ= 0.1250	×	Cochrane Review [290]
Antimicrobial-coated Sutures Odds Ratio	0.72 (95% CI 0.59 to 0.88)	Log-Normal	μ= -0.3285; σ= 0.1020	×	Meta Analysis [291]
Probability of SSI within 30 days	12.27%	Beta	α=1538; β=11001	×	GlobalSurg2 [289] Table 2
Probability of death within 30 days for patients without SSI	1.50%	Beta	α=162; β=10665	×	GlobalSurg2 [289] Table 2
Probability of death within 30 days for patients with SSI	4.83%	Beta	α=73; β=1438	×	GlobalSurg2 [289] Table 2
Utilities					
No SSI health state	0.616	Beta	α = 1281.45; β= 799.41	✓	ROSSINI re-analysis Generalised Linear Model Approach
SSI health state decrement	0.056	Normal	μ= 0.0560 σ= 0.0241	✓	ROSSINI re-analysis Generalised Linear Model Approach

Appendix Table A6.20 Deterministic sensitivity analysis (DSA) scenarios

Scenario number	Description
DSA1	The additional cost and decrement of SSI was taken from the ROSSINI re-analysis cross comparison approach. The additional cost of SSI was changed to £1785, and the SSI 30 day utility decrement was changed to 0.0749. The monthly utility associated with the no SSI health state was changed to 0.6223
DSA2	The additional cost and decrement of SSI was taken from the ROSSINI re-analysis Case Control approach. The additional cost of SSI was changed to £1,555, and the SSI 30 day utility decrement was changed to 0.0421. The monthly utility associated with the no SSI health state was changed to 0.703.
SSI: Surgical Site Infection	

Appendix A6.3 Economic evaluation results updated with ROSSINI re-analysis estimates

Deterministic results

The base case point estimate results are shown in Appendix Table A6.21. Both Coated Sutures and Wound Irrigation strategies were cheaper and more effective than usual care. However, the Coated Sutures strategy dominated the Wound Irrigation strategy and was the most cost-effective strategy. Substituting in the cost and quality of life estimates of the other ROSSINI re-analysis approaches did not change the decision recommendations (Appendix Table A6.21). The Case Control approach had the highest QALYs per strategy and lowest incremental QALY differences due to the higher assumed utility of no SSI health state and the lower assumed SSI utility decrement.

Appendix Table A6.21 Base case and deterministic sensitivity analysis results

Strategy	Cost	Incremental Costs	QALY	Incremental QALY	ICER
Base case results UK setting					
Coated Sutures	£197		0.05044		Dominant
Wound irrigation	£231	£34	0.05036	-0.000083	Dominated
Usual Care	£258	£61	0.05027	-0.000169	Dominated
DSA1: Cross-Comparison estimates UK setting					
Coated Sutures	£168		0.05083		Dominant
Wound irrigation	£196	£29	0.05073	-0.000106	Dominated
Usual Care	£219	£51	0.05062	-0.000217	Dominated
DSA2: Case Control estimates UK setting					
Coated Sutures	£147		0.05774		Dominant
Wound irrigation	£172	£25	0.05768	-0.000067	Dominated
Usual Care	£191	£44	0.05761	-0.000137	Dominated
Base case results LMIC setting ($Int)					
Coated Sutures	$306		0.05044		Dominant
Wound irrigation	$358	$52	0.05036	-0.000083	Dominated
Usual Care	$401	$95	0.05027	-0.000169	Dominated
DSA1: Cross-Comparison estimates LMIC setting ($Int)					
Coated Sutures	$260		0.05083		Dominant
Wound irrigation	$304	$44	0.05073	-0.000106	Dominated
Usual Care	$340	$80	0.05062	-0.000217	Dominated
DSA2: Case Control estimates LMIC setting ($Int)					
Coated Sutures	$227		0.05774		Dominant
Wound irrigation	$266	$39	0.05768	-0.000067	Dominated
Usual Care	$296	$68	0.05761	-0.000137	Dominated
QALY: Quality Adjusted Life Year; ICER: Incremental Cost-effectiveness Ratio					

Probabilistic results

The mean PSA iterations are shown in Appendix Table A6.22 and the UK setting and Appendix Table A6.23. The mean total costs and QALYs were similar to the base case results. Coated Sutures had the lowest costs, highest QALYs and highest Net Monetary Benefit (NMB) on average based on the mean output of the 10,000 iterations.

Appendix Table A6.22 PSA results averaged across iterations

Strategy	**Cost (95% PI)**	**QALY (95% PI)**	**NMB (95% PI)**
Coated Sutures	£197 (£195 to £198)	0.05045 (0.05044 to 0.05047)	£812 (£811 to £814)
Wound Irrigation	£231 (£230 to £233)	0.05037 (0.05035 to 0.05039)	£776 (£774 to £778)
Usual Care	£257 (£255 to £259)	0.05029 (0.05027 to 0.05031)	£749 (£747 to £750)
PI: Prediction Interval; NMB: Net Monetary Benefit; QALY: Quality Adjusted Life Year			

Incremental cost-effectiveness scatterplots are shown in Appendix Figures A6.1-6.3 for the UK setting with an incremental cost-effectiveness scatterplot report for all settings reported in Appendix Table A6.24. As the costs rebasing is the only difference between the model settings, the patterns (with costs multiplied by a constant) in the scatterplots would be the same. As most of the iterations ended up in the Southeast or Northwest quadrant, the proportions of cost-effective iterations was similar across settings even with different willingness to pay thresholds.

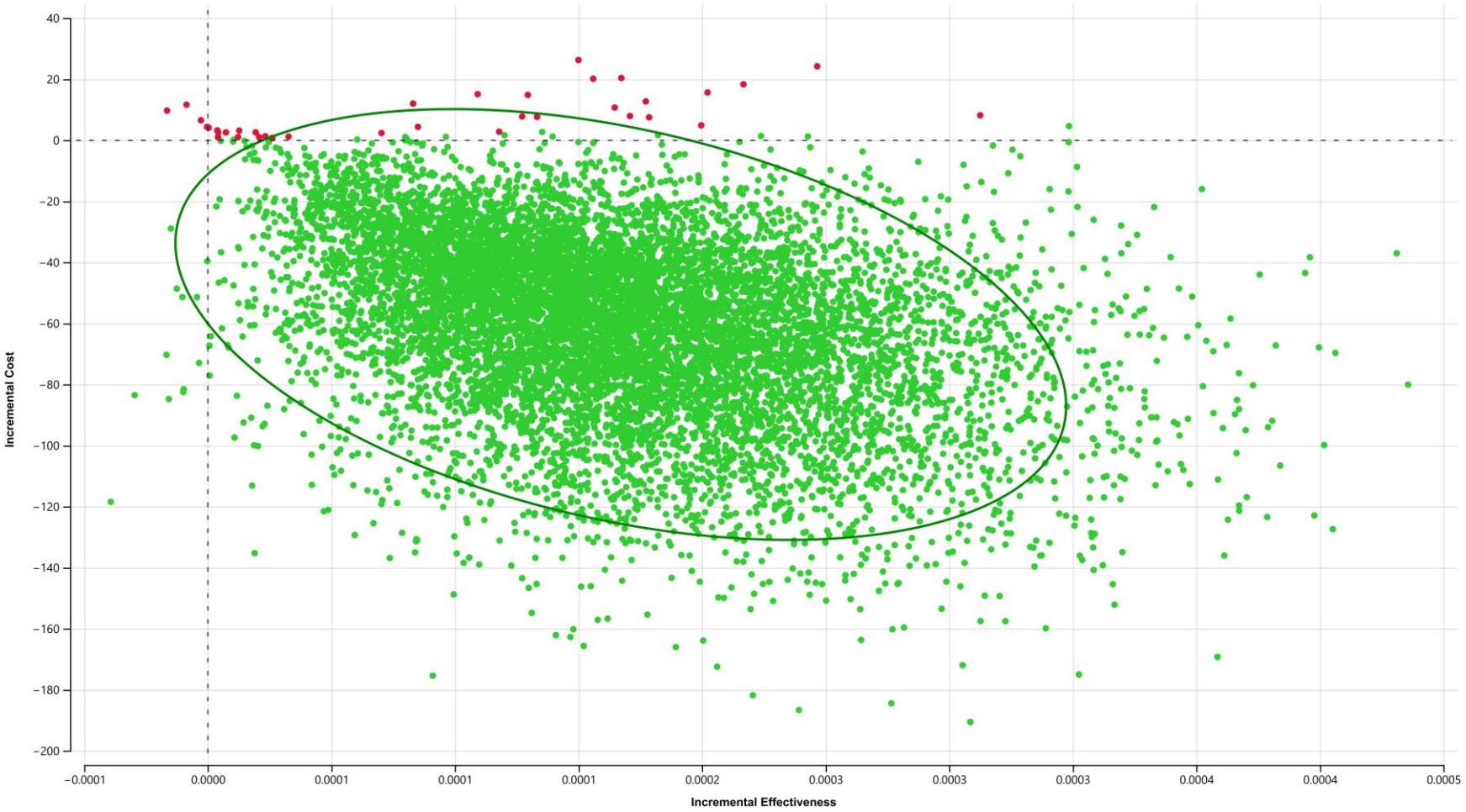
Appendix Table A6.23 Probabilistic sensitivity analysis results averaged across iterations (international dollars)

Strategy	Cost (95% PI)	QALY (95% PI)	Ghana NMB (95% PI)	India NMB (95% PI)	Mexico NMB (95% PI)
Coated Sutures	$305 ($303 to $307)	0.04474 (0.04418 to 0.0453)	-$202 (-$200 to -$204)	-$165 (-$163 to -$167)	$239 ($237 to $241)
Wound Irrigation	$358 ($356 to $361)	0.04476 (0.04419 to 0.04532)	-$255 (-$253 to -$258)	-$218 (-$216 to -$221)	$185 ($182 to $187)
Usual Care	$398 ($396 to $401)	0.04476 (0.04419 to 0.04533)	-$296 (-$293 to -$298)	-$259 (-$256 to -$261)	$144 ($141 to $146)

PI: Prediction Interval; NMB: Net Monetary Benefit; QALY: Quality Adjusted Life Year

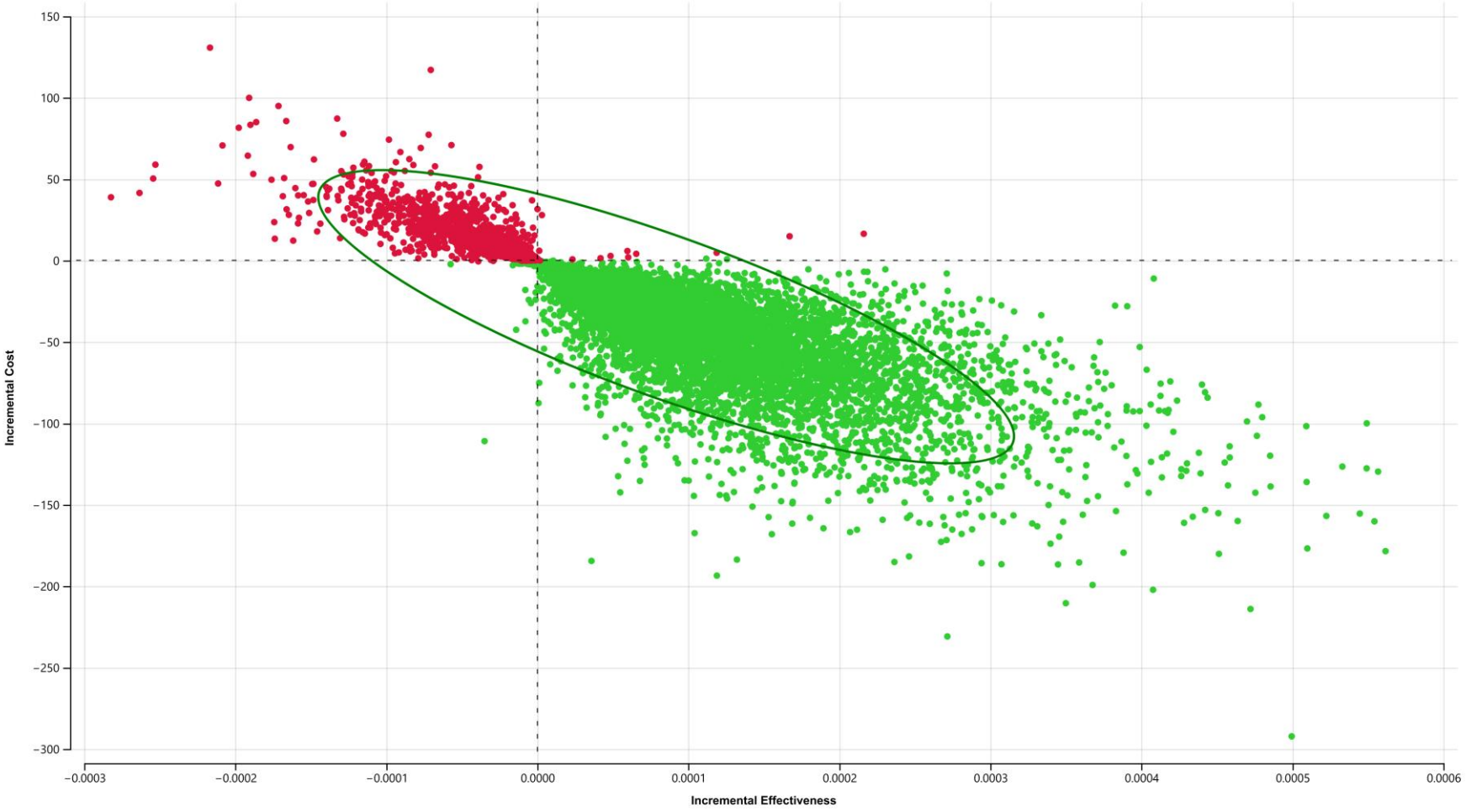
Appendix Table A6.24 Incremental cost-effectiveness report

Comparison					Country			
Coated Sutures versus Usual Care incremental cost-effectiveness					UK	Ghana	India	Mexico
COMPONENT	QUADRANT	INCREFF	INCRCOST	INCRCE	Proportion	Proportion	Proportion	Proportion
C1	IV	IE>0	IC<0	Superior	99.4%	99.4%	99.4%	99.4%
C2	I	IE>0	IC>0	ICER <threshold	0.1%	0.0%	0.0%	0.0%
C3	III	IE<0	IC<0	ICER> threshold	0.1%	0.1%	0.1%	0.1%
C4	I	IE>0	IC>0	ICER> threshold	0.3%	0.4%	0.4%	0.4%
C5	III	IE<0	IC<0	ICER<threshold	0.0%	0.0%	0.0%	0.0%
C6	II	IE<0	IC>0	Inferior	0.0%	0.0%	0.0%	0.0%
Coated Sutures versus Wound Irrigation incremental cost-effectiveness								
C1	IV	IE>0	IC<0	Superior	84.2%	84.2%	84.2%	84.2%
C2	I	IE>0	IC>0	ICER<threshold	0.0%	0.0%	0.0%	0.0%
C3	III	IE<0	IC<0	ICER> threshold	1.2%	1.2%	1.2%	1.2%
C4	I	IE>0	IC>0	ICER> threshold	0.2%	0.2%	0.2%	0.2%
C5	III	IE<0	IC<0	ICER<threshold	0.1%	0.0%	0.0%	0.0%
C6	II	IE<0	IC>0	Inferior	14.4%	14.4%	14.4%	14.4%
Wound Irrigation versus Usual Care incremental cost-effectiveness								
C1	IV	IE>0	IC<0	Superior	81.1%	81.1%	81.1%	81.1%
C2	I	IE>0	IC>0	ICER<threshold	0.5%	0.0%	0.1%	0.2%
C3	III	IE<0	IC<0	ICER> threshold	0.1%	0.1%	0.1%	0.1%
C4	I	IE>0	IC>0	ICER> threshold	4.9%	5.4%	5.3%	5.2%
C5	III	IE<0	IC<0	ICER<threshold	0.0%	0.0%	0.0%	0.0%
C6	II	IE<0	IC>0	Inferior	13.4%	13.4%	13.4%	13.4%
INCREFF: Incremental effectiveness; INCRCOST: Incremental cost; INCRCE: Incremental cost-effectiveness; ICER: Incremental Cost-effectiveness ratio								

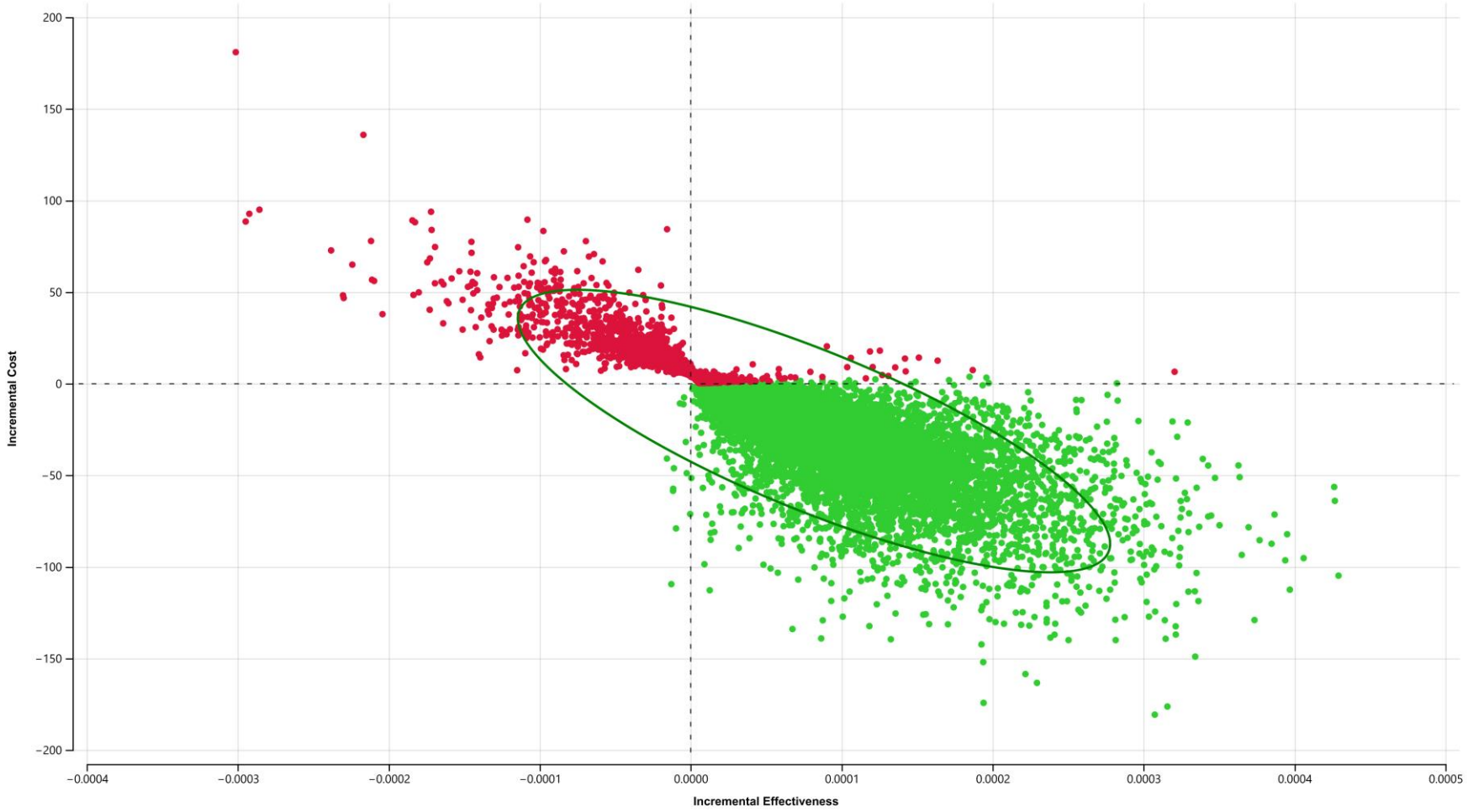


Appendix Figure A6.1 Coated Sutures versus Usual Care incremental cost-effectiveness scatterplot

Appendix Figure A6.2 Wound Irrigation versus Usual Care incremental cost-effectiveness scatterplot



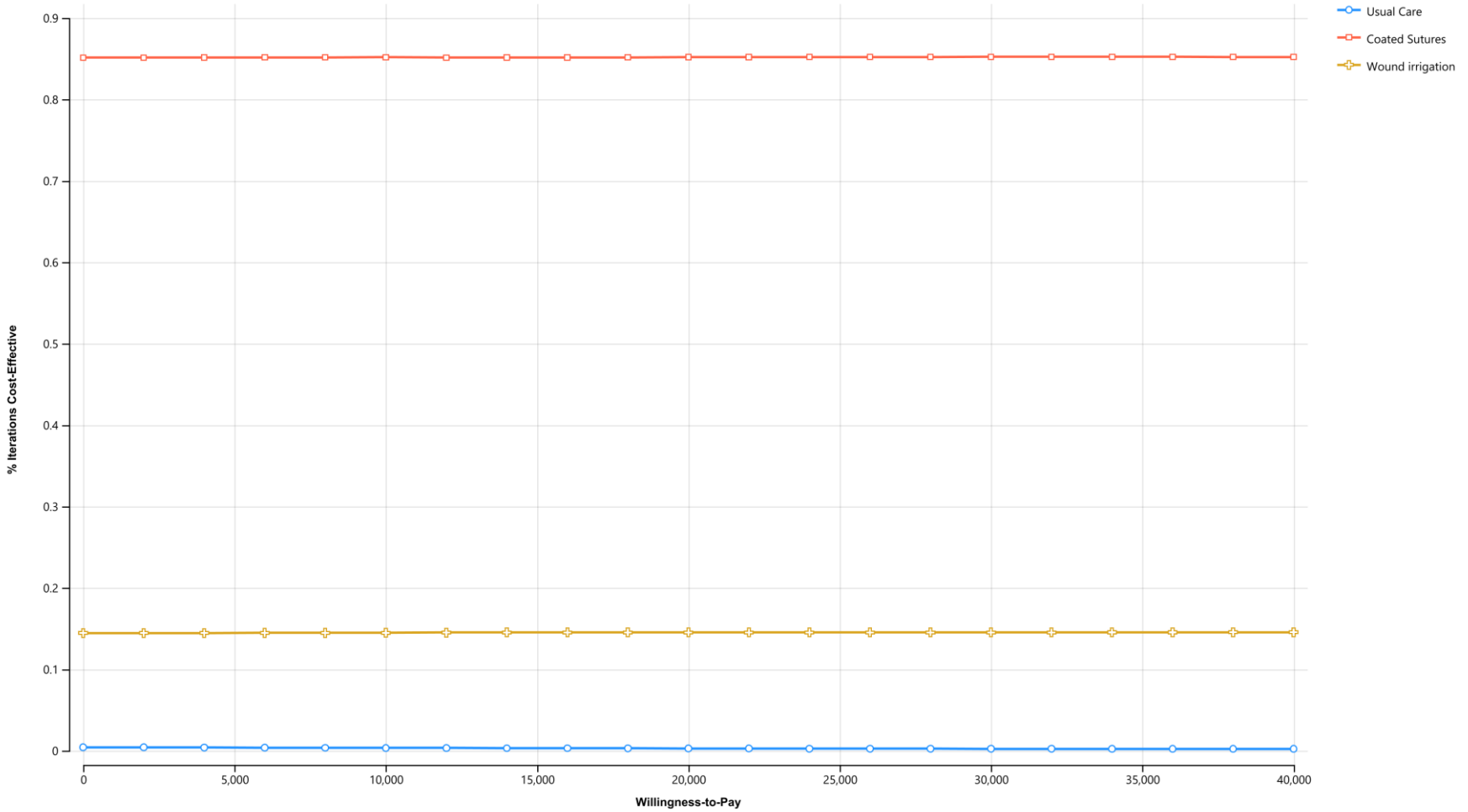
Appendix Figure A6.3 Coated Sutures versus Wound Irrigation incremental cost-effectiveness scatterplot



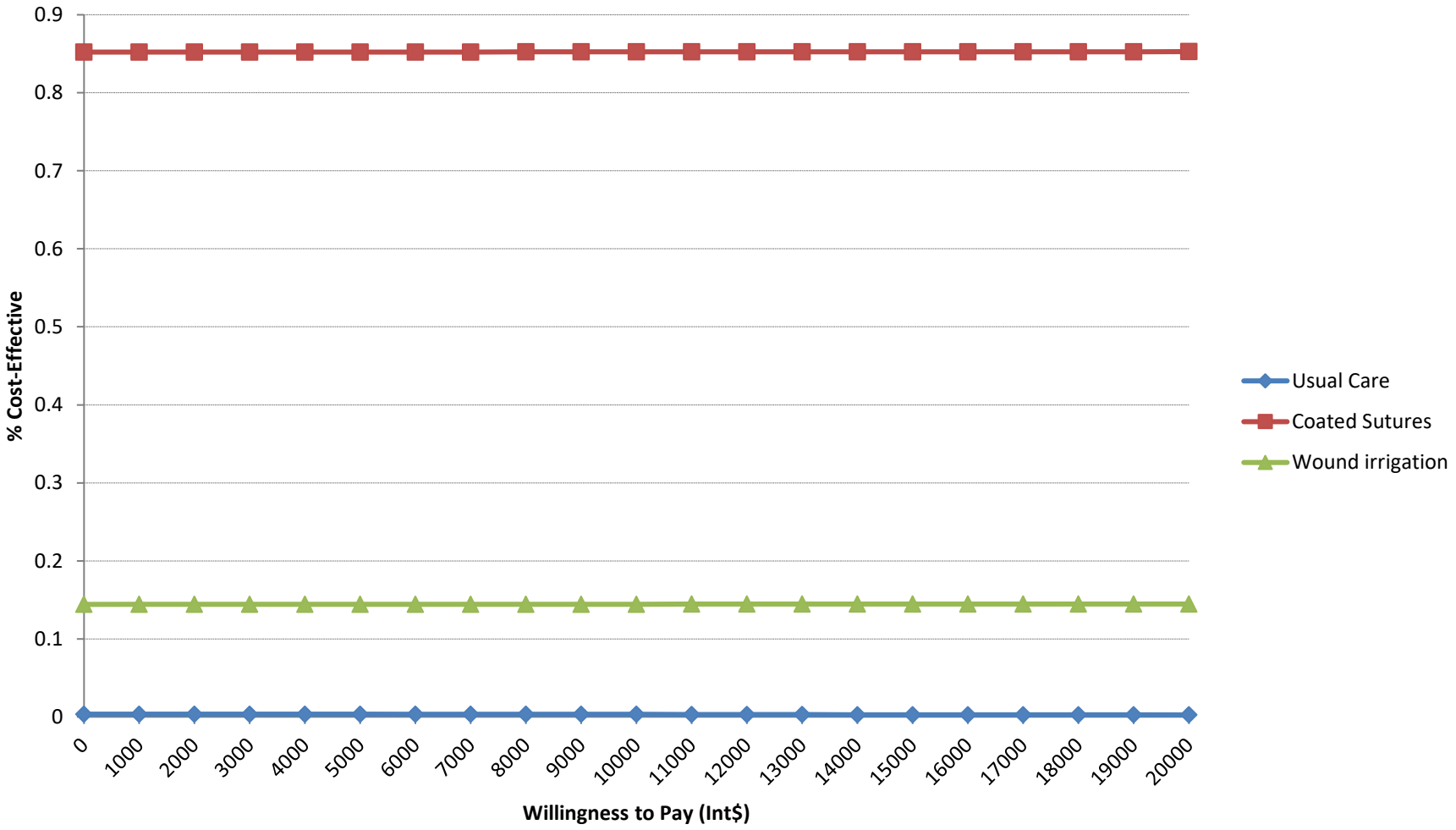
For Coated Sutures versus Usual Care (Appendix Figure A6.1), 99.4% of the iterations were in the southeast quadrant indicating that Coated Sutures was cheaper and more effective compared to Usual Care.The incremental cost-effectiveness scatterplot of Wound Irrigation versus Usual Care is shown in Appendix Figure A6.2. With Wound Irrigation having a non-significant difference in SSI compared to Usual Care, there were instances of the relative risk being above 1 versus Usual Care in the PSA that resulted in more SSIs making Wound Irrigation more expensive and less effective than Usual Care. 84.2% of the PSA iterations resided in the Southeast Quadrant suggesting that Wound Irrigation dominated Usual Care while 14.4% of the PSA iterations resided in the Northwest Quadrant suggesting that Wound Irrigation was dominated by Usual Care. For the 0.1% of the PSA iterations that resided in the Northeast Quadrant, all of these iterations would be considered not cost-effective.

The incremental cost-effectiveness scatterplot of Coated Sutures versus Wound Irrigation is shown in Appendix Figure A6.3. With the two SSI-reducing interventions, 81.1% of PSA iterations reside in the southeast quadrant, indicating that Coated Sutures was cheaper and more effective compared to Wound Irrigation. 14.4% of PSA iterations were in the northwest quadrant indicating that Coated Sutures was more expensive and less effective compared to Wound Irrigation. This generally happened when the treatment effectiveness for a given PSA iteration was larger for Wound Irrigation than it was for Coated Sutures.

The PSA iterations were quantified into a CEAC in Appendix Figure A6.4 for the UK setting and Appendix Figure A6.5 for the LMIC setting. Coated Sutures was the most cost-effective strategy across all settings respective cost-effectiveness thresholds. The proportions varied little across the range of WTP thresholds. The Wound Irrigation strategy was a distant second with it being the most cost effective strategy with Usual Care coming last.



Appendix Figure A6.4 Cost-effectiveness acceptability curve (UK setting)



Appendix Figure A6.5 Cost-effectiveness acceptability curve (LMIC setting)

Value of Information Analysis

The expected value of perfect information (EVPI) is shown in Appendix Table A6.24. At a WTP threshold of zero per QALY, the population EVPIs for India, Mexico, and Ghana were $50,051,757, $771,607, and $160,559, respectively. The expected value of perfect parameter information (EVPPI) results for selected groups of parameters is shown in Appendix Table A6.25. EVPPI for treatment effectiveness commanded most of the value of reducing uncertainty, and increased as the WTP threshold increases. With this current iteration of the model , there is now some value to reduce decision uncertainty for SSI costs and utilities for all settings even when WTP threshold is set to zero per QALY.

Appendix Table A6.25 Population expected value of perfect information

Willingness to pay threshold	Per patient EVPI	India population EVPI	Mexico population EVPI	Ghana population EVPI
$0	$3.75	$50,051,757	$771,607	$160,559
$1,000	$3.75	$50,134,219	$772,878	$160,824
$2,000	$3.76	$50,216,757	$774,151	$161,089
$3,000	$3.77	$50,299,397	$775,425	$161,354
$4,000	$3.77	$50,382,178	$776,701	$161,619
$5,000	$3.78	$50,465,089	$777,979	$161,885
$6,000	$3.78	$50,548,158	$779,260	$162,152
$7,000	$3.79	$50,631,520	$780,545	$162,419
$8,000	$3.80	$50,714,992	$781,832	$162,687
$9,000	$3.80	$50,798,625	$783,121	$162,955
$10,000	$3.81	$50,882,332	$784,411	$163,224
$11,000	$3.82	$50,966,156	$785,704	$163,493
$12,000	$3.82	$51,050,054	$786,997	$163,762
$13,000	$3.83	$51,134,049	$788,292	$164,031
$14,000	$3.83	$51,218,129	$789,588	$164,301
$15,000	$3.84	$51,302,296	$790,886	$164,571
$16,000	$3.85	$51,386,529	$792,184	$164,841
$17,000	$3.85	$51,470,876	$793,484	$165,112
$18,000	$3.86	$51,555,357	$794,787	$165,383
$19,000	$3.87	$51,639,896	$796,090	$165,654
$20,000	$3.87	$51,724,459	$797,394	$165,925
EVPI: expected value of perfect information				

Appendix Table A6.26 Expected value of perfect parameter information (per patient)

Willingness to pay threshold (Int $)	Treatment effectiveness parameters (Int $)	SSI decrements parameters (Int $)	SSI cost parameters (Int $)
$0	$3.62	$0.02	$0.02
$1,000	$3.63	$0.02	$0.02
$2,000	$3.63	$0.02	$0.02
$3,000	$3.64	$0.02	$0.02
$4,000	$3.64	$0.02	$0.02
$5,000	$3.65	$0.02	$0.02
$6,000	$3.66	$0.02	$0.02
$7,000	$3.66	$0.02	$0.02
$8,000	$3.67	$0.02	$0.02
$9,000	$3.68	$0.02	$0.02
$10,000	$3.68	$0.02	$0.02
$11,000	$3.69	$0.02	$0.02
$12,000	$3.70	$0.02	$0.02
$13,000	$3.70	$0.02	$0.02
$14,000	$3.71	$0.01	$0.01
$15,000	$3.72	$0.01	$0.01
$16,000	$3.72	$0.01	$0.01
$17,000	$3.73	$0.01	$0.01
$18,000	$3.74	$0.01	$0.01
$19,000	$3.74	$0.01	$0.01
$20,000	$3.75	$0.01	$0.01

Chapter 7 Appendix

Appendix A7.1 KIWI CRFs

FALCON Hospital Resource Use Form

(To be completed at discharge by doctor, research nurse, or translator)

	FALCON Trial Number	
	Centre name	
	Patient Name	
Date today	d d m m y y y y	
After surgery, and during the patient's inpatient stay:		
Were any antibiotics prescribed for treating a suspected wound infection?	☐ Yes	☐ No
	If yes, how many days? _____days	
During the inpatient stay, how many of the following were performed?		
Wound dressings changes	_____changes	
Full Blood Count results	_____results	
Urea and Electrolytes results	_____results	
Liver Function Test results	_____results	
C-reactive Protein results	_____results	
Microbiology (Wound Swab) results	_____results	
Was imaging used to diagnose suspected SSI?	☐ Yes, CT Scan ☐ Yes, Ultrasound Scan	☐ No
Was the patient discharged with:		
Pain killer medications	☐ Yes	☐ No
Antibiotics for a wound infection	☐ Yes	☐ No
Wound dressings	☐ Yes	☐ No
Form completed by		
Print full name		
Signature and date form completed	d d m m y y y y	

FALCON Post-Discharge Resource Use Form

(To be completed by doctor, research nurse, or translator at 30 day, 45 day and 60 day follow-up – 45 day Follow-up and 60 day follow-up are telephone based and for patients with an ongoing wound infection

please ask the patient each of the following questions)

What follow-up form is being completed?	☐ 30 day	☐ 45 day	☐ 60 day
	FALCON Trial Number		
	Centre ID number		
	Patient Name	_____	
Date today	d d m m y y y y		
Does the patient have an ongoing wound infection	☐ Yes	☐ No	
Has the patient been discharged	☐ Yes	☐ No	
If the patient has not been discharged, skip to Form completed by Section			
Section 1: Since we last contacted you, have you visited			
The hospital	☐ Yes	☐ No	
If patient has not visited the hospital, skip to section 2			
(i) Did you attend the hospital	☐ On your own	☐ With a companion	
(ii) In total, how much did getting there cost?	for patient: _____	for companion: _____	
(iii) Did you lose income in order to attend?	☐ Yes	☐ No	
	If yes, how much income? _____		
(iv) Did your companion lose income in order to attend?	☐ Yes	☐ No	☐ Not applicable
	If yes, how much income? _____		

FALCON Resource Usage Form, page 2	FALCON Trial Number						
	Centre Name						
(v) How much did the hospital visit charge you?	please insert value: _____						
Section 2: Since we last contacted you, you visited a community doctor							
Community doctor	☐ Yes			☐ No			
If patient has not visited a community doctor, skip to section 3							
(i) Did you attend	☐ On your own			☐ With a companion			
(ii) In total, how much did getting there cost?	for patient: _____			for companion: _____			
(iii) Did you lose income in order to attend?	☐ Yes			☐ No			
	If yes, how much income? _____						
(iv) Did your companion lose income in order to attend	☐ Yes	☐ No	☐ Not applicable				
	If yes, how much income? _____						
(v) How much did the consultation charge you?	please insert value: _____						
Section 3: Since we last contacted you, have you visited a nurse or other community health worker							
Nurse or other community worker	☐ Yes			☐ No			
If patient has not visited a nurse or other community health worker, skip to section 4							
(i) Did you attend	☐ On your own			☐ With a companion			

FALCON Resource Usage Form, page 3	FALCON Trial Number						
	Centre Name						
(ii) Typically, how much did getting there cost?	for patient: _____	for companion: _____					
(iii) Did you lose income in order to attend?	☐ Yes	☐ No					
	If yes, how much income? _____						
(iv) Did your companion lose income in order to attend?	☐ Yes	☐ No	☐ Not applicable				
	If yes, how much income? _____						
(v)How much did the consultation charge you?	please insert value: _____						
Section 4: Since we last contacted you, have you visited at home by a health care worker							
Health care worker home visit	☐ Yes	☐ No					
If yes, how much did the consultation charge you?	please insert value: _____						
Section 5: Since we last contacted you, have you purchased any wound dressings and/or medication							
Wound dressings and medications	☐ Yes	☐ No					
	If yes, how much did it cost? _____						
Form completed by							
Print full name							
Signature		Date form completed	d	d	m	m	y	y	y	y

Appendix Table A7.1 Generalised linear model goodness of fit

Family distribution	Link function	Akaike information criterion (AIC)
Gaussian	identity	4937.818
Gaussian	log	4924.221
Gamma	log	4493.796

Appendix Table A7.2 Indication for surgery

Indication for Surgery	Frequency	Percent
Malignant disease	29	8.66%
Benign disease	171	51.04%
Trauma	5	1.49%
Obstetric	129	38.51%
Missing	1	0.30%

Appendix Table A7.4 Main abdominal operation performed

Main Abdominal operation performed	Clean-Contaminated				Contaminated-Dirty			
	Mexico		India		Ghana		India	
	No SSI	SSI	No SSI	SSI	No SSI	SSI	No SSI	SSI
Abdominoperineal resection	0	0	0	0	1	1	0	0
Abscess drainage	0	0	0	0	1	0	0	0
Anastomosis	4	0	2	1	3	1	0	1
Anterior Resection	0	0	2	1	0	0	0	1
Appendicectomy	1	0	0	0	24	4	2	1
Caesearean section	50	1	68	4	0	0	1	1
Cholecystectomy	12	0	0	0	1	0	2	1
Colectomy	0	0	0	1	4	0	2	1
Colostomy	0	0	1	1	1	0	3	1
Femoral Hernia repair	0	0	0	0	1	0	0	0
Gastrectomy	1	0	0	0	0	0	0	0
Gastric perforation repair	0	0	2	0	18	7	1	3
Hartmanns procedure	0	0	1	0	0	1	2	0
Hemicolectomy	0	0	2	0	1	1	1	0
Hysterectomy	11	0	3	1	0	0	0	0
Ileal conduit	0	0	0	1	0	0	0	0
Ileostomy	0	0	1	0	0	1	1	2
Inguinal hernia repair	0	0	0	0	5	0	0	0
Laparotomy	2	0	5	0	20	3	10	6
Necrosectomy	0	0	0	0	0	0	0	0
Nephrectomy	1	0	0	1	0	0	0	0
Pancreaticoduodenectomy	1	0	0	0	0	0	0	1
Umbilical Hernia repair	0	0	0	0	1	1	2	0

Appendix Table A7.5 Postoperative costs of Contaminated-Dirty cases in Mexico and Nigeria

	Mexico		Nigeria	
	No SSI	SSI	No SSI	SSI
Sample size	1	1	2	2
Postoperative inpatient costs, Mean (SE)	€245 (-)	€164 (-)	€419 (€151)	€838 (€53)
Post-discharge healthcare resource use, Mean (SE)	€79 (-)	0 (-)	€76 (€37)	€77 (€4)
Total postoperative healthcare costs, Mean (SE)	€324 (-)	€164 (-)	€495 (€114)	€915 (€57)
Travel and income loss, Mean (SE)	0 (-)	0 (-)	€372 (€372)	0 (0)
Societal costs, Mean (SE)	€324 (-)	€164 (-)	€867 (€258)	€915 (€57)

Chapter 8 Appendix

Appendix A8.1 Participant information sheet

AVOCET Study: A valuation of Postoperative Complication Health States



Participant Information Sheet

We would like to invite you to take part in a research study. Before you decide, we will explain why the research is being done and what it will involve for you. Please take the time to read this information carefully. You may ask questions about anything you do not understand or want to know more about.

What is the purpose of this study?

We want to know how people feel about the idea of having wound problems after surgery on the tummy (abdomen). Wound problems are the most common complication after surgery and they can have different impacts on someone's quality of life. We will test different methods for assessing your views of having a wound problem. We will measure and assess your preferences by asking you to choose between different wound problem health state descriptions. The health state descriptions of wound problem will be text based with an option of including photographs of the health states. Please be advised that both the text based and photograph based health state descriptions are graphic in nature. In case of any distress, the researcher will pause the interview and ask if you would like to continue. You can stop participating in the interview at any time without needing to give a reason.

Why is this research important?

Decision makers have to make choices on health spending to improve population health. As health budgets are limited, understanding people's preferences on different health conditions can help inform decisions on where the budget would be best spent. One area where information on people's preferences is currently lacking is in the area of wound problems after surgery on the tummy.

What will I be asked to do?

You will be invited to take part in a remote interview (Zoom or Microsoft Teams) with a researcher at the University of Birmingham. During the interview, you will be asked to complete an exercise to help-value the health impact of different wound problems. The exercise was tested beforehand to make sure the questions are easy enough to understand and answer. You will also be asked to answer some basic questions about yourself to help with the analysis.

At the interview we will remind you about the details of the project and ask you to confirm with the consent form stating that you are happy to take part.
The interview exercise is split into four sections:

A few questions about yourself
First, we will ask you a few questions about yourself, simply to help with the analysis.

1) Rating scale
You will be asked to rate each of the health state descriptions on a scale from 0 to 100 and a generic health-related quality of life measure (EQ-5D-5L)

2) A health trade off exercise
We will ask you to choose between different health states by varying the length of life for each of the descriptions, one at a time.

3) Health state photographs
Lastly, you will be asked if you want to see photographs that are representative of each of the health states. This is an optional aspect of the interview. If you choose to see a photograph of a health state, you will be asked if you believe that this would have affected your response in the health trade off exercise.

How long will the study last?

It will be a one-off questionnaire lasting for approximately 50 to 60 minutes.

Do I have to take part?

It is up to you to decide whether to take part or not. You will be given time to go through this information leaflet and the opportunity to ask questions. Your participation in this research is voluntary. If you choose to take part, you will still be free to withdraw (quit) up to two weeks after your interview without needing to give a reason.

If you begin participating, you can also stop at any time without needing to give a reason.

What do I receive for taking part?

When you complete the questionnaire, you will be offered an online £15 shopping voucher.

Who is funding the study?

The study is being funded by the University of Birmingham.

Where can I get further information?

If you would like more information about the project, please contact the researcher;
Mark Monahan (Research Fellow), m.monahan.1@bham.ac.uk (0121 414 3197)
Health Economics Unit, Institute of Applied Health Research, University of Birmingham

Appendix A8.2 Health state photographs and sources

Health State A photographs



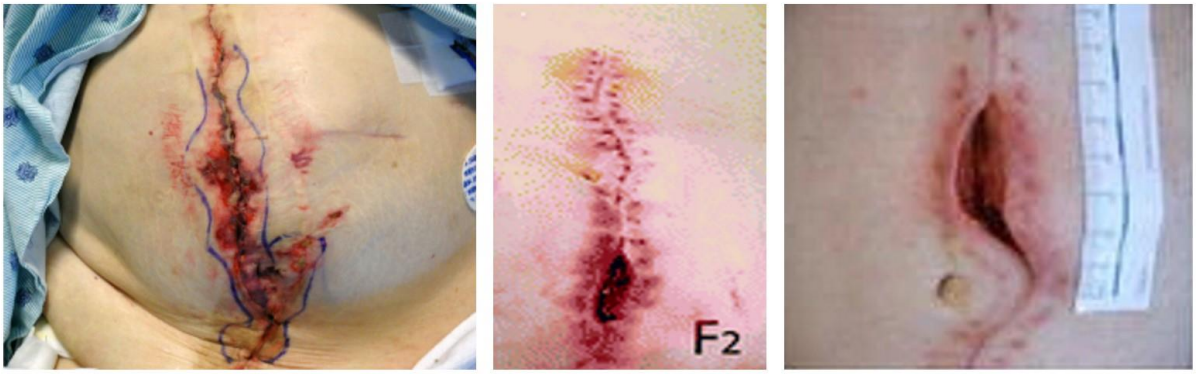
Photograph sources: Left panel, ROSSINI-2 training material; Middle panel, Shutterstock Standard License; Right panel, Shutterstock Standard License

Health State B photographs



Photograph sources: Left panel, Shutterstock Standard License; Middle panel, Shutterstock Standard License; Right panel, ROSSINI-2 training material

Health State C photographs



Photograph sources: Left panel, Figure 1 from [493]; Middle panel, Figure 1 from [47]; Right panel, Figure 1 from [494]

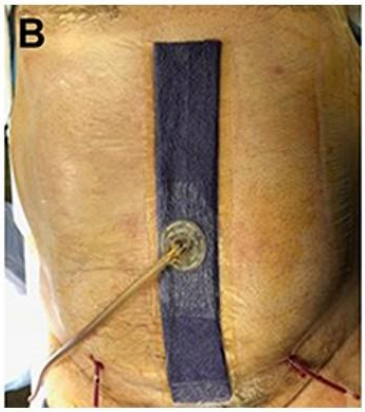
Health State D photographs



Photograph sources: Left panel, Shutterstock Standard License; Middle panel, Shutterstock Standard License; Right panel, Figure 4A from [495]

Health State E photographs





Photograph sources: Left panel, Figure 2 from [493]; Middle panel, Figure 3 from [496]; Right panel, Figure 3B from [497]

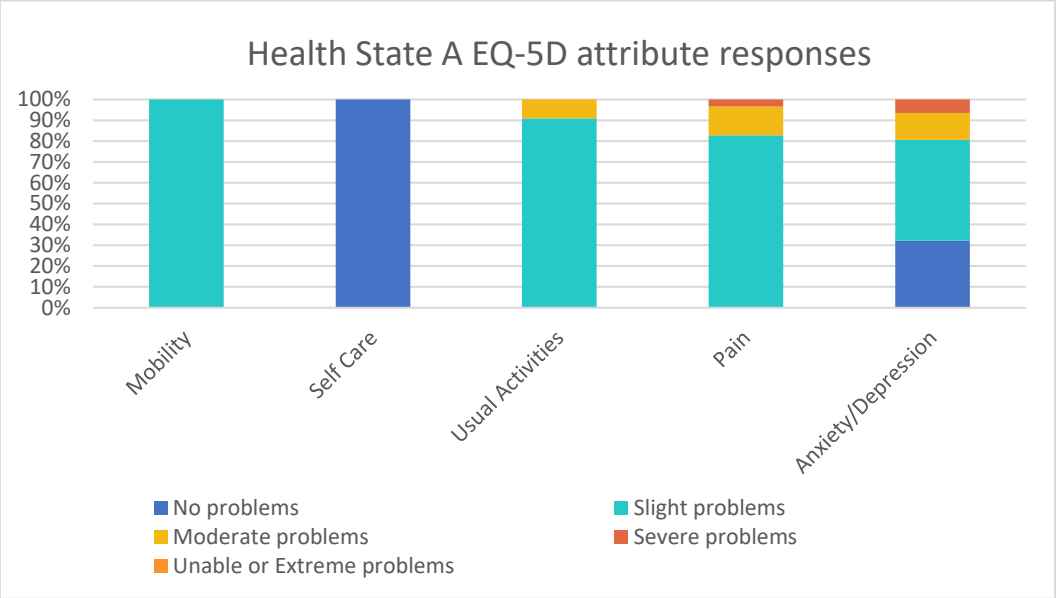
Health State F photographs

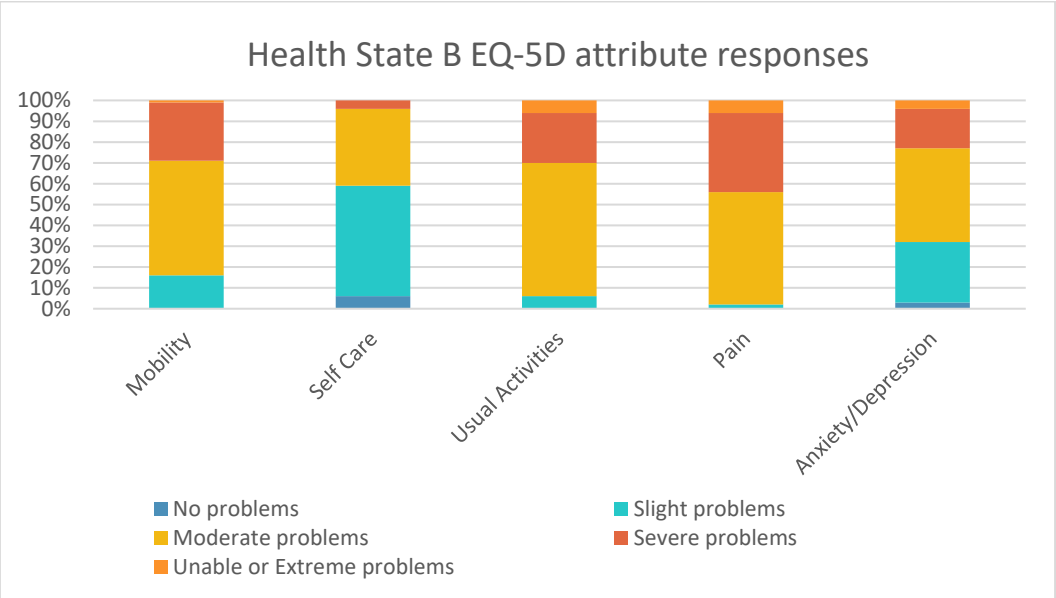


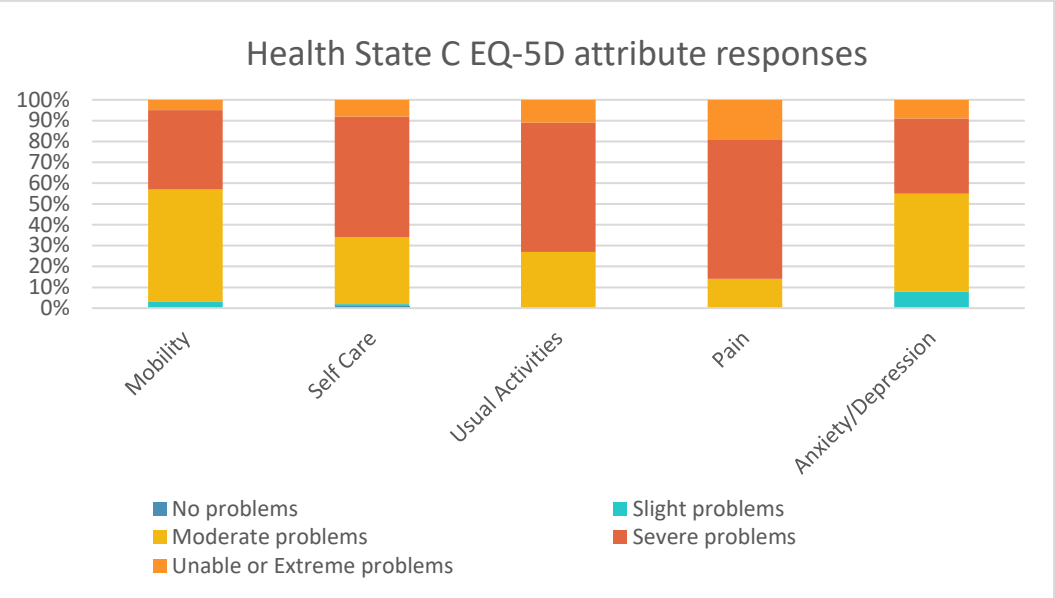


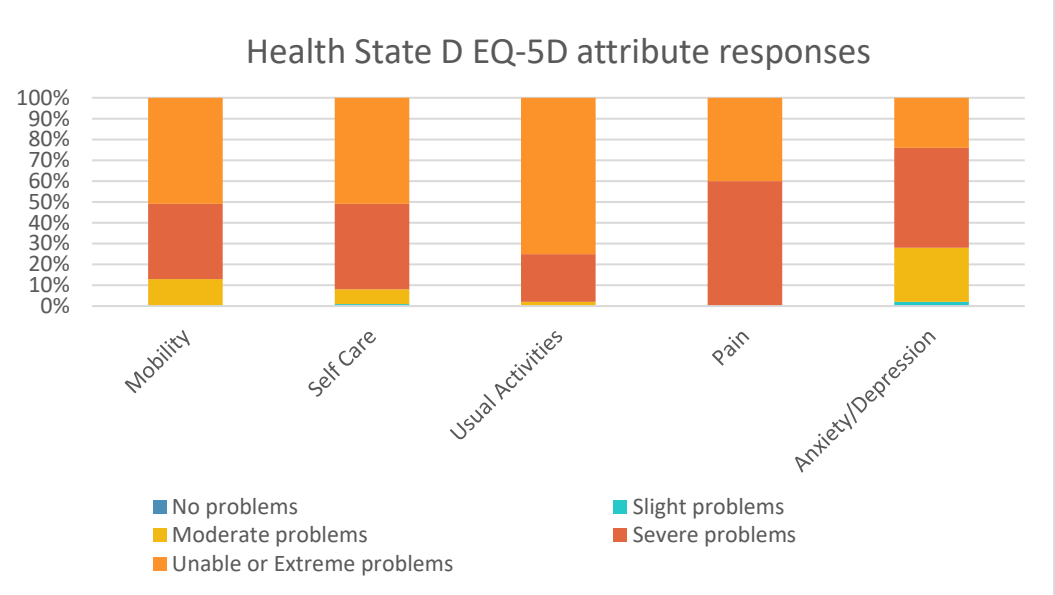
Photograph sources: Left panel, Shutterstock Standard License; Middle panel, Figure 1 from [498]; Right panel, Figure 6 from [499]

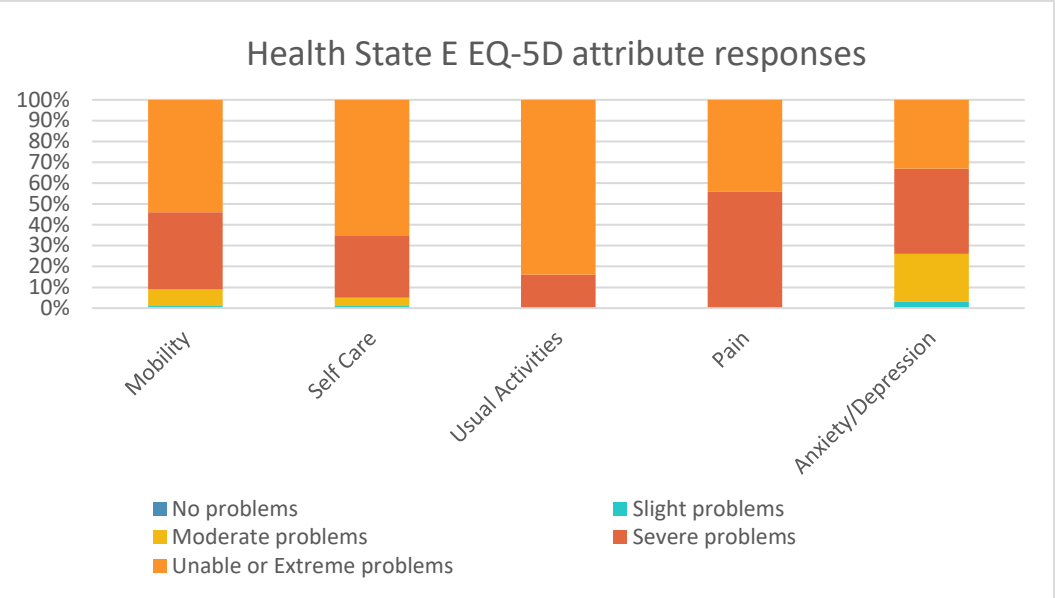
Appendix A8.3 EQ-5D response distributions by attribute

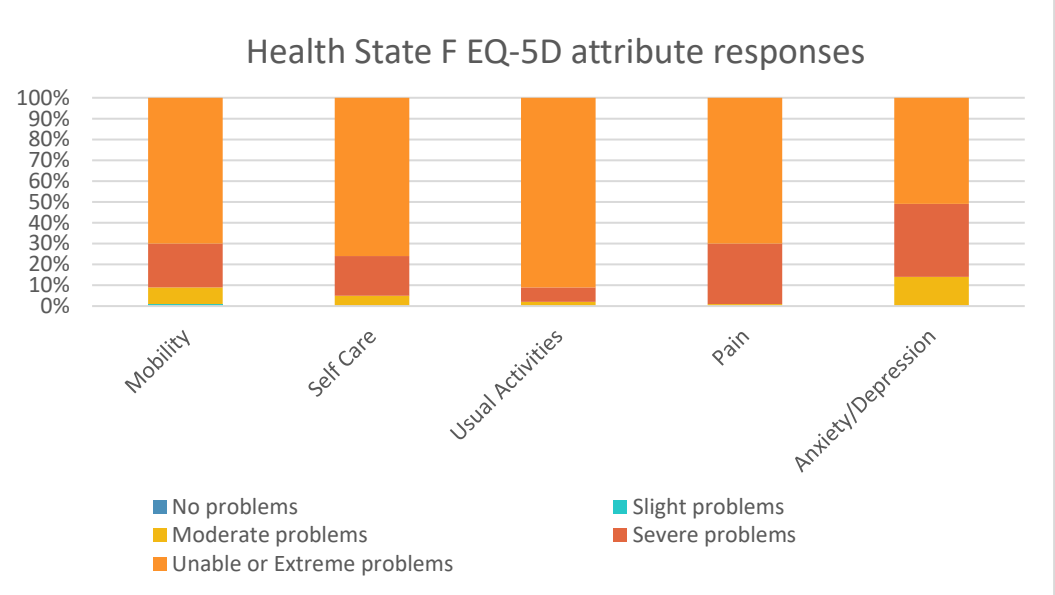





Health State C EQ-5D attribute responses
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Mobility
Self Care
Usual Activities
Pain
Anxiety/Depression
No problems
Slight problems
Moderate problems
Severe problems
Unable or Extreme problems


Health State D EQ-5D attribute responses
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Mobility
Self Care
Usual Activities
Pain
Anxiety/Depression
No problems
Slight problems
Moderate problems
Severe problems
Unable or Extreme problems


Health State E EQ-5D attribute responses
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Mobility
Self Care
Usual Activities
Pain
Anxiety/Depression
No problems
Slight problems
Moderate problems
Severe problems
Unable or Extreme problems


Health State F EQ-5D attribute responses
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Mobility
Self Care
Usual Activities
Pain
Anxiety/Depression
No problems
Slight problems
Moderate problems
Severe problems
Unable or Extreme problems

Appendix Table A8.1 Paired t tests for equality of disutility means by technique

Variable	Mean Difference	P-value	95% Confidence Interval
EQ-5D-5L versus Visual Analogue Scale			
Mild SSI disutility (Health State B- Health State A)	-0.0848	0.0000	-0.1185 to -0.0509
Moderate SSI disutility (Health State C- Health State A)	-0.2102	0.0000	-0.2474 to -0.1731
Severe SSI disutility (Health State D- Health State A)	-0.4631	0.0000	-0.5070 to -0.4192
Severe SSI plus vacuum dressing disutility (Health State E- Health State A)	-0.4751	0.0000	-0.5202 to -0.4299
Severe SSI plus bowel coming through disutility (Health State F- Health State A)	-0.5281	0.0000	-0.5731 to -0.4831
Time-Trade Off versus EQ-5D-5L			
Mild SSI disutility (Health State B- Health State A)	0.1037	0.0000	0.0604 to 0.1469
Moderate SSI disutility (Health State C- Health State A)	0.2059	0.0000	0.1535 to 0.2582
Severe SSI disutility (Health State D- Health State A)	0.4479	0.0000	0.3950 to 0.5008
Severe SSI plus vacuum dressing disutility (Health State E- Health State A)	0.4358	0.0000	0.3793 to 0.4922
Severe SSI plus bowel coming through disutility (Health State F- Health State A)	0.4406	0.0000	0.3809 to 0.5003
Time Trade Off versus Visual Analogue Scale			
Mild SSI disutility (Health State B- Health State A)	0.0190	0.1076	-0.0042 to 0.0422
Moderate SSI disutility (Health State C- Health State A)	-0.0044	0.8020	-0.0387 to 0.0300
Severe SSI disutility (Health State D- Health State A)	-0.0152	0.3967	-0.0507 to 0.0203
Severe SSI plus vacuum dressing disutility (Health State E- Health State A)	-0.0393	0.0577	-0.0799 to 0.0013
Severe SSI plus bowel coming through disutility (Health State F- Health State A)	-0.0874	0.0002	-0.1323 to -0.0426

Appendix Table A8.2 Generalised Linear Model Regressions

Dependent Variable (Family) [Power Link Function]	***Health State A Time Trade Off Decrement (Poisson) [-1.9]***			***Health State B Time Trade Off Decrement (Poisson) [-2]***			***Health State C Time Trade Off Score (Gaussian) [2]***		
	Coefficient	**Standard Error**	**P-value**	**Coefficient**	**Standard Error**	**P-value**	**Coefficient**	**Standard Error**	**P-value**
Age group 25 years and above	2.039	6.632	0.758	0.191	2.722	0.944	0.034	0.087	0.697
Age group below 25 years (Reference Category)	-	-	-	-	-	-	-	-	-
Male gender	-1.138	4.177	0.785	-0.445	1.716	0.795	-0.024	0.041	0.565
Female gender (Reference Category)	-	-	-	-	-	-	-	-	-
Surgical Experience	5.07	3.801	0.785	2.985	1.431	**0.037**	-0.087	0.04	**0.029**
No Surgical Experience (Reference Category)	-	-	-	-	-	-	-	-	-
Undergraduate Degree	4.101	3.168	0.196	0.492	2.024	0.808	0.045	0.088	0.614
Postgraduate Degree (Reference Category)	-	-	-	-	-	-	-	-	-
Asian or Asian British Ethnicity	-6.602	3.887	0.089	-4.01	1.414	**0.005**	0.1	0.049	**0.042**
Black/African/Caribbean/ Black British Ethnicity	-6.631	6.729	0.324	-2.839	2.286	0.214	0.026	0.052	0.616
Other ethnic group	-4.95	5.914	0.403	-1.966	2.042	0.336	0.059	0.064	0.357
White Ethnicity (Reference Category)	-	-	-	-	-	-	-	-	-
Interview Duration in minutes	0.322	0.373	0.388	0.187	0.127	0.141	-0.002	0.003	0.551
Own EQ-5D-5L score	0.471	18.321	0.979	3.627	6.193	0.558	-0.116	0.188	0.537
Intercept	1.74	18.474	0.925	-1.174	5.853	0.841	0.377	0.242	0.12

Dependent Variable (Family) [Power Link Function]	***Health State D Time Trade Off (Poisson) [2]***			***Health State E Time Trade Off (Gaussian) [-2]***			***Health State F Time Trade Off Score (Gamma) [-1.9]***		
	Coefficient	**Standard Error**	**P-value**	**Coefficient**	**Standard Error**	**P-value**	**Coefficient**	**Standard Error**	**P-value**
Age group 25 years and above	-0.023	0.08	0.774	3.156	2.246	0.16	2.172	6.443	0.736
Age group below 25 years (Reference Category)	-	-	-	-	-	-	-	-	-
Male gender	0.003	0.04	0.941	-0.292	2.218	0.895	3.267	4.47	0.465
Female gender (Reference Category)	-	-	-	-	-	-	-	-	-
Surgical Experience	0.081	0.032	0.941	-4.548	2.406	0.059	-8.505	4.865	0.08
No Surgical Experience (Reference Category)	-	-	-	-	-	-	-	-	-
Undergraduate Degree	-0.032	0.071	0.654	2.629	1.405	0.061	0.529	5.585	0.925
Postgraduate Degree (Reference Category)	-	-	-	-	-	-	-	-	-
Asian or Asian British Ethnicity	-0.088	0.04	**0.028**	3.398	2.311	0.141	4.215	5.281	0.425
Black/African/Caribbean/ Black British Ethnicity	-0.03	0.055	0.587	-0.707	2.358	0.764	-4.857	4.155	0.242
Other ethnic group	-0.032	0.072	0.659	1.962	4.935	0.691	1.803	10.697	0.866
White Ethnicity (Reference Category)	-	-	-	-	-	-	-	-	-
Interview Duration in minutes	0.001	0.004	0.704	-0.181	0.105	0.084	-0.288	0.283	0.308
Own EQ-5D-5L score	0.134	0.185	0.469	4.288	4.674	0.359	7.294	12.902	0.572
Intercept	0.025	0.218	0.907	9.009	5.195	0.083	19.448	15.071	0.197

Dependent Variable (Family) [Power Link Function]	***Health State A Visual Analogue Score decrement (Gamma) [1.3]***			***Health State B Visual Analogue Score (Gaussian) [2]***			***Health State C Visual Analogue Score (Gaussian) [-1]***		
	Coefficient	**Standard Error**	**P-value**	**Coefficient**	**Standard Error**	**P-value**	**Coefficient**	**Standard Error**	**P-value**
Age group 25 years and above	-0.032	0.046	0.496	0.053	0.062	0.397	-0.256	0.334	0.443
Age group below 25 years (Reference Category)	-	-	-	-	-	-	-	-	-
Male gender	-0.041	0.026	0.108	0.032	0.026	0.211	-0.259	0.226	0.252
Female gender (Reference Category)	-	-	-	-	-	-	-	-	-
Surgical Experience	0.012	0.027	0.108	0.006	0.025	0.795	-0.071	0.238	0.767
No Surgical Experience (Reference Category)	-	-	-	-	-	-	-	-	-
Undergraduate Degree	-0.025	0.047	0.596	0.024	0.056	0.671	-0.077	0.378	0.84
Postgraduate Degree (Reference Category)	-	-	-	-	-	-	-	-	-
Asian or Asian British Ethnicity	0.01	0.032	0.746	-0.003	0.032	0.927	0.142	0.29	0.623
Black/African/Caribbean/ Black British Ethnicity	0.039	0.034	0.251	-0.033	0.035	0.337	0.241	0.359	0.502
Other ethnic group	-0.097	0.035	**0.006**	0.077	0.045	0.089	-0.446	0.227	0.049
White Ethnicity (Reference Category)	-	-	-	-	-	-	-	-	-
Interview Duration in minutes	-0.001	0.002	0.518	0	0.002	0.881	-0.011	0.013	0.378
Own EQ-5D-5L score	-0.071	0.106	0.502	0.064	0.125	0.61	-1.27	0.943	0.178
Intercept	0.458	0.13	**0**	0.098	0.116	0.396	4.547	1.039	**0**

Dependent Variable (Family) [Power Link Function]	***Health State D Visual Analogue Score (Poisson) [-0.5]***			***Health State E Visual Analogue Score (Poisson) [1.3]***			***Health State F Visual Analogue Score (Poisson) [-1.1]***		
	Coefficient	**Standard Error**	**P-value**	**Coefficient**	**Standard Error**	**P-value**	**Coefficient**	**Standard Error**	**P-value**
Age group 25 years and above	-0.081	0.197	0.683	0.045	0.066	0.495	-0.812	1.993	0.684
Age group below 25 years (Reference Category)	-	-	-	-	-	-	-	-	-
Male gender	-0.074	0.102	0.466	0.011	0.023	0.641	-0.162	1.317	0.902
Female gender (Reference Category)	-	-	-	-	-	-	-	-	-
Surgical Experience	-0.063	0.1	0.466	0.013	0.022	0.544	-0.309	1.194	0.795
No Surgical Experience (Reference Category)	-	-	-	-	-	-	-	-	-
Undergraduate Degree	0.072	0.204	0.723	0.014	0.06	0.815	0.506	2.328	0.828
Postgraduate Degree (Reference Category)	-	-	-	-	-	-	-	-	-
Asian or Asian British Ethnicity	0.102	0.139	0.463	-0.019	0.029	0.52	0.756	1.827	0.679
Black/African/Caribbean/ Black British Ethnicity	0.166	0.157	0.291	-0.055	0.023	**0.016**	6.125	3.658	0.094
Other ethnic group	-0.151	0.118	0.199	0.003	0.029	0.919	0.639	1.777	0.719
White Ethnicity (Reference Category)	-	-	-	-	-	-	-	-	-
Interview Duration in minutes	-0.002	0.006	0.786	0.001	0.001	0.639	-0.04	0.06	0.506
Own EQ-5D-5L score	-0.254	0.482	0.598	0.007	0.11	0.951	2.587	4.846	0.593
Intercept	2.24	0.548	**0**	0.103	0.109	0.345	5.488	5.772	0.342

Dependent Variable (Family) [Power Link Function]	***Health State A EQ-5D decrement (Gamma) [1.3]***			***Health State B EQ-5D decrement (Gamma) [1.6]***			***Health State C EQ-5D score (Gaussian) [1]***		
	Coefficient	**Standard Error**	**P-value**	**Coefficient**	**Standard Error**	**P-value**	**Coefficient**	**Standard Error**	**P-value**
Age group 25 years and above	0.008	0.03	0.784	-0.037	0.043	0.393	0.05	0.112	0.658
Age group below 25 years (Reference Category)	-	-	-	-	-	-	-	-	-
Male gender	-0.028	0.015	0.058	-0.01	0.039	0.794	-0.026	0.051	0.613
Female gender (Reference Category)	-	-	-	-	-	-	-	-	-
Surgical Experience	0.002	0.015	0.058	0.063	0.036	0.076	0.017	0.047	0.716
No Surgical Experience (Reference Category)	-	-	-	-	-	-	-	-	-
Undergraduate Degree	-0.012	0.017	0.501	0.001	0.043	0.98	0.057	0.097	0.555
Postgraduate Degree (Reference Category)	-	-	-	-	-	-	-	-	-
Asian or Asian British Ethnicity	0.01	0.021	0.627	0.095	0.057	0.094	-0.134	0.067	0.047
Black/African/Caribbean/ Black British Ethnicity	0.044	0.035	0.204	0.211	0.082	0.01	-0.084	0.077	0.275
Other ethnic group	-0.025	0.014	0.068	-0.068	0.04	0.087	0.102	0.075	0.174
White Ethnicity (Reference Category)	-	-	-	-	-	-	-	-	-
Interview Duration in minutes	0.001	0.002	0.413	0.004	0.003	0.153	-0.004	0.003	0.21
Own EQ-5D-5L score	-0.152	0.069	0.027	-0.432	0.139	**0.002**	0.539	0.245	**0.027**
Intercept	0.224	0.069	**0.001**	0.435	0.15	**0.004**	-0.288	0.231	0.214

Dependent Variable (Family) [Power Link Function]	***Health State D EQ-5D decrement (Poisson) [0.3]***			***Health State E EQ-5D decrement (Poisson) [1.9]***			***Health State F EQ-5D decrement (Gaussian) [2]***		
	Coefficient	**Standard Error**	**P-value**	**Coefficient**	**Standard Error**	**P-value**	**Coefficient**	**Standard Error**	**P-value**
Age group 25 years and above	-0.036	0.054	0.503	-0.055	0.088	0.527	-0.037	0.164	0.821
Age group below 25 years (Reference Category)	-	-	-	-	-	-	-	-	-
Male gender	0.015	0.03	0.61	-0.016	0.07	0.823	-0.05	0.13	0.697
Female gender (Reference Category)	-	-	-	-	-	-	-	-	-
Surgical Experience	0.026	0.027	0.61	0.079	0.056	0.155	0.085	0.098	0.385
No Surgical Experience (Reference Category)	-	-	-	-	-	-	-	-	-
Undergraduate Degree	-0.021	0.049	0.661	-0.06	0.099	0.545	-0.123	0.177	0.487
Postgraduate Degree (Reference Category)	-	-	-	-	-	-	-	-	-
Asian or Asian British Ethnicity	0.005	0.035	0.885	0.048	0.076	0.527	-0.138	0.138	0.317
Black/African/Caribbean/ Black British Ethnicity	0.03	0.046	0.525	0.043	0.082	0.6	0.182	0.102	0.074
Other ethnic group	-0.066	0.042	0.121	-0.05	0.069	0.469	0.139	0.132	0.292
White Ethnicity (Reference Category)	-	-	-	-	-	-	-	-	-
Interview Duration in minutes	0.001	0.002	0.477	-0.002	0.003	0.5	-0.002	0.007	0.831
Own EQ-5D-5L score	-0.034	0.115	0.767	-0.228	0.242	0.345	0.211	0.375	0.573
Intercept	0.81	0.119	**0**	0.551	0.281	**0.05**	0.742	0.505	0.141

Appendix Table A8.3 Generalised Linear Model Modified Parks tests results

	Health State A		***Health State B***		***Health State C***		***Health State D***		***Health State E***		***Health State F***	
Time trade off												
Family	**Chi2**	**P-value**	**Chi2**	**P-value**	**Chi2**	**P-value**	**Chi2**	**P-value**	**Chi2**	**P-value**	**Chi2**	**P-value**
Poisson:	0.3658	0.5453	0.4956	0.4814	0.4971	0.4808	0.0364	0.8488	0.3578	0.5497	0.9304	0.3348
Gamma:	0.5595	0.4544	5.6388	0.0176	3.0682	0.0798	2.7381	0.098	2.3948	0.1217	0.0915	0.7622
Gaussian	3.8327	0.0503	0.9344	0.3337	0.1167	0.7327	1.6215	0.2029	0.1233	0.7255	4.9806	0.0256
Inverse Gaussian	4.4138	0.0356	16.3641	0.0001	7.8301	0.0051	9.7268	0.0018	6.2342	0.0125	2.464	0.1165
Visual Analogue Score												
Poisson:	0.8628	0.3529	0.6397	0.4238	0.3043	0.5812	0.1753	0.6755	0.1282	0.7203	0.0082	0.928
Gamma:	0.0502	0.8226	2.0852	0.1487	1.3475	0.2457	1.7694	0.1835	1.5339	0.2155	3.07	0.0798
Gaussian	4.3344	0.0373	0.0242	0.8763	0.0033	0.9541	0.2429	0.6221	0.2729	0.6014	2.4695	0.1161
Inverse Gaussian	1.8967	0.1685	4.3607	0.0368	3.133	0.0767	5.0252	0.025	4.4901	0.0341	11.655	0.0006
EQ-5D-5L												
Poisson:	9.8195	0.0017	1.3821	0.2397	13.5996	0.0002	0.0325	0.857	0.0209	0.8849	11.1566	0.0008
Gamma:	2.2126	0.1369	0.6015	0.438	48.3333	0	1.5244	0.217	1.1426	0.2851	14.1966	0.0002
Gaussian	22.8459	0	9.7769	0.0018	0.1792	0.6721	0.7642	0.382	0.6076	0.4357	8.4824	0.0036
Inverse Gaussian	0.0252	0.874	7.4353	0.0064	104.3802	0	5.2398	0.0221	3.9726	0.0462	17.6025	0

Appendix Table A8.4 Generalised Linear Model link function diagnostics

	Health State A	***Health State B***	***Health State C***	***Health State D***	***Health State E***	***Health State F***
	P-value (except Akaike information criterion)					
Time trade off						
Pearson Correlation Test	0.7787	0.8627	0.9152	0.9171	0.4702	0.8594
Pregibon Link Test	0.1471	0.1567	0.1135	0.8782	0.1518	0.1122
Modified Hosmer and Lemeshow	0.0924	0.2824	0.1057	0.1147	0.5341	0.378
Akaike information criterion	1.2727	1.4976	-0.3257	0.485	-0.4161	-0.4161
Visual Analogue Score						
Pearson Correlation Test	0.9171	0.9542	0.9971	0.9772	0.8598	0.994
Pregibon Link Test	0.8782	0.462	0.9804	0.4057	0.4826	0.7709
Modified Hosmer and Lemeshow	0.1147	0.7579	0.5141	0.4165	0.7669	0.3922
Akaike information criterion	0.485	-1.073	-1.1285	1.237	1.1655	1.004
EQ-5D-5L						
Pearson Correlation Test	0.3888	0.7667	1	0.82	0.9603	0.9598
Pregibon Link Test	0.0566	0.6752	0.2429	0.0614	0.2019	0.4531
Modified Hosmer and Lemeshow	0.1158	0.2503	0.97	0.625	0.2779	0.2927
Akaike information criterion	-1.1279	0.2294	-0.0221	1.6795	1.7124	0.1505

Chapter 9 Appendix

Appendix Table A9.1 Cost per QALY deterministic sensitivity analysis scenario 1 results

Strategy	Healthcare Cost (Int$)	Incremental Healthcare Costs (Int$)	Societal Cost (Int$)	QALY	Incremental QALY	ICER (Int$)
DSA1: Overall RR for Chlorhexidine versus Povidone–iodine (0.94) applied						
India Clean-Contaminated						
Triclosan-coated Sutures	127		5.87	0.058669		Dominant
Alcoholic Chlorhexidine	134	6.36	6.13	0.058582	-0.00009	Dominated
Usual Care	136	9.03	6.52	0.058452	-0.00022	Dominated
India Contaminated-Dirty						
Alcoholic Chlorhexidine	105		16.94	0.056674		Dominant
Usual Care	106	0.86	18.02	0.056422	-0.00025	Dominated
Triclosan-coated Sutures	106	1.02	17.66	0.056506	-0.00017	Dominated
Mexico Clean-Contaminated						
Alcoholic Chlorhexidine	112		-6.13	0.058582		
Usual Care	112	0.59	-6.52	0.058452	-0.00013	Dominated
Triclosan-coated Sutures	123	11.21	-5.87	0.058669	0.00009	128,905
Ghana Contaminated-Dirty						
Alcoholic Chlorhexidine	142	0.00	10.38	0.0568		Dominant
Triclosan-coated Sutures	151	9.02	11.18	0.056506	-0.00029	Dominated
Usual Care	153	11.14	11.41	0.056422	-0.00038	Dominated
ICER: Incremental cost-effectiveness ratio; NMB: Net Monetary Benefit; QALY: Quality Adjusted Life Year						

Appendix Table A9.2 Cost per DALY averted deterministic sensitivity analysis scenario 1 results

Strategy	Healthcare Cost (Int$)	Incremental Healthcare Costs (Int$)	Societal Cost (Int$)	DALY	Incremental DALY averted	ICER (Int$)
DSA1: Overall RR for Chlorhexidine versus Povidone–iodine (0.94) applied						
India Clean-Contaminated						
Triclosan-coated Sutures	127		5.87	0.10573		Dominant
Alcoholic Chlorhexidine	134	6.36	6.13	0.110429	-0.004699	Dominated
Usual Care	136	9.03	6.52	0.117478	-0.011748	Dominated
India Contaminated-Dirty						
Alcoholic Chlorhexidine	105		16.94	0.213504		Dominant
Usual Care	106	0.86	18.02	0.227132	-0.01363	Dominated
Triclosan-coated Sutures	106	1.02	17.66	0.222589	-0.00909	Dominated
Mexico Clean-Contaminated						
Alcoholic Chlorhexidine	112		-6.13	0.124598		
Usual Care	112	0.59	-6.52	0.132551	-0.00795	Dominated
Triclosan-coated Sutures	123	11.21	-5.87	0.119296	0.00530	2,115
Ghana Contaminated-Dirty						
Alcoholic Chlorhexidine	142		10.38	0.200766		Dominant
Triclosan-coated Sutures	151	9.02	11.18	0.21621	-0.01544	Dominated
Usual Care	153	11.14	11.41	0.220622	-0.01986	Dominated
DALY: Disability Adjusted Life Year; ICER: Incremental cost-effectiveness ratio; NMB: Net Monetary Benefit						

Appendix Table A9.3 Cost per QALY deterministic sensitivity analysis scenario 2 results

Strategy	Healthcare Cost (Int$)	Incremental Healthcare Costs (Int$)	Societal Cost (Int$)	QALY	Incremental QALY	ICER (Int$)
DSA2: Overall RR for Coated Sutures versus Uncoated Sutures (0.94) applied						
India Clean-Contaminated						
Triclosan-coated Sutures	132		6.13	0.058582		Dominant
Usual Care	136	4.74	6.52	0.058452	-0.00013	Dominated
Alcoholic Chlorhexidine	137	5.29	6.33	0.058517	-0.00007	Dominated
India Contaminated-Dirty						
Alcoholic Chlorhexidine	103		16.40	0.0568		Dominant
Triclosan-coated Sutures	103	0.25	16.94	0.056674	-0.00013	Dominated
Usual Care	106	3.18	18.02	0.056422	-0.00038	Dominated
Mexico Clean-Contaminated						
Usual Care	112		-6.52	0.058452		
Alcoholic Chlorhexidine	114	1.56	-6.33	0.058517	0.00007	23,951
Triclosan-coated Sutures	126	11.93	-6.13	0.058582	0.00007	182,896
Ghana Contaminated-Dirty						
Alcoholic Chlorhexidine	142	0.00	10.38	0.0568		Dominant
Triclosan-coated Sutures	145	3.37	10.73	0.056674	-0.00013	Dominated
Usual Care	153	11.14	11.41	0.056422	-0.00038	Dominated
ICER: Incremental cost-effectiveness ratio; NMB: Net Monetary Benefit; QALY: Quality Adjusted Life Year						

Appendix Table A9.4 Cost per DALY averted deterministic sensitivity analysis scenario 2 results

Strategy	Healthcare Cost (Int$)	Incremental Healthcare Costs (Int$)	Societal Cost (Int$)	DALY	Incremental DALY averted	ICER (Int$)
DSA2: Overall RR for Triclosan-coated Sutures versus Uncoated Sutures (0.94) applied						
India Clean-Contaminated						
Triclosan-coated Sutures	132		6.13	0.110429		Dominant
Usual Care	136	4.74	6.52	0.117478	-0.007049	Dominated
Alcoholic Chlorhexidine	137	5.29	6.33	0.113953	-0.003524	Dominated
India Contaminated-Dirty						
Alcoholic Chlorhexidine	103		16.40	0.20669		Dominant
Triclosan-coated Sutures	103	0.25	16.94	0.213504	-0.00681	Dominated
Usual Care	106	3.18	18.02	0.227132	-0.02044	Dominated
Mexico Clean-Contaminated						
Usual Care	112		-6.52	0.132551		
Alcoholic Chlorhexidine	114	1.56	-6.33	0.128575	0.00398	393
Triclosan-coated Sutures	126	11.93	-6.13	0.124598	0.00795	3,001
Ghana Contaminated-Dirty						
Alcoholic Chlorhexidine	142		10.38	0.200766		Dominant
Triclosan-coated Sutures	151	9.02	11.18	0.21621	-0.01544	Dominated
Usual Care	153	11.14	11.41	0.220622	-0.01986	Dominated
DALY: Disability Adjusted Life Year; ICER: Incremental cost-effectiveness ratio; NMB: Net Monetary Benefit						

Appendix Table A9.5 Cost per QALY deterministic sensitivity analysis scenario 3 results

Strategy	Healthcare Cost (Int$)	Incremental Healthcare Costs (Int$)	Societal Cost (Int$)	QALY	Incremental QALY	ICER (Int$)
DSA3: Overall 30 day postoperative risk of SSI was applied to both wound contamination strata						
India Clean-Contaminated						
Triclosan-coated Sutures	168		8.32	0.057853		Dominant
Alcoholic Chlorhexidine	180	12.72	8.97	0.057637	-0.00022	Dominated
Usual Care	181	13.51	9.24	0.057545	-0.00031	Dominated
India Contaminated-Dirty						
Alcoholic Chlorhexidine	84		12.02	0.057822		Dominant
Usual Care	86	1.32	13.21	0.057545	-0.00028	Dominated
Triclosan-coated Sutures	86	1.89	12.94	0.057606	-0.00022	Dominated
Mexico Clean-Contaminated						
Usual Care	142		-9.24	0.057545		
Alcoholic Chlorhexidine	143	0.66	-8.97	0.057637	0.00009	7,169
Triclosan-coated Sutures	150	6.96	-8.32	0.057853	0.00022	32,248
Ghana Contaminated-Dirty						
Alcoholic Chlorhexidine	108	0.00	7.61	0.057822		Dominant
Triclosan-coated Sutures	114	6.38	8.20	0.057606	-0.00022	Dominated
Usual Care	116	7.75	8.36	0.057545	-0.00028	Dominated
ICER: Incremental cost-effectiveness ratio; NMB: Net Monetary Benefit; QALY: Quality Adjusted Life Year						

Appendix Table A9.6 Cost per DALY averted deterministic sensitivity analysis scenario 3 results

Strategy	Healthcare Cost (Int$)	Incremental Healthcare Costs (Int$)	Societal Cost (Int$)	DALY	Incremental DALY averted	ICER (Int$)
DSA3: Overall 30 day postoperative risk of SSI was applied to both wound contamination strata						
India Clean-Contaminated						
Triclosan-coated Sutures	168		8.32	0.149826		Dominant
Alcoholic Chlorhexidine	180	12.72	8.97	0.161479	-0.011653	Dominated
Usual Care	181	13.51	9.24	0.166473	-0.016647	Dominated
India Contaminated-Dirty						
Alcoholic Chlorhexidine	84		12.02	0.151491		Dominant
Usual Care	86	1.32	13.21	0.166473	-0.01498	Dominated
Triclosan-coated Sutures	86	1.89	12.94	0.163144	-0.01165	Dominated
Mexico Clean-Contaminated						
Usual Care	142		-9.24	0.187834		
Alcoholic Chlorhexidine	143	0.66	-8.97	0.182199	0.00564	118
Triclosan-coated Sutures	150	6.96	-8.32	0.16905	0.01878	529
Ghana Contaminated-Dirty						
Alcoholic Chlorhexidine	108		7.61	0.147149		Dominant
Triclosan-coated Sutures	114	6.38	8.20	0.158468	-0.01132	Dominated
Usual Care	116	7.75	8.36	0.161702	-0.01455	Dominated
DALY: Disability Adjusted Life Year; ICER: Incremental cost-effectiveness ratio; NMB: Net Monetary Benefit						

Appendix Table A9.7 Cost per QALY deterministic sensitivity analysis scenario 4 results

Strategy	Healthcare Cost (Int$)	Incremental Healthcare Costs (Int$)	Societal Cost (Int$)	QALY	Incremental QALY	ICER (Int$)
DSA4: Additional healthcare cost of an SSI from the Generalised Linear Model was used for each wound contamination strata: ($298: Clean-Contaminated; $356: Contaminated-Dirty)						
India Clean-Contaminated						
Triclosan-coated Sutures	72		5.87	0.058669		Dominant
Usual Care	75	2.93	6.52	0.058452	-0.00022	Dominated
Alcoholic Chlorhexidine	78	5.31	6.33	0.058517	-0.00015	Dominated
India Contaminated-Dirty						
Alcoholic Chlorhexidine	130		16.40	0.0568		Dominant
Triclosan-coated Sutures	135	5.40	17.66	0.056506	-0.00029	Dominated
Usual Care	136	5.84	18.02	0.056422	-0.00038	Dominated
Mexico Clean-Contaminated						
Usual Care	87		-6.52	0.058452		
Alcoholic Chlorhexidine	89	2.33	-6.33	0.058517	0.00007	35,737
Triclosan-coated Sutures	100	10.85	-5.87	0.058669	0.00015	71,275
Ghana Contaminated-Dirty						
Alcoholic Chlorhexidine	111	0.00	10.38	0.0568		Dominant
Triclosan-coated Sutures	117	6.61	11.18	0.056506	-0.00029	Dominated
Usual Care	119	8.05	11.41	0.056422	-0.00038	Dominated
ICER: Incremental cost-effectiveness ratio; NMB: Net Monetary Benefit; QALY: Quality Adjusted Life Year						

Appendix Table A9.8 Cost per DALY averted deterministic sensitivity analysis scenario 4 results

Strategy	Healthcare Cost (Int$)	Incremental Healthcare Costs (Int$)	Societal Cost (Int$)	DALY	Incremental DALY averted	ICER (Int$)
DSA4: Additional healthcare cost of an SSI from the Generalised Linear Model was used for each wound contamination strata: ($298: Clean-Contaminated; $356: Contaminated-Dirty)						
India Clean-Contaminated						
Triclosan-coated Sutures	72		5.87	0.10573		Dominant
Usual Care	75	2.93	6.52	0.117478	-0.011748	Dominated
Alcoholic Chlorhexidine	78	5.31	6.33	0.113953	-0.008223	Dominated
India Contaminated-Dirty						
Alcoholic Chlorhexidine	130		16.40	0.20669		Dominant
Triclosan-coated Sutures	135	5.40	17.66	0.222589	-0.01590	Dominated
Usual Care	136	5.84	18.02	0.227132	-0.02044	Dominated
Mexico Clean-Contaminated						
Usual Care	87		-6.52	0.132551		
Alcoholic Chlorhexidine	89	2.33	-6.33	0.128575	0.00398	586
Triclosan-coated Sutures	100	10.85	-5.87	0.119296	0.01326	1,169
Ghana Contaminated-Dirty						
Alcoholic Chlorhexidine	111		10.38	0.200766		Dominant
Triclosan-coated Sutures	117	6.61	11.18	0.21621	-0.01544	Dominated
Usual Care	119	8.05	11.41	0.220622	-0.01986	Dominated
DALY: Disability Adjusted Life Year; ICER: Incremental cost-effectiveness ratio; NMB: Net Monetary Benefit						

Appendix Table A9.9 Cost per QALY deterministic sensitivity analysis scenario 5 results

Strategy	Healthcare Cost (Int$)	Incremental Healthcare Costs (Int$)	Societal Cost (Int$)	QALY	Incremental QALY	ICER (Int$)
DSA5: The overall additional cost of an SSI from the unadjusted analysis was used for each wound contamination strata ($469 Clean-Contaminated; $583 Contaminated-Dirty)						
India Clean-Contaminated						
Triclosan-coated Sutures	96		5.87	0.058669		Dominant
Usual Care	102	5.58	6.52	0.058452	-0.00022	Dominated
Alcoholic Chlorhexidine	104	7.17	6.33	0.058517	-0.00015	Dominated
India Contaminated-Dirty						
Alcoholic Chlorhexidine	103		16.40	0.0568		Dominant
Usual Care	106	3.18	18.02	0.056422	-0.00038	Dominated
Triclosan-coated Sutures	106	3.33	17.66	0.056506	-0.00029	Dominated
Mexico Clean-Contaminated						
Usual Care	113		-6.52	0.058452		
Alcoholic Chlorhexidine	115	1.53	-6.33	0.058517	0.00007	23,522
Triclosan-coated Sutures	124	8.99	-5.87	0.058669	0.00015	59,060
Ghana Contaminated-Dirty						
Alcoholic Chlorhexidine	142	0.00	10.38	0.0568		Dominant
Triclosan-coated Sutures	151	9.00	11.18	0.056506	-0.00029	Dominated
Usual Care	153	11.12	11.41	0.056422	-0.00038	Dominated
ICER: Incremental cost-effectiveness ratio; NMB: Net Monetary Benefit; QALY: Quality Adjusted Life Year						

Appendix Table A9.10 Cost per DALY averted deterministic sensitivity analysis scenario 5 results

Strategy	Healthcare Cost (Int$)	Incremental Healthcare Costs (Int$)	Societal Cost (Int$)	DALY	Incremental DALY averted	ICER (Int$)
DSA5: The overall additional cost of an SSI from the unadjusted analysis was used for each wound contamination strata ($469 Clean-Contaminated; $583 Contaminated-Dirty)						
India Clean-Contaminated						
Triclosan-coated Sutures	96		5.87	0.10573		Dominant
Usual Care	102	5.58	6.52	0.117478	-0.011748	Dominated
Alcoholic Chlorhexidine	104	7.17	6.33	0.113953	-0.008223	Dominated
India Contaminated-Dirty						
Alcoholic Chlorhexidine	103		16.40	0.20669		Dominant
Usual Care	106	3.18	18.02	0.227132	-0.02044	Dominated
Triclosan-coated Sutures	106	3.33	17.66	0.222589	-0.01590	Dominated
Mexico Clean-Contaminated						
Usual Care	113		-6.52	0.132551		
Alcoholic Chlorhexidine	115	1.53	-6.33	0.128575	0.00398	386
Triclosan-coated Sutures	124	8.99	-5.87	0.119296	0.01326	969
Ghana Contaminated-Dirty						
Alcoholic Chlorhexidine	142		10.38	0.200766		Dominant
Triclosan-coated Sutures	151	9.00	11.18	0.21621	-0.01544	Dominated
Usual Care	153	11.12	11.41	0.220622	-0.01986	Dominated
DALY: Disability Adjusted Life Year; ICER: Incremental cost-effectiveness ratio; NMB: Net Monetary Benefit						

Appendix Table A9.11 Cost per DALY averted deterministic sensitivity analysis scenario 6 results

Strategy	Healthcare Cost (Int$)	Incremental Healthcare Costs (Int$)	Societal Cost (Int$)	DALY	Incremental DALY averted	ICER (Int$)
DSA6: Mean SSI resolution time in days was halved						
India Clean-Contaminated						
Triclosan-coated Sutures	127		5.87	0.102673		Dominant
Usual Care	136	9.03	6.52	0.114081	-0.011408	Dominated
Alcoholic Chlorhexidine	137	9.58	6.33	0.110659	-0.007986	Dominated
India Contaminated-Dirty						
Alcoholic Chlorhexidine	103		16.40	0.200714		Dominant
Usual Care	106	3.18	18.02	0.220565	-0.01985	Dominated
Triclosan-coated Sutures	106	3.33	17.66	0.216154	-0.01544	Dominated
Mexico Clean-Contaminated						
Usual Care	112		-6.52	0.129154		
Alcoholic Chlorhexidine	114	1.56	-6.33	0.12528	0.00387	403
Triclosan-coated Sutures	123	9.06	-5.87	0.116239	0.01292	1,002
Ghana Contaminated-Dirty						
Alcoholic Chlorhexidine	142		10.38	0.19479		Dominant
Triclosan-coated Sutures	151	9.02	11.18	0.209774	-0.01498	Dominated
Usual Care	153	11.14	11.41	0.214055	-0.01926	Dominated
DALY: Disability Adjusted Life Year; ICER: Incremental cost-effectiveness ratio; NMB: Net Monetary Benefit						

Appendix Table A9.12 Cost per QALY deterministic sensitivity analysis scenario 7 results

Strategy	Healthcare Cost (Int$)	Incremental Healthcare Costs (Int$)	Societal Cost (Int$)	QALY	Incremental QALY	ICER (Int$)
DSA7: Visual Analogue Scores Health state utilities and decrements were used						
India Clean-Contaminated						
Triclosan-coated Sutures	127		5.87	0.045525		Dominant
Usual Care	136	9.03	6.52	0.045308	-0.00022	Dominated
Alcoholic Chlorhexidine	137	9.58	6.33	0.045373	-0.00015	Dominated
India Contaminated-Dirty						
Alcoholic Chlorhexidine	103		16.40	0.043662		Dominant
Usual Care	106	3.18	18.02	0.043285	-0.00038	Dominated
Triclosan-coated Sutures	106	3.33	17.66	0.043369	-0.00029	Dominated
Mexico Clean-Contaminated						
Usual Care	112		-6.52	0.045308		
Alcoholic Chlorhexidine	114	1.56	-6.33	0.045373	0.00007	24,031
Triclosan-coated Sutures	123	9.06	-5.87	0.045525	0.00015	59,688
Ghana Contaminated-Dirty						
Alcoholic Chlorhexidine	142		10.38	0.043662		Dominant
Triclosan-coated Sutures	151	9.02	11.18	0.043369	-0.00029	Dominated
Usual Care	153	11.14	11.41	0.043285	-0.00038	Dominated
ICER: Incremental cost-effectiveness ratio; NMB: Net Monetary Benefit; QALY: Quality Adjusted Life Year						

Appendix Table A9.13 Cost per DALY averted deterministic sensitivity analysis scenario 7 results

Strategy	Healthcare Cost (Int$)	Incremental Healthcare Costs (Int$)	Societal Cost (Int$)	DALY	Incremental DALY averted	ICER (Int$)
DSA7: Visual Analogue Scores Health state utilities and decrements were used						
India Clean-Contaminated						
Triclosan-coated Sutures	127		5.87	0.105664		Dominant
Usual Care	136	9.03	6.52	0.117404	-0.011740	Dominated
Alcoholic Chlorhexidine	137	9.58	6.33	0.113882	-0.008218	Dominated
India Contaminated-Dirty						
Alcoholic Chlorhexidine	103		16.40	0.206561		Dominant
Usual Care	106	3.18	18.02	0.22699	-0.02043	Dominated
Triclosan-coated Sutures	106	3.33	17.66	0.22245	-0.01589	Dominated
Mexico Clean-Contaminated						
Usual Care	112		-6.52	0.132478		
Alcoholic Chlorhexidine	114	1.56	-6.33	0.128503	0.00397	393
Triclosan-coated Sutures	123	9.06	-5.87	0.11923	0.01325	977
Ghana Contaminated-Dirty						
Alcoholic Chlorhexidine	142		10.38	0.200637		Dominant
Triclosan-coated Sutures	151	9.02	11.18	0.216071	-0.01543	Dominated
Usual Care	153	11.14	11.41	0.220481	-0.01984	Dominated
DALY: Disability Adjusted Life Year; ICER: Incremental cost-effectiveness ratio; NMB: Net Monetary Benefit						

Appendix Table A9.14 Cost per QALY deterministic sensitivity analysis scenario 8 results

Strategy	Healthcare Cost (Int$)	Incremental Healthcare Costs (Int$)	Societal Cost (Int$)	QALY	Incremental QALY	ICER (Int$)
DSA8: Health state decrement trajectory associated with Deep Incisional SSI and Deep Organ SSI health states assumed not to be constant						
India Clean-Contaminated						
Triclosan-coated Sutures	127		5.87	0.059003		Dominant
Usual Care	136	9.03	6.52	0.058823	-0.00018	Dominated
Alcoholic Chlorhexidine	137	9.58	6.33	0.058877	-0.00013	Dominated
India Contaminated-Dirty						
Alcoholic Chlorhexidine	103		16.40	0.057453		Dominant
Usual Care	106	3.18	18.02	0.057139	-0.00031	Dominated
Triclosan-coated Sutures	106	3.33	17.66	0.057209	-0.00024	Dominated
Mexico Clean-Contaminated						
Usual Care	112		-6.52	0.058823		
Alcoholic Chlorhexidine	114	1.56	-6.33	0.058877	0.00005	28,877
Triclosan-coated Sutures	123	9.06	-5.87	0.059003	0.00013	71,723
Ghana Contaminated-Dirty						
Alcoholic Chlorhexidine	142	0.00	10.38	0.057453		Dominant
Triclosan-coated Sutures	151	9.02	11.18	0.057209	-0.00024	Dominated
Usual Care	153	11.14	11.41	0.057139	-0.00031	Dominated
ICER: Incremental cost-effectiveness ratio; NMB: Net Monetary Benefit; QALY: Quality Adjusted Life Year						

Appendix Table A9.15 Cost per QALY deterministic sensitivity analysis scenario 9 results

Strategy	Healthcare Cost (Int$)	Incremental Healthcare Costs (Int$)	Societal Cost (Int$)	QALY	Incremental QALY	ICER (Int$)
DSA9: Health state utilities and decrements were taken from the ROSSINI re-analysis						
India Clean-Contaminated						
Triclosan-coated Sutures	127		5.87	0.06		Dominant
Usual Care	136	9.03	6.52	0.05993	-0.00007	Dominated
Alcoholic Chlorhexidine	137	9.58	6.33	0.059951	-0.00005	Dominated
India Contaminated-Dirty						
Alcoholic Chlorhexidine	103		16.40	0.059401		Dominant
Usual Care	106	3.18	18.02	0.05928	-0.00012	Dominated
Triclosan-coated Sutures	106	3.33	17.66	0.059307	-0.00009	Dominated
Mexico Clean-Contaminated						
Usual Care	112		-6.52	0.05993		
Alcoholic Chlorhexidine	114	1.56	-6.33	0.059951	0.00002	74,795
Triclosan-coated Sutures	123	9.06	-5.87	0.06	0.00005	185,775
Ghana Contaminated-Dirty						
Alcoholic Chlorhexidine	142	0.00	10.38	0.059401		Dominant
Triclosan-coated Sutures	151	9.02	11.18	0.059307	-0.00009	Dominated
Usual Care	153	11.14	11.41	0.05928	-0.00012	Dominated
ICER: Incremental cost-effectiveness ratio; NMB: Net Monetary Benefit; QALY: Quality Adjusted Life Year						

Appendix Table A9.16 Cost per DALY averted deterministic sensitivity analysis scenario 9 results

Strategy	Healthcare Cost (Int$)	Incremental Healthcare Costs (Int$)	Societal Cost (Int$)	DALY	Incremental DALY averted	ICER (Int$)
DSA9: Health state utilities and decrements were taken from the ROSSINI re-analysis						
India Clean-Contaminated						
Triclosan-coated Sutures	127		5.87	0.101012		Dominant
Usual Care	136	9.03	6.52	0.112235	-0.011224	Dominated
Alcoholic Chlorhexidine	137	9.58	6.33	0.108868	-0.007856	Dominated
India Contaminated-Dirty						
Alcoholic Chlorhexidine	103		16.40	0.197467		Dominant
Usual Care	106	3.18	18.02	0.216996	-0.01953	Dominated
Triclosan-coated Sutures	106	3.33	17.66	0.212656	-0.01519	Dominated
Mexico Clean-Contaminated						
Triclosan-coated Sutures	112		-6.52	0.127309		
Alcoholic Chlorhexidine	114	1.56	-6.33	0.123489	0.00382	409
Usual Care	123	9.06	-5.87	0.114578	0.01273	1,016
Ghana Contaminated-Dirty						
Alcoholic Chlorhexidine	142		10.38	0.191543		Dominant
Triclosan-coated Sutures	151	9.02	11.18	0.206277	-0.01473	Dominated
Usual Care	153	11.14	11.41	0.210487	-0.01894	Dominated
DALY: Disability Adjusted Life Year; ICER: Incremental cost-effectiveness ratio; NMB: Net Monetary Benefit						

Appendix Table A9.17 Cost per QALY deterministic sensitivity analysis scenario 10 results

Strategy	Healthcare Cost (Int$)	Incremental Healthcare Costs (Int$)	Societal Cost (Int$)	QALY	Incremental QALY	ICER (Int$)
DSA10: cost-effectiveness of a Combined Treatment (Chlorhexidine and Coated Sutures) was assessed relative to the other strategies						
India Clean-Contaminated						
Triclosan-coated Sutures	127		5.87	0.058669		
Combined Treatment	128	0.87	5.69	0.058728	0.00006	14,854
Usual Care	136	8.16	6.52	0.058452	-0.00028	Dominated
Alcoholic Chlorhexidine	137	8.71	6.33	0.058517	-0.00021	Dominated
India Contaminated-Dirty						
Alcoholic Chlorhexidine	103		16.40	0.0568		
Combined Treatment	103	0.30	16.07	0.056877	0.00008	3,860
Usual Care	106	2.88	18.02	0.056422	-0.00045	Dominated
Triclosan-coated Sutures	106	3.04	17.66	0.056506	-0.00037	Dominated
Mexico Clean-Contaminated						
Usual Care	112	0.00	-6.52	0.058452		
Alcoholic Chlorhexidine	114	1.56	-6.33	0.058517	0.00007	23,951
Triclosan-coated Sutures	123	9.06	-5.87	0.058669	0.00015	Extended dominated
Combined Treatment	125	10.83	-5.69	0.058728	0.00021	51,360
Ghana Contaminated-Dirty						
Combined Treatment	140		10.18	0.056877		Dominant
Alcoholic Chlorhexidine	142	1.87	10.38	0.0568	-0.00008	Dominated
Triclosan-coated Sutures	151	10.89	11.18	0.056506	-0.00037	Dominated
Usual Care	153	13.01	11.41	0.056422	-0.00045	Dominated
ICER: Incremental cost-effectiveness ratio; NMB: Net Monetary Benefit; QALY: Quality Adjusted Life Year						

Appendix Table A9.18 Cost per DALY averted deterministic sensitivity analysis scenario 10 results

Strategy	Healthcare Cost (Int$)	Incremental Healthcare Costs (Int$)	Societal Cost (Int$)	DALY	Incremental DALY averted	ICER (Int$)
DSA10: cost-effectiveness of a Combined Treatment (Chlorhexidine and Coated Sutures) was assessed relative to the other strategies						
India Clean-Contaminated						
Triclosan-coated Sutures	127		5.87	0.105730		
Combined Treatment	128	0.87	5.69	0.102558	0.003172	275
Usual Care	136	8.16	6.52	0.117478	-0.014920	Dominated
Alcoholic Chlorhexidine	137	8.71	6.33	0.113953	-0.011395	Dominated
India Contaminated-Dirty						
Alcoholic Chlorhexidine	103	0.00	16.40	0.20669		
Combined Treatment	103	0.30	16.07	0.202556	0.004134	71
Usual Care	106	2.88	18.02	0.227132	-0.024576	Dominated
Triclosan-coated Sutures	106	3.04	17.66	0.222589	-0.020033	Dominated
Mexico Clean-Contaminated						
Usual Care	112		-6.52	0.132551		
Alcoholic Chlorhexidine	114	1.56	-6.33	0.128575	0.003977	393
Triclosan-coated Sutures	123	9.06	-5.87	0.119296	0.009279	Extended dominated
Combined Treatment	125	10.83	-5.69	0.115717	0.012857	843
Ghana Contaminated-Dirty						
Combined Treatment	140	0.00	10.18	0.196751	0.000000	Dominant
Alcoholic Chlorhexidine	142	1.87	10.38	0.200766	-0.004015	Dominated
Triclosan-coated Sutures	151	10.89	11.18	0.21621	-0.015444	Dominated
Usual Care	153	13.01	11.41	0.220622	-0.019856	Dominated
DALY: Disability Adjusted Life Year; ICER: Incremental cost-effectiveness ratio; NMB: Net Monetary Benefit						

Appendix Table A9.19 Cost per QALY deterministic sensitivity analysis scenario 13 results

Strategy	Healthcare Cost (Int$)	Incremental Healthcare Costs (Int$)	Societal Cost (Int$)	QALY	Incremental QALY	ICER (Int$)
DSA13: Societal costs based on numbers of days of paid employment off within a month by changes in health status were included and valued by the 2020 daily minimum wage for each country						
India Clean-Contaminated						
Triclosan-coated Sutures	127		57.44	0.058669		Dominant
Usual Care	136	9.03	58.19	0.058452	-0.00022	Dominated
Alcoholic Chlorhexidine	137	9.58	58.00	0.058517	-0.00015	Dominated
India Contaminated Dirty						
Alcoholic Chlorhexidine	103		69.48	0.0568		Dominant
Usual Care	106	3.18	71.16	0.056422	-0.00038	Dominated
Triclosan-coated Sutures	106	3.33	70.90	0.056506	-0.00029	Dominated
Mexico Clean-Contaminated						
Usual Care	112		74.61	0.058452		
Alcoholic Chlorhexidine	114	1.56	74.73	0.058517	0.00007	23,951
Triclosan-coated Sutures	123	9.06	75.02	0.058669	0.00015	59,489
Ghana Contaminated-Dirty						
Alcoholic Chlorhexidine	142		46.31	0.0568		Dominant
Triclosan-coated Sutures	151	9.02	47.25	0.056506	-0.00029	Dominated
Usual Care	153	11.14	47.52	0.056422	-0.00038	Dominated
ICER: Incremental cost-effectiveness ratio; NMB: Net Monetary Benefit; QALY: Quality Adjusted Life Year						

Appendix Table A9.20 Cost per DALY averted deterministic sensitivity analysis scenario 13 results

Strategy	Healthcare Cost (Int$)	Incremental Healthcare Costs (Int$)	Societal Cost (Int$)	DALY	Incremental DALY averted	ICER (Int$)
DSA13: Societal costs based on numbers of days of paid employment off within a month by changes in health status were included and valued by the 2020 daily minimum wage for each country						
India Clean-Contaminated						
Triclosan-coated Sutures	127		57.44	0.10573		Dominant
Alcoholic Chlorhexidine	134	6.36	58.19	0.110429	-0.004699	Dominated
Usual Care	136	9.03	58.00	0.117478	-0.011748	Dominated
India Contaminated-Dirty						
Alcoholic Chlorhexidine	105		69.48	0.213504		Dominant
Usual Care	106	0.86	71.16	0.227132	-0.01363	Dominated
Triclosan-coated Sutures	106	1.02	70.90	0.222589	-0.00909	Dominated
Mexico Clean-Contaminated						
Alcoholic Chlorhexidine	112		74.61	0.124598		
Usual Care	112	0.59	74.73	0.132551	-0.00795	Dominated
Triclosan-coated Sutures	123	11.21	75.02	0.119296	0.00530	2,115
Ghana Contaminated-Dirty						
Alcoholic Chlorhexidine	142		46.31	0.200766		Dominant
Triclosan-coated Sutures	151	9.02	47.25	0.21621	-0.01544	Dominated
Usual Care	153	11.14	47.52	0.220622	-0.01986	Dominated
DALY: Disability Adjusted Life Year; ICER: Incremental cost-effectiveness ratio; NMB: Net Monetary Benefit						

Appendix Table A9.21 Cost per QALY deterministic sensitivity analysis scenario 14 results

Strategy	Healthcare Cost (Int$)	Incremental Healthcare Costs (Int$)	Societal Cost (Int$)	QALY	Incremental QALY	ICER (Int$)
DSA14: The time horizon was extended to 2 months						
India Clean Contaminated						
Triclosan-coated Sutures	137		87.08	0.116236		Dominant
Usual Care	147	10.11	87.76	0.11573	-0.00051	Dominated
Alcoholic Chlorhexidine	147	10.33	87.56	0.115882	-0.00035	Dominated
India Contaminated Dirty						
Alcoholic Chlorhexidine	110		97.90	0.111883		Dominant
Usual Care	114	3.87	99.53	0.111001	-0.00088	Dominated
Triclosan-coated Sutures	114	3.87	99.48	0.111197	-0.00069	Dominated
Mexico Clean Contaminated						
Usual Care	119		120.92	0.11573		
Alcoholic Chlorhexidine	121	1.35	121.11	0.115882	0.00015	8,862
Triclosan-coated Sutures	129	8.55	121.53	0.116236	0.00035	24,119
Ghana Contaminated Dirty						
Alcoholic Chlorhexidine	155	0.00	65.73	0.111883		Dominant
Triclosan-coated Sutures	165	10.01	66.56	0.111197	-0.00069	Dominated
Usual Care	167	12.41	66.80	0.111001	-0.00088	Dominated
ICER: Incremental cost-effectiveness ratio; NMB: Net Monetary Benefit; QALY: Quality Adjusted Life Year						

Appendix Table A9.22 Cost per QALY deterministic sensitivity analysis scenario 15 results

Strategy	Healthcare Cost (Int$)	Incremental Healthcare Costs (Int$)	Societal Cost (Int$)	QALY	Incremental QALY	ICER (Int$)
DSA15: Minimum level of effectiveness required for Chlorhexidine intervention to be the most cost-effective option						
India Clean Contaminated (threshold value:0.882)						
Triclosan-coated Sutures	127		5.87	0.058669		
Alcoholic Chlorhexidine	128	0.11	5.75	0.058709	0.00004	2781
Usual Care	136	8.92	6.52	0.058452	-0.00026	Dominated
India Contaminated-Dirty (threshold value:0.957)						
Usual Care	106		18.02	0.056422		
Triclosan-coated Sutures	106	0.16	17.66	0.056506	0.00008	1861
Alcoholic Chlorhexidine	107	0.27	17.24	0.056604	0.00010	2781
Mexico Clean-Contaminated (threshold value:0.961)						
Usual Care	112		-6.52	0.058452		
Alcoholic Chlorhexidine	113	0.91	-6.27	0.058536	0.00008	10780
Triclosan-coated Sutures	123	9.70	-5.87	0.058669	0.00013	73164
Ghana Contaminated-Dirty (threshold value:0.974)						
Triclosan-coated Sutures	151	0.00	11.18	0.056506	0.00000	
Alcoholic Chlorhexidine	151	0.05	11.12	0.05653	0.00002	2043
Usual Care	153	2.07	11.41	0.056422	-0.00011	Dominated
ICER: Incremental cost-effectiveness ratio; NMB: Net Monetary Benefit; QALY: Quality Adjusted Life Year						

Appendix Table A9.23 Cost per DALY averted deterministic sensitivity analysis scenario 15 results

Strategy	Healthcare Cost (Int$)	Incremental Healthcare Costs (Int$)	Societal Cost (Int$)	DALY	Incremental DALY averted	ICER (Int$)
DSA15: Minimum level of effectiveness required for Chlorhexidine intervention to be the most cost-effective option						
India Clean-Contaminated (threshold value:0.884)						
Triclosan-coated Sutures	127	0.00	5.87	0.10573	0.00000	
Alcoholic Chlorhexidine	128	0.39	5.77	0.103894	0.00184	214
Usual Care	136	8.64	6.52	0.117478	-0.01358	Dominated
India Contaminated-Dirty (threshold value:0.964)						
Usual Care	106	0.00	18.02	0.227132	0.000000	
Triclosan-coated Sutures	106	0.16	17.66	0.222589	0.004543	34
Alcoholic Chlorhexidine	107	0.80	17.36	0.218851	0.003738	214
Mexico Clean-Contaminated (threshold value:0.978)						
Usual Care	112		-6.52	0.238843		
Alcoholic Chlorhexidine	113	0.79	-6.38	0.229887	0.008956	746
Triclosan-coated Sutures	123	9.82	-5.87	0.216716	0.013171	816
Ghana Contaminated-Dirty (threshold value:0.975)						
Triclosan-coated Sutures	151	0.00	11.18	0.359845	0.000000	
Alcoholic Chlorhexidine	151	0.17	11.12	0.358349	0.001497	114
Usual Care	153	1.95	11.41	0.365943	-0.007595	Dominated
DALY: Disability Adjusted Life Year; ICER: Incremental cost-effectiveness ratio; NMB: Net Monetary Benefit						

Appendix Table A9.24 Cost per QALY deterministic sensitivity analysis scenario 16 results

Strategy	Healthcare Cost (Int$)	Incremental Healthcare Costs (Int$)	Societal Cost (Int$)	QALY	Incremental QALY	ICER (Int$)
DSA16: Minimum level of effectiveness required for Triclosan-coated Sutures intervention to be cost-effective versus Usual Care						
India Clean-Contaminated (threshold value:0.985)						
Usual Care	136		6.52	0.058452		
Triclosan-coated Sutures	137	0.09	6.43	0.058484	0.00003	2781
Alcoholic Chlorhexidine	137	0.46	6.33	0.058517	0.00003	14082
India Contaminated-Dirty (threshold value:0.933)						
Triclosan-coated Sutures	103		16.82	0.056702		
Alcoholic Chlorhexidine	103	0.27	16.40	0.0568	0.00010	2781
Usual Care	106	3.18	18.02	0.056422	-0.00038	Dominated
Mexico Clean-Contaminated (threshold value:0.916)						
Usual Care	112		-6.52	0.058452		
Alcoholic Chlorhexidine	114	1.56	-6.33	0.058517	0.00007	Extended domination
Triclosan-coated Sutures	117	4.38	-5.31	0.058858	0.00041	10,780
Ghana Contaminated-Dirty (threshold value:0.916)						
Triclosan-coated Sutures	142		10.45	0.056776		
Alcoholic Chlorhexidine	142	0.05	10.38	0.0568	0.00002	2,043
Usual Care	153	11.14	11.41	0.056422	-0.00038	Dominated
ICER: Incremental cost-effectiveness ratio; NMB: Net Monetary Benefit; QALY: Quality Adjusted Life Year						

Appendix Table A9.25 Cost per DALY averted deterministic sensitivity analysis scenario 16 results

Strategy	Healthcare Cost (Int$)	Incremental Healthcare Costs (Int$)	Societal Cost (Int$)	DALY	Incremental DALY averted	ICER (Int$)
DSA16: Minimum level of effectiveness required for Coated sutures intervention to be the most cost-effective option						
India Clean-Contaminated (threshold value:0.986)						
Usual Care	136	0.00	6.52	0.117478	0.00000	0
Triclosan-coated Sutures	137	0.16	6.43	0.115789	0.00169	93
Alcoholic Chlorhexidine	137	0.39	6.33	0.113953	0.00184	214
India Contaminated-Dirty (threshold value:0.926)						
Triclosan-coated Sutures	102	0.00	16.69	0.210428	0.00000	
Alcoholic Chlorhexidine	103	0.80	16.40	0.20669	0.00374	214
Usual Care	106	3.18	18.02	0.227132	-0.02044	Dominated
Mexico Clean-Contaminated (threshold value:0.888)						
Usual Care	112	0.00	-6.52	0.132551	0.00000	
Alcoholic Chlorhexidine	114	1.56	-6.33	0.128575	0.00398	393
Triclosan-coated Sutures	122	8.16	-5.79	0.11764	0.01093	746
Ghana Contaminated-Dirty (threshold value:0.915)						
Triclosan-coated Sutures	142	0.00	10.44	0.201907	0.00000	
Alcoholic Chlorhexidine	142	0.13	10.38	0.200766	0.00114	114
Usual Care	153	11.14	11.41	0.220622	-0.01986	Dominated
DALY: Disability Adjusted Life Year; ICER: Incremental cost-effectiveness ratio; NMB: Net Monetary Benefit						

Appendix Table A9.26 Cost per QALY deterministic sensitivity analysis scenario 17 results

Strategy	Healthcare Cost (Int$)	Incremental Healthcare Costs (Int$)	Societal Cost (Int$)	QALY	Incremental QALY	ICER (Int$)
DSA17: Minimum baseline 30 day postoperative probability of SSI required for any of the interventions to be cost-effective versus Usual Care						
India Clean-Contaminated (threshold value:0.023)						
Usual Care	45		0.98	0.0603		
Triclosan-coated Sutures	45	0.09	0.88	0.060333	0.00003	2,781
Alcoholic Chlorhexidine	48	3.20	0.95	0.06031	-0.00002	Dominated
India Contaminated-Dirty (threshold value:0.142)						
Usual Care	65		8.49	0.058644	0.00000	
Alcoholic Chlorhexidine	66	0.50	7.73	0.058823	0.00018	2,781
Triclosan-coated Sutures	66	0.48	8.32	0.058684	-0.00014	Dominated
Mexico Clean-Contaminated (threshold value:0.202)						
Usual Care	134		-8.48	0.057798		
Alcoholic Chlorhexidine	135	0.91	-8.23	0.057883	0.00008	10,780
Triclosan-coated Sutures	142	7.54	-7.63	0.058081	0.00020	37,978
Ghana Contaminated-Dirty (threshold value:0.035)						
Usual Care	28		1.32	0.06014		
Alcoholic Chlorhexidine	29	0.09	1.20	0.060183	0.00004	2,043
Triclosan-coated Sutures	29	0.28	1.29	0.060149	-0.00003	Dominated
ICER: Incremental cost-effectiveness ratio; NMB: Net Monetary Benefit; QALY: Quality Adjusted Life Year						

Appendix Table A9.27 Cost per DALY averted deterministic sensitivity analysis scenario 17 results

Strategy	Healthcare Cost (Int$)	Incremental Healthcare Costs (Int$)	Societal Cost (Int$)	DALY	Incremental DALY averted	ICER (Int$)
DSA17: Minimum baseline 30 day postoperative probability of SSI required for any of the interventions to be cost-effective versus Usual Care						
India Clean-Contaminated (threshold value:0.02)						
Usual Care	43	0.00	0.84	0.015076	0.00000	
Triclosan-coated Sutures	43	0.32	0.75	0.013569	0.00151	214
Alcoholic Chlorhexidine	46	3.03	0.81	0.014624	-0.00106	Dominated
India Contaminated-Dirty (threshold value:0.10)						
Usual Care	55	0.00	6.00	0.075641	0.00000	
Triclosan-coated Sutures	56	1.19	5.46	0.074128	0.00151	784
Alcoholic Chlorhexidine	56	1.46	6.00	0.068833	0.00681	214
Mexico Clean-Contaminated (threshold value:0.113)						
Usual Care	92	0.00	-4.74	0.096234	0.00000	
Alcoholic Chlorhexidine	95	2.15	-4.59	0.093347	0.00289	746
Triclosan-coated Sutures	105	10.44	-4.26	0.08661	0.00674	1549
Ghana Contaminated-Dirty (threshold value:0.031)						
Usual Care	27	0.00	1.19	0.022997	0.00000	
Alcoholic Chlorhexidine	27	0.24	1.08	0.020927	0.00207	114
Triclosan-coated Sutures	27	0.17	1.17	0.022537	-0.00161	Dominated
DALY: Disability Adjusted Life Year; ICER: Incremental cost-effectiveness ratio; NMB: Net Monetary Benefit						

Appendix Table A9.28 Cost per QALY deterministic sensitivity analysis scenario 18 results

Strategy	Healthcare Cost (Int$)	Incremental Healthcare Costs (Int$)	Societal Cost (Int$)	QALY	Incremental QALY	ICER (Int$)
DSA18: Minimum level of costs associated with SSI required for any of the interventions to remain cost-effective versus Usual Care						
India Clean-Contaminated (threshold value:71)						
Usual Care	40	0.00	6.52	0.058452	0.00000	
Triclosan-coated Sutures	41	0.60	5.87	0.058669	0.00022	2,781
Alcoholic Chlorhexidine	43	2.84	6.33	0.058517	-0.00015	Dominated
India Contaminated-Dirty (threshold value:101)						
Usual Care	59	0.00	18.02	0.056422	0.00000	
Alcoholic Chlorhexidine	60	1.05	16.40	0.0568	0.00038	2,781
Triclosan-coated Sutures	60	0.04	17.66	0.056506	-0.00029	Dominated
Mexico Clean-Contaminated (threshold value:647)						
Usual Care	141	0.00	-6.52	0.058452	0.00000	
Alcoholic Chlorhexidine	142	0.70	-6.33	0.058517	0.00007	10780
Triclosan-coated Sutures	149	7.05	-5.87	0.058669	0.00015	46318
Ghana Contaminated-Dirty (threshold value:29)						
Usual Care	21	0.00	11.41	0.056422	0.00000	
Triclosan-coated Sutures	21	0.53	11.18	0.056506	0.00008	Extended domination
Alcoholic Chlorhexidine	22	0.77	10.38	0.0568	0.00038	2,043
ICER: Incremental cost-effectiveness ratio; NMB: Net Monetary Benefit; QALY: Quality Adjusted Life Year						

Appendix Table A9.29 Cost per DALY averted deterministic sensitivity analysis scenario 18 results

Strategy	Healthcare Cost (Int$)	Incremental Healthcare Costs (Int$)	Societal Cost (Int$)	DALY	Incremental DALY averted	ICER (Int$)
DSA18: Minimum level of costs associated with SSI required for any of the interventions to remain cost-effective versus Usual Care						
India Clean-Contaminated (threshold value:-52)						
Usual Care	21	0.00	6.52	0.117478	0.00000	
Triclosan-coated Sutures	23	2.51	5.87	0.10573	0.01175	214
Alcoholic Chlorhexidine	25	1.50	6.33	0.113953	-0.00822	Dominated
India Contaminated-Dirty (threshold value:-22)						
Usual Care	22	0.00	18.02	0.227132	0.00000	
Triclosan-coated Sutures	24	1.83	17.66	0.222589	0.00454	Extended domination
Alcoholic Chlorhexidine	27	4.37	16.40	0.20669	0.02044	214
Mexico Clean-Contaminated (threshold value:162)						
Usual Care	65	0.00	-6.52	0.132551	0.00000	
Alcoholic Chlorhexidine	68	2.97	-6.33	0.128575	0.00398	746
Triclosan-coated Sutures	81	12.33	-5.87	0.119296	0.00928	1329
Ghana Contaminated-Dirty (threshold value:-26)						
Usual Care	4	0.00	11.41	0.220622	0.00000	
Triclosan-coated Sutures	5	0.86	11.18	0.21621	0.00441	Extended domination
Alcoholic Chlorhexidine	7	2.26	10.38	0.200766	0.01986	114
DALY: Disability Adjusted Life Year; ICER: Incremental cost-effectiveness ratio; NMB: Net Monetary Benefit						

Appendix Table A9.30 Cost per QALY deterministic sensitivity analysis scenario 19 results

Strategy	Healthcare Cost (Int$)	Incremental Healthcare Costs (Int$)	Societal Cost (Int$)	QALY	Incremental QALY	ICER (Int$)
DSA19: minimum level of SSI disutility required for any of the interventions to remain cost-effective versus Usual Care						
India Clean-Contaminated (threshold value:-3.4)						
Triclosan-coated Sutures	127	0.00	5.87	0.089858	0.00000	
Usual Care	136	9.03	6.52	0.093106	0.00325	2,781
Alcoholic Chlorhexidine	137	0.55	6.33	0.092132	-0.00097	Dominated
India Contaminated-Dirty (threshold value:-0.699)						
Alcoholic Chlorhexidine	103		16.40	0.072173		
Usual Care	106	3.18	18.02	0.073315	0.00114	2,781
Triclosan-coated Sutures	106	0.16	17.66	0.073061	-0.00025	Dominated
Mexico Clean-Contaminated (threshold value:0.49)						
Usual Care	112	0.00	-6.52	0.055795	0.00000	
Alcoholic Chlorhexidine	114	1.56	-6.33	0.055939	0.00014	10780
Triclosan-coated Sutures	123	9.06	-5.87	0.056278	0.00034	26775
Ghana Contaminated-Dirty (threshold value:-3.28)						
Alcoholic Chlorhexidine	142		10.38	0.115772		
Triclosan-coated Sutures	151	9.02	11.18	0.120014	0.00424	Extended domination
Usual Care	153	11.14	11.41	0.121226	0.00545	2,043
ICER: Incremental cost-effectiveness ratio; NMB: Net Monetary Benefit; QALY: Quality Adjusted Life Year						

Appendix Table A9.31 Expected value of perfect information (international dollars 2020)

Cost per QALY approach							
Mexico Clean contaminated		**India contaminated dirty**		**India clean-contaminated**		**Ghana contaminated dirty**	
WTP (Int$)	EVPI (Int$)	WTP (Int$)	EVPI (Int$)	WTP (Int$)	EVPI (Int$)	WTP (Int$)	EVPI (Int$)
0	3.74	0	2.16	0	0.77	0	0.52
1078	3.83	278.1	2.13	278.1	0.77	204.3	0.52
2156	3.92	556.2	2.10	556.2	0.77	408.6	0.52
3234	4.01	834.3	2.06	834.3	0.77	612.9	0.52
4312	4.10	1112.4	2.03	1112.4	0.78	817.2	0.52
5390	4.20	1390.5	2.00	1390.5	0.78	1021.5	0.52
6468	4.29	1668.6	1.97	1668.6	0.78	1225.8	0.53
7546	4.39	1946.7	1.94	1946.7	0.78	1430.1	0.53
8624	4.49	2224.8	1.92	2224.8	0.78	1634.4	0.53
9702	4.59	2502.9	1.89	2502.9	0.79	1838.7	0.53
10780	4.69	2781	1.86	2781	0.79	2043	0.53
11858	4.79	3059.1	1.83	3059.1	0.79	2247.3	0.54
12936	4.90	3337.2	1.81	3337.2	0.79	2451.6	0.54
14014	5.00	3615.3	1.78	3615.3	0.80	2655.9	0.54
15092	5.11	3893.4	1.76	3893.4	0.80	2860.2	0.54
16170	5.22	4171.5	1.73	4171.5	0.80	3064.5	0.54
17248	5.33	4449.6	1.71	4449.6	0.80	3268.8	0.54
18326	5.44	4727.7	1.68	4727.7	0.81	3473.1	0.55
19404	5.56	5005.8	1.66	5005.8	0.81	3677.4	0.55
20482	5.67	5283.9	1.64	5283.9	0.81	3881.7	0.55
21560	5.79	5562	1.62	5562	0.81	4086	0.55

Cost per DALY averted approach							
Mexico Clean contaminated		**India contaminated dirty**		**India clean-contaminated**		**Ghana contaminated dirty**	
WTP (Int$)	EVPI (Int$)	WTP (Int$)	EVPI (Int$)	WTP (Int$)	EVPI (Int$)	WTP (Int$)	EVPI (Int$)
0	3.74	0	2.16	0	0.77	0	0.52
74.6	4.12	21.4	2.03	21.4	0.78	11.4	0.52
149.2	4.52	42.8	1.91	42.8	0.78	22.8	0.53
223.8	4.94	64.2	1.80	64.2	0.79	34.2	0.53
298.4	5.40	85.6	1.71	85.6	0.80	45.6	0.54
373	5.88	107	1.61	107	0.81	57	0.54
447.6	6.19	128.4	1.53	128.4	0.83	68.4	0.55
522.2	6.43	149.8	1.46	149.8	0.84	79.8	0.55
596.8	6.71	171.2	1.39	171.2	0.85	91.2	0.56
671.4	7.00	192.6	1.33	192.6	0.86	102.6	0.56
746	7.32	214	1.28	214	0.87	114	0.57
820.6	7.67	235.4	1.24	235.4	0.88	125.4	0.57
895.2	8.04	256.8	1.20	256.8	0.90	136.8	0.58
969.8	8.44	278.2	1.16	278.2	0.91	148.2	0.59
1044.4	8.80	299.6	1.13	299.6	0.92	159.6	0.59
1119	8.58	321	1.10	321	0.94	171	0.60
1193.6	8.38	342.4	1.08	342.4	0.95	182.4	0.60
1268.2	8.20	363.8	1.06	363.8	0.96	193.8	0.61
1342.8	8.04	385.2	1.05	385.2	0.98	205.2	0.62
1417.4	7.89	406.6	1.03	406.6	0.99	216.6	0.62
1492	7.76	428	1.02	428	1.01	228	0.63
EVPI: Expected Value of Perfect Information; WTP: Willingness to Pay							

Appendix Table A9.32 Expected value of perfect parameter information treatment effectiveness (international dollars 2020)

Cost per QALY approach							
Mexico Clean contaminated		**India contaminated dirty**		**India clean-contaminated**		**Ghana contaminated dirty**	
WTP (Int$)	EVPPI (Int$)	WTP (Int$)	EVPPI (Int$)	WTP (Int$)	EVPPI (Int$)	WTP (Int$)	EVPPI (Int$)
0	0.03	0	0.63	0	0.52	0	0.49
1078	0.04	278.1	0.63	278.1	0.52	204.3	0.49
2156	0.06	556.2	0.63	556.2	0.53	408.6	0.49
3234	0.08	834.3	0.63	834.3	0.53	612.9	0.50
4312	0.11	1112.4	0.63	1112.4	0.53	817.2	0.50
5390	0.14	1390.5	0.64	1390.5	0.53	1021.5	0.50
6468	0.18	1668.6	0.64	1668.6	0.53	1225.8	0.50
7546	0.22	1946.7	0.64	1946.7	0.54	1430.1	0.51
8624	0.26	2224.8	0.64	2224.8	0.54	1634.4	0.51
9702	0.32	2502.9	0.65	2502.9	0.54	1838.7	0.51
10780	0.37	2781	0.65	2781	0.54	2043	0.51
11858	0.44	3059.1	0.65	3059.1	0.54	2247.3	0.52
12936	0.51	3337.2	0.65	3337.2	0.54	2451.6	0.52
14014	0.59	3615.3	0.66	3615.3	0.55	2655.9	0.52
15092	0.68	3893.4	0.66	3893.4	0.55	2860.2	0.52
16170	0.77	4171.5	0.66	4171.5	0.55	3064.5	0.53
17248	0.86	4449.6	0.66	4449.6	0.55	3268.8	0.53
18326	0.97	4727.7	0.67	4727.7	0.55	3473.1	0.53
19404	1.07	5005.8	0.67	5005.8	0.56	3677.4	0.53
20482	1.18	5283.9	0.67	5283.9	0.56	3881.7	0.53
21560	1.30	5562	0.67	5562	0.56	4086	0.54

Cost per DALY averted approach							
Mexico Clean contaminated		**India contaminated dirty**		**India clean-contaminated**		**Ghana contaminated dirty**	
WTP (Int$)	EVPPI (Int$)	WTP (Int$)	EVPPI (Int$)	WTP (Int$)	EVPPI (Int$)	WTP (Int$)	EVPPI (Int$)
0	0.03	0	0.62	0	0.52	0	0.49
74.6	0.11	21.4	0.62	21.4	0.53	11.4	0.50
149.2	0.28	42.8	0.63	42.8	0.54	22.8	0.51
223.8	0.54	64.2	0.64	64.2	0.54	34.2	0.51
298.4	0.91	85.6	0.65	85.6	0.55	45.6	0.52
373	1.36	107	0.66	107	0.56	57	0.53
447.6	1.83	128.4	0.68	128.4	0.57	68.4	0.53
522.2	2.31	149.8	0.69	149.8	0.57	79.8	0.54
596.8	2.82	171.2	0.70	171.2	0.58	91.2	0.55
671.4	3.37	192.6	0.71	192.6	0.60	102.6	0.55
746	3.94	214	0.73	214	0.62	114	0.56
820.6	4.53	235.4	0.74	235.4	0.63	125.4	0.57
895.2	5.14	256.8	0.75	256.8	0.65	136.8	0.57
969.8	5.76	278.2	0.76	278.2	0.66	148.2	0.58
1044.4	5.85	299.6	0.78	299.6	0.68	159.6	0.59
1119	5.81	321	0.79	321	0.70	171	0.59
1193.6	5.78	342.4	0.81	342.4	0.71	182.4	0.60
1268.2	5.76	363.8	0.82	363.8	0.73	193.8	0.61
1342.8	5.75	385.2	0.83	385.2	0.75	205.2	0.61
1417.4	5.74	406.6	0.85	406.6	0.76	216.6	0.62
1492	5.74	428	0.86	428	0.78	228	0.63
EVPPI: Expected Value of Perfect Parameter Information; WTP: Willingness to Pay							

Appendix Table A9.33 Expected value of perfect parameter information SSI cost (international dollars 2020)

Cost per QALY approach							
Mexico Clean contaminated		**India contaminated dirty**		**India clean-contaminated**		**Ghana contaminated dirty**	
WTP (Int$)	EVPPI (Int$)	WTP (Int$)	EVPPI (Int$)	WTP (Int$)	EVPPI (Int$)	WTP (Int$)	EVPPI (Int$)
0	1.66	0	0.00	0	0.02	0	0.00
1078	1.71	278.1	0.00	278.1	0.02	204.3	0.00
2156	1.76	556.2	0.00	556.2	0.02	408.6	0.00
3234	1.81	834.3	0.00	834.3	0.02	612.9	0.00
4312	1.87	1112.4	0.00	1112.4	0.02	817.2	0.00
5390	1.92	1390.5	0.00	1390.5	0.03	1021.5	0.00
6468	1.97	1668.6	0.00	1668.6	0.03	1225.8	0.00
7546	2.03	1946.7	0.00	1946.7	0.03	1430.1	0.00
8624	2.09	2224.8	0.00	2224.8	0.03	1634.4	0.00
9702	2.15	2502.9	0.00	2502.9	0.03	1838.7	0.00
10780	2.21	2781	0.00	2781	0.03	2043	0.00
11858	2.27	3059.1	0.00	3059.1	0.04	2247.3	0.00
12936	2.33	3337.2	0.00	3337.2	0.04	2451.6	0.00
14014	2.39	3615.3	0.00	3615.3	0.04	2655.9	0.00
15092	2.45	3893.4	0.00	3893.4	0.04	2860.2	0.00
16170	2.52	4171.5	0.00	4171.5	0.05	3064.5	0.00
17248	2.59	4449.6	0.00	4449.6	0.05	3268.8	0.00
18326	2.65	4727.7	0.00	4727.7	0.05	3473.1	0.00
19404	2.72	5005.8	0.00	5005.8	0.05	3677.4	0.00
20482	2.79	5283.9	0.00	5283.9	0.06	3881.7	0.00
21560	2.84	5562	0.00	5562	0.06	4086	0.00

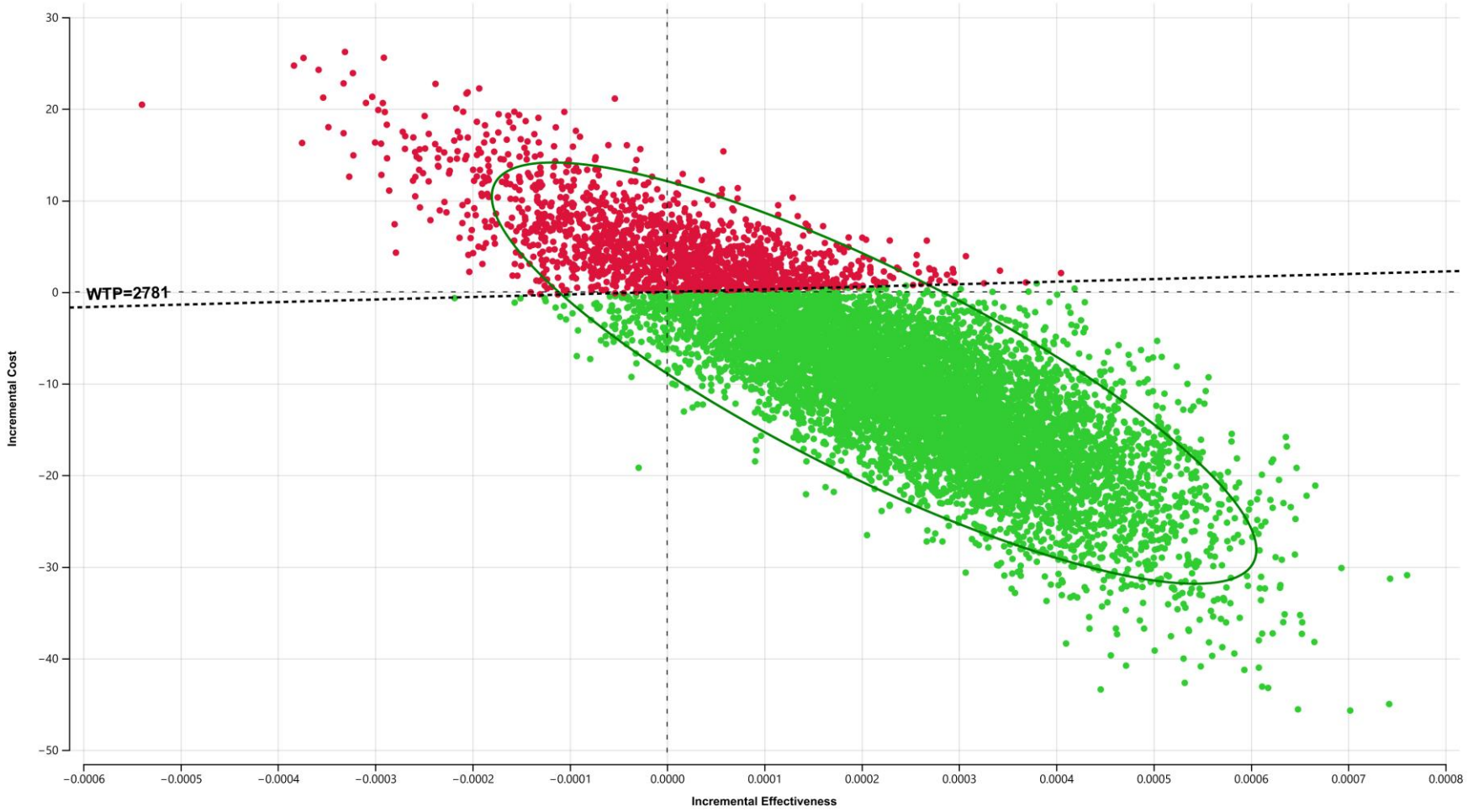
Cost per DALY averted approach							
Mexico Clean contaminated		**India contaminated dirty**		**India clean-contaminated**		**Ghana contaminated dirty**	
WTP (Int$)	EVPPI (Int$)	WTP (Int$)	EVPPI (Int$)	WTP (Int$)	EVPPI (Int$)	WTP (Int$)	EVPPI (Int$)
0	1.66	0	1.30	0	0.00	0	0.00
74.6	1.87	21.4	1.17	21.4	0.00	11.4	0.00
149.2	2.10	42.8	1.05	42.8	0.00	22.8	0.00
223.8	2.35	64.2	0.94	64.2	0.00	34.2	0.00
298.4	2.62	85.6	0.84	85.6	0.00	45.6	0.00
373	2.84	107	0.74	107	0.00	57	0.00
447.6	2.87	128.4	0.66	128.4	0.00	68.4	0.00
522.2	2.93	149.8	0.58	149.8	0.00	79.8	0.00
596.8	3.01	171.2	0.51	171.2	0.00	91.2	0.00
671.4	3.12	192.6	0.45	192.6	0.00	102.6	0.00
746	3.25	214	0.39	214	0.00	114	0.00
820.6	3.41	235.4	0.34	235.4	0.00	125.4	0.00
895.2	3.60	256.8	0.30	256.8	0.00	136.8	0.00
969.8	3.80	278.2	0.26	278.2	0.00	148.2	0.00
1044.4	4.04	299.6	0.22	299.6	0.00	159.6	0.00
1119	3.76	321	0.19	321	0.00	171	0.00
1193.6	3.40	342.4	0.16	342.4	0.00	182.4	0.00
1268.2	3.07	363.8	0.13	363.8	0.00	193.8	0.00
1342.8	2.77	385.2	0.11	385.2	0.00	205.2	0.00
1417.4	2.50	406.6	0.09	406.6	0.00	216.6	0.00
1492	2.24	428	0.08	428	0.00	228	0.00
EVPPI: Expected Value of Perfect Parameter Information; WTP: Willingness to Pay							

Appendix Table A9.34 Expected value of perfect parameter information SSI utility decrements (international dollars 2020)

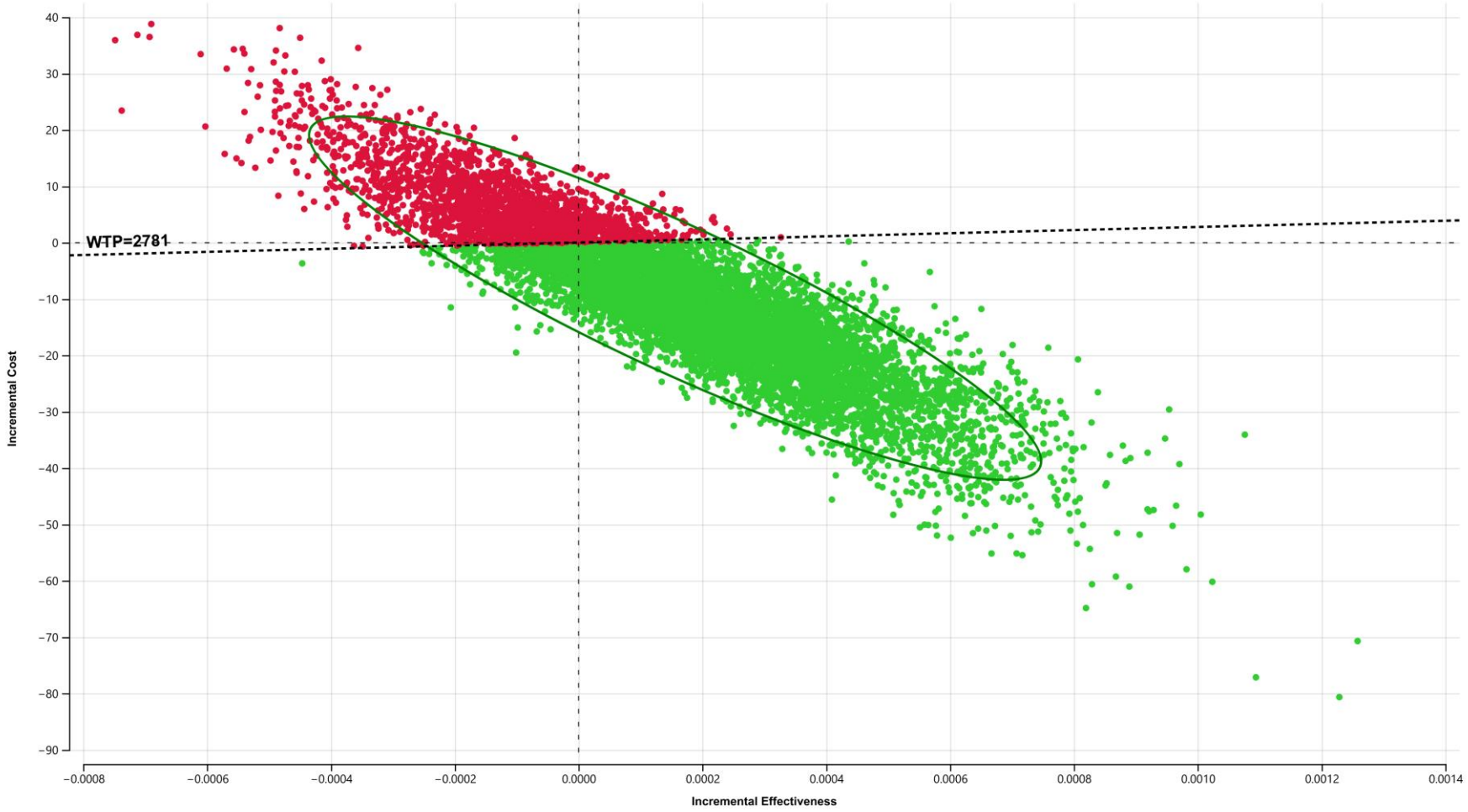
Cost per QALY approach							
Mexico Clean contaminated		**India contaminated dirty**		**India clean-contaminated**		**Ghana contaminated dirty**	
WTP (Int$)	EVPPI (Int$)	WTP (Int$)	EVPPI (Int$)	WTP (Int$)	EVPPI (Int$)	WTP (Int$)	EVPPI (Int$)
0	0.00	0	0.00	0	0.00	0	0.00
1078	0.00	278.1	0.00	278.1	0.00	204.3	0.00
2156	0.00	556.2	0.00	556.2	0.00	408.6	0.00
3234	0.00	834.3	0.00	834.3	0.00	612.9	0.00
4312	0.00	1112.4	0.00	1112.4	0.00	817.2	0.00
5390	0.00	1390.5	0.00	1390.5	0.00	1021.5	0.00
6468	0.00	1668.6	0.00	1668.6	0.00	1225.8	0.00
7546	0.00	1946.7	0.00	1946.7	0.00	1430.1	0.00
8624	0.00	2224.8	0.00	2224.8	0.00	1634.4	0.00
9702	0.00	2502.9	0.00	2502.9	0.00	1838.7	0.00
10780	0.00	2781	0.00	2781	0.00	2043	0.00
11858	0.00	3059.1	0.00	3059.1	0.00	2247.3	0.00
12936	0.00	3337.2	0.00	3337.2	0.00	2451.6	0.00
14014	0.00	3615.3	0.00	3615.3	0.00	2655.9	0.00
15092	0.00	3893.4	0.00	3893.4	0.00	2860.2	0.00
16170	0.00	4171.5	0.00	4171.5	0.00	3064.5	0.00
17248	0.00	4449.6	0.00	4449.6	0.00	3268.8	0.00
18326	0.00	4727.7	0.00	4727.7	0.00	3473.1	0.00
19404	0.00	5005.8	0.00	5005.8	0.00	3677.4	0.00
20482	0.00	5283.9	0.00	5283.9	0.00	3881.7	0.00
21560	0.00	5562	0.00	5562	0.00	4086	0.00

Cost per DALY averted approach							
Mexico Clean contaminated		**India contaminated dirty**		**India clean-contaminated**		**Ghana contaminated dirty**	
WTP (Int$)	EVPPI (Int$)	WTP (Int$)	EVPPI (Int$)	WTP (Int$)	EVPPI (Int$)	WTP (Int$)	EVPPI (Int$)
0	0.00	0	0.00	0	0.00	0	0.00
74.6	0.00	21.4	0.00	21.4	0.00	11.4	0.00
149.2	0.00	42.8	0.00	42.8	0.00	22.8	0.00
223.8	0.00	64.2	0.00	64.2	0.00	34.2	0.00
298.4	0.00	85.6	0.00	85.6	0.00	45.6	0.00
373	0.00	107	0.00	107	0.00	57	0.00
447.6	0.00	128.4	0.00	128.4	0.00	68.4	0.00
522.2	0.00	149.8	0.00	149.8	0.00	79.8	0.00
596.8	0.00	171.2	0.00	171.2	0.00	91.2	0.00
671.4	0.00	192.6	0.00	192.6	0.00	102.6	0.00
746	0.00	214	0.00	214	0.00	114	0.00
820.6	0.00	235.4	0.00	235.4	0.00	125.4	0.00
895.2	0.00	256.8	0.00	256.8	0.00	136.8	0.00
969.8	0.00	278.2	0.00	278.2	0.00	148.2	0.00
1044.4	0.01	299.6	0.00	299.6	0.00	159.6	0.00
1119	0.00	321	0.00	321	0.00	171	0.00
1193.6	0.00	342.4	0.00	342.4	0.00	182.4	0.00
1268.2	0.00	363.8	0.00	363.8	0.00	193.8	0.00
1342.8	0.00	385.2	0.00	385.2	0.00	205.2	0.00
1417.4	0.00	406.6	0.00	406.6	0.00	216.6	0.00
1492	0.00	428	0.00	428	0.00	228	0.00
EVPPI: Expected Value of Perfect Parameter Information; WTP: Willingness to Pay							

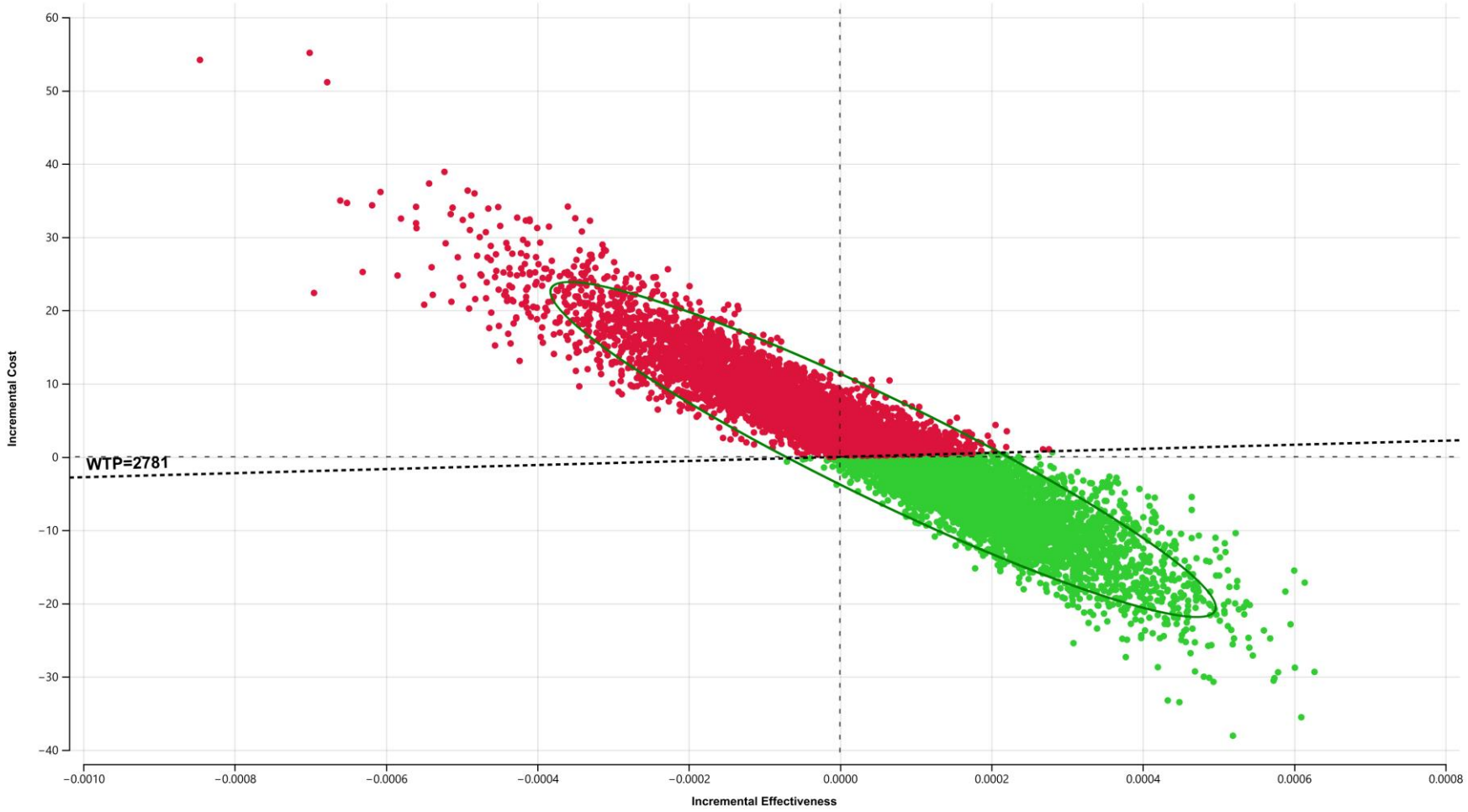
Appendix Figure A9.1 India Clean-Contaminated incremental cost-effectiveness scatterplot Triclosan-coated Sutures versus Usual Care (Cost per QALY approach)



Appendix Figure A9.2 India Clean-Contaminated incremental cost-effectiveness scatterplot Triclosan-coated Sutures versus Alcoholic Chlorhexidine (Cost per QALY approach)



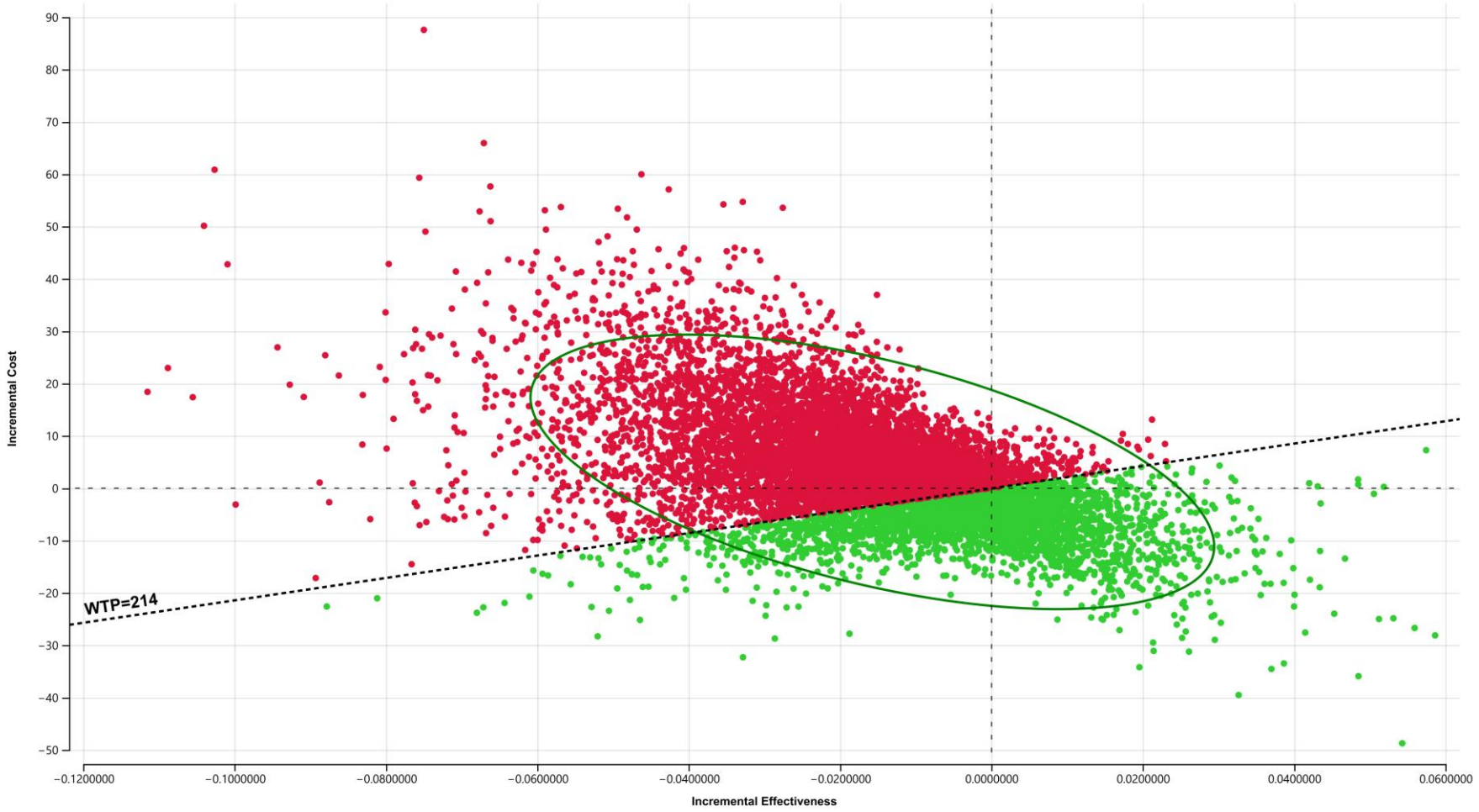
Appendix Figure A9.3 Incremental cost-effectiveness scatterplot Alcoholic Chlorhexidine versus Usual Care India Clean-Contaminated (Cost per QALY approach)



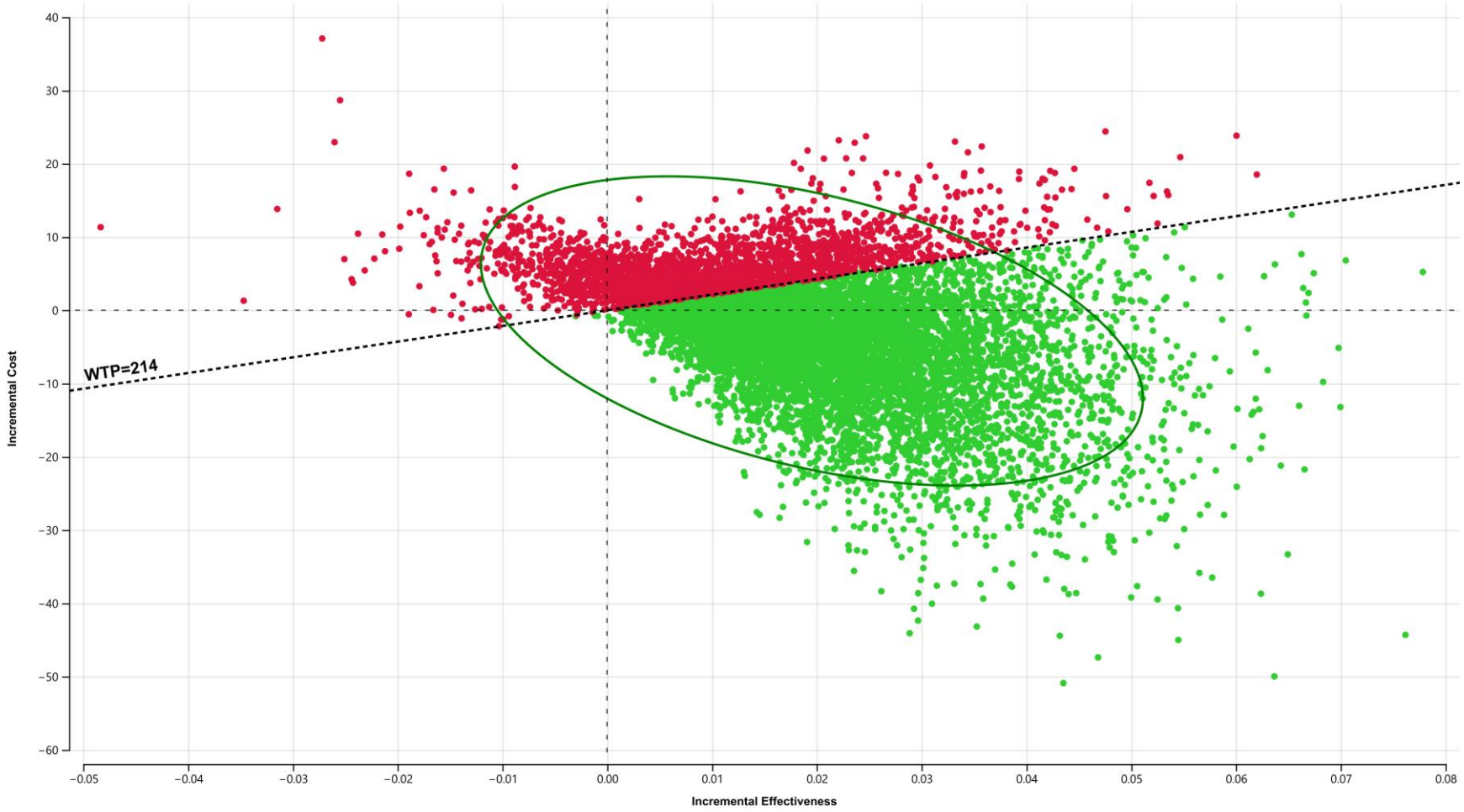
Appendix Figure A9.4 Incremental cost-effectiveness scatterplot Triclosan-coated Sutures versus Usual Care India Clean-Contaminated (Cost per DALY averted approach)



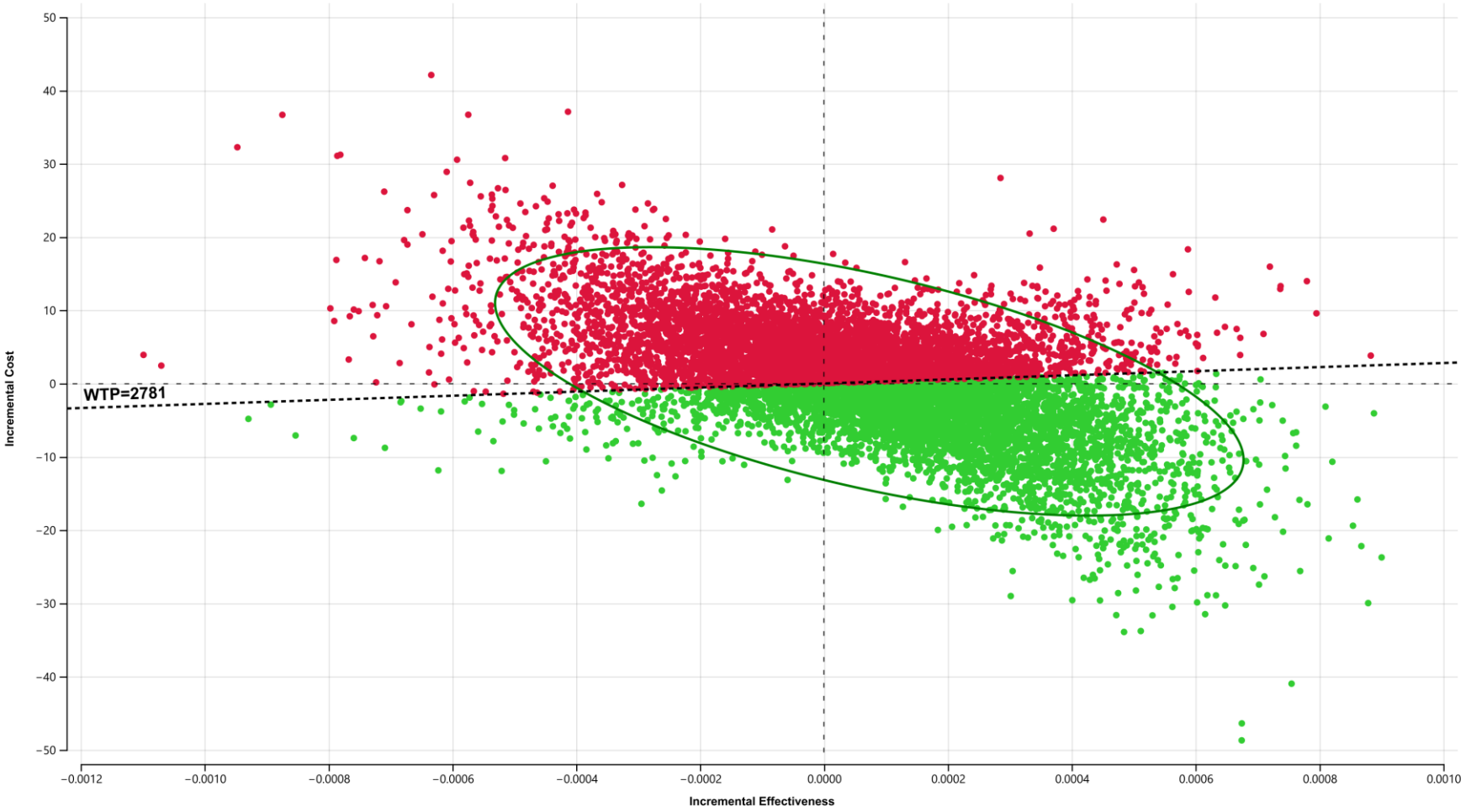
Appendix Figure A9.5 Incremental cost-effectiveness scatterplot Triclosan-coated Sutures versus Alcoholic Chlorhexidine India Clean-Contaminated (Cost per DALY averted approach)



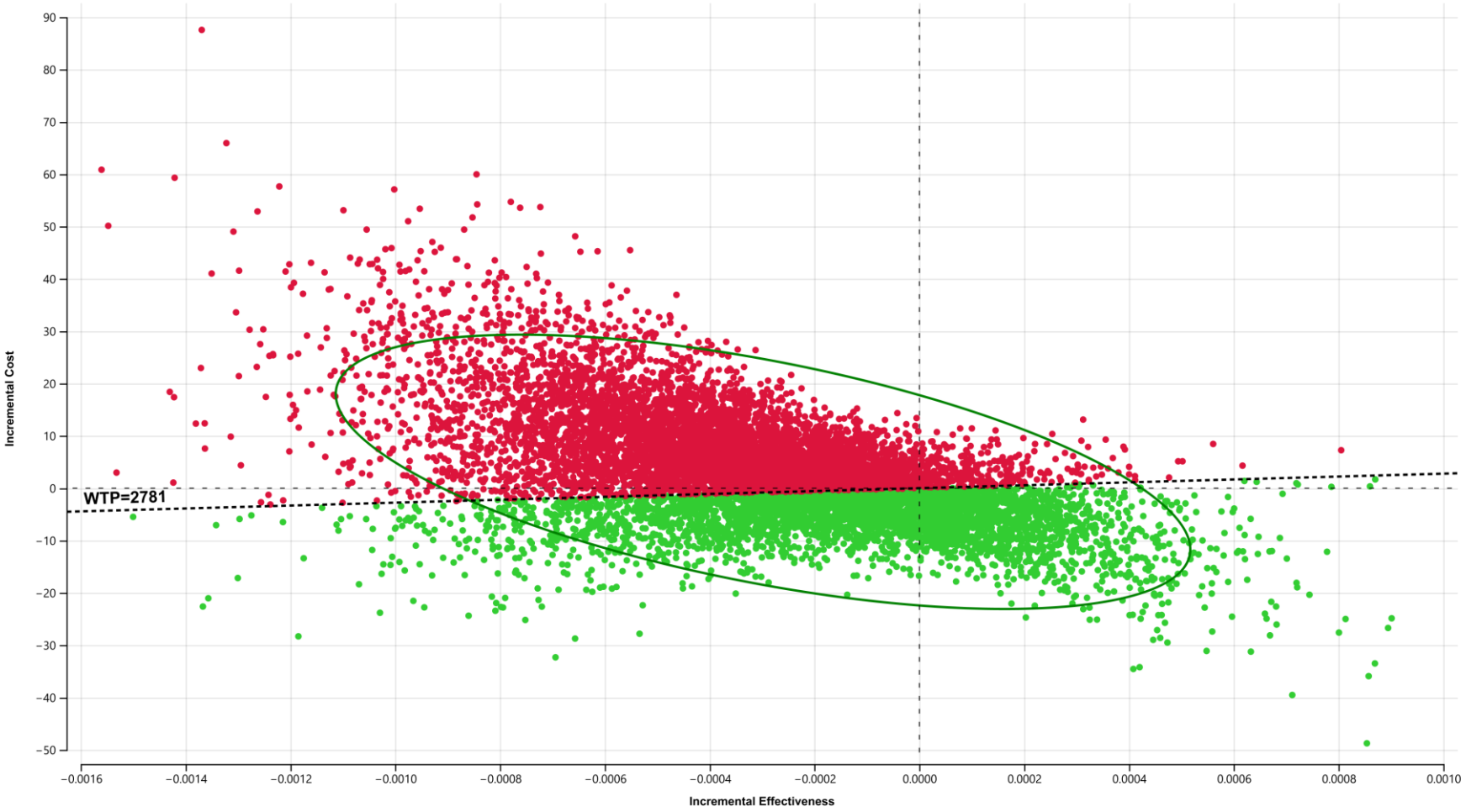
Appendix Figure A9.6 Incremental cost-effectiveness scatterplot Alcoholic Chlorhexidine versus Usual Care India Clean-Contaminated (Cost per DALY averted approach)



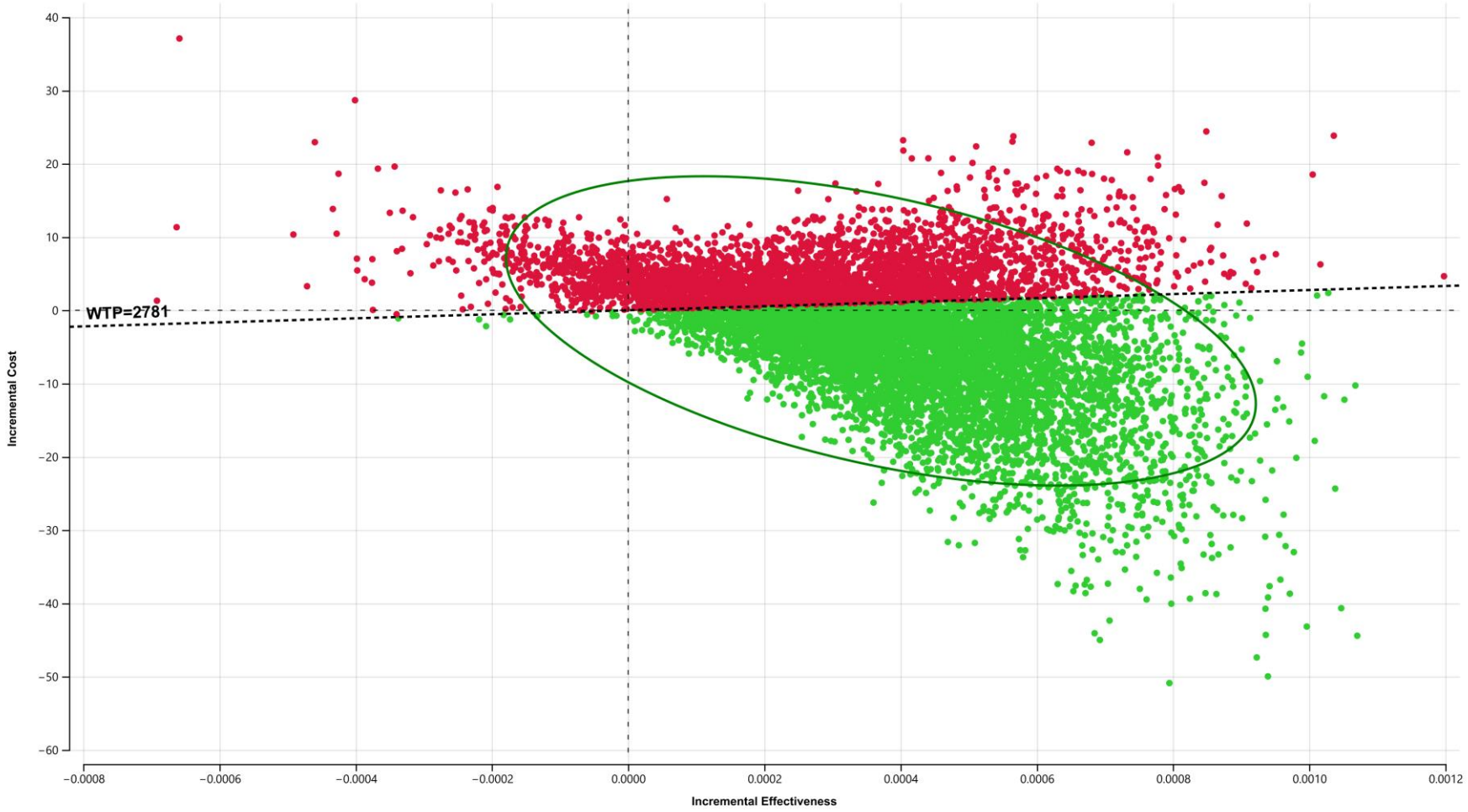
Appendix Figure A9.7 Incremental cost-effectiveness scatterplot Triclosan-coated Sutures versus Usual Care India Contaminated-Dirty (Cost per QALY approach)



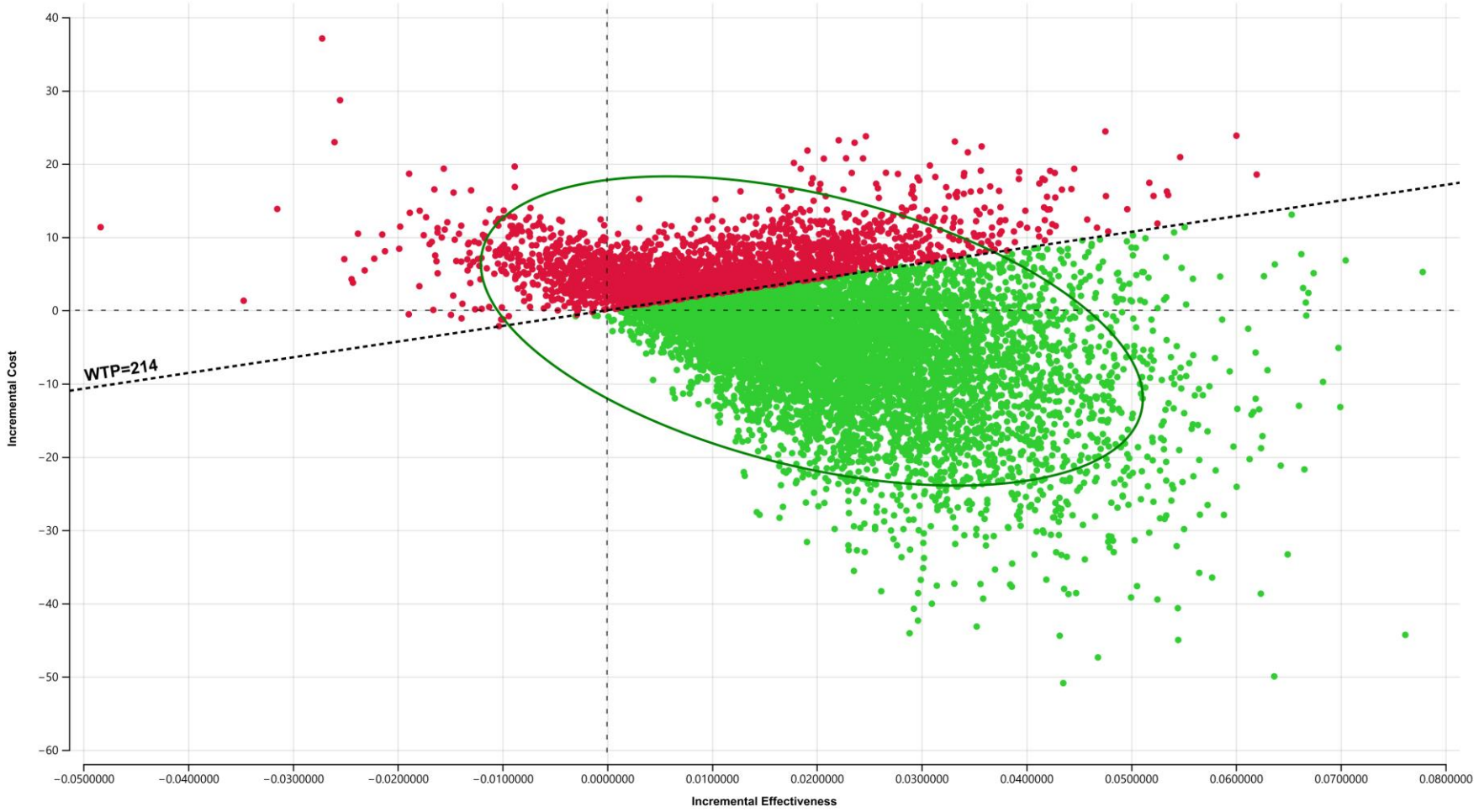
Appendix Figure A9.8 Incremental cost-effectiveness scatterplot Triclosan-coated Sutures versus Alcoholic Chlorhexidine India Contaminated-Dirty (Cost per QALY approach)



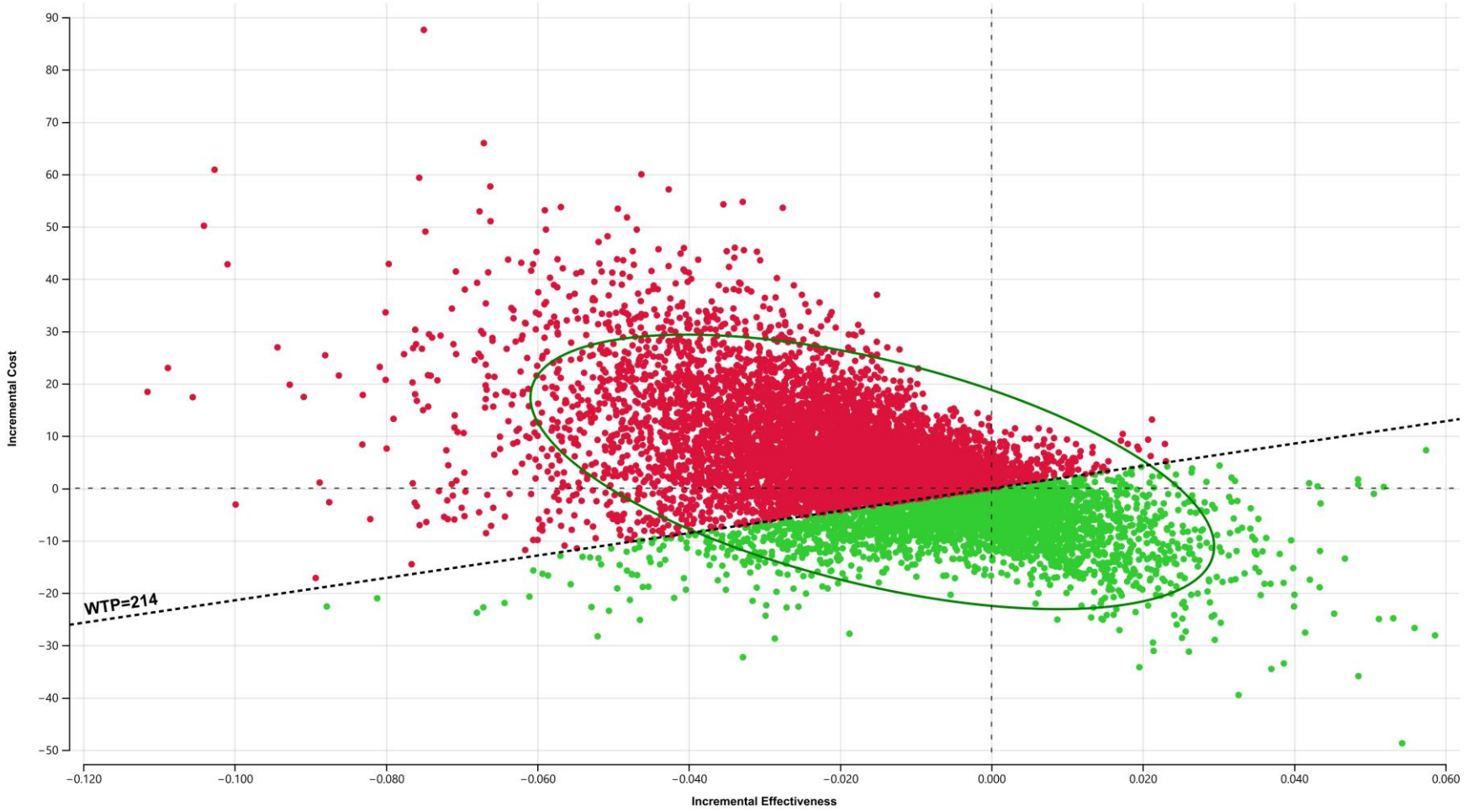
Appendix Figure A9.9 Incremental cost-effectiveness scatterplot Alcoholic Chlorhexidine versus Usual Care India Contaminated-Dirty (Cost per QALY approach)



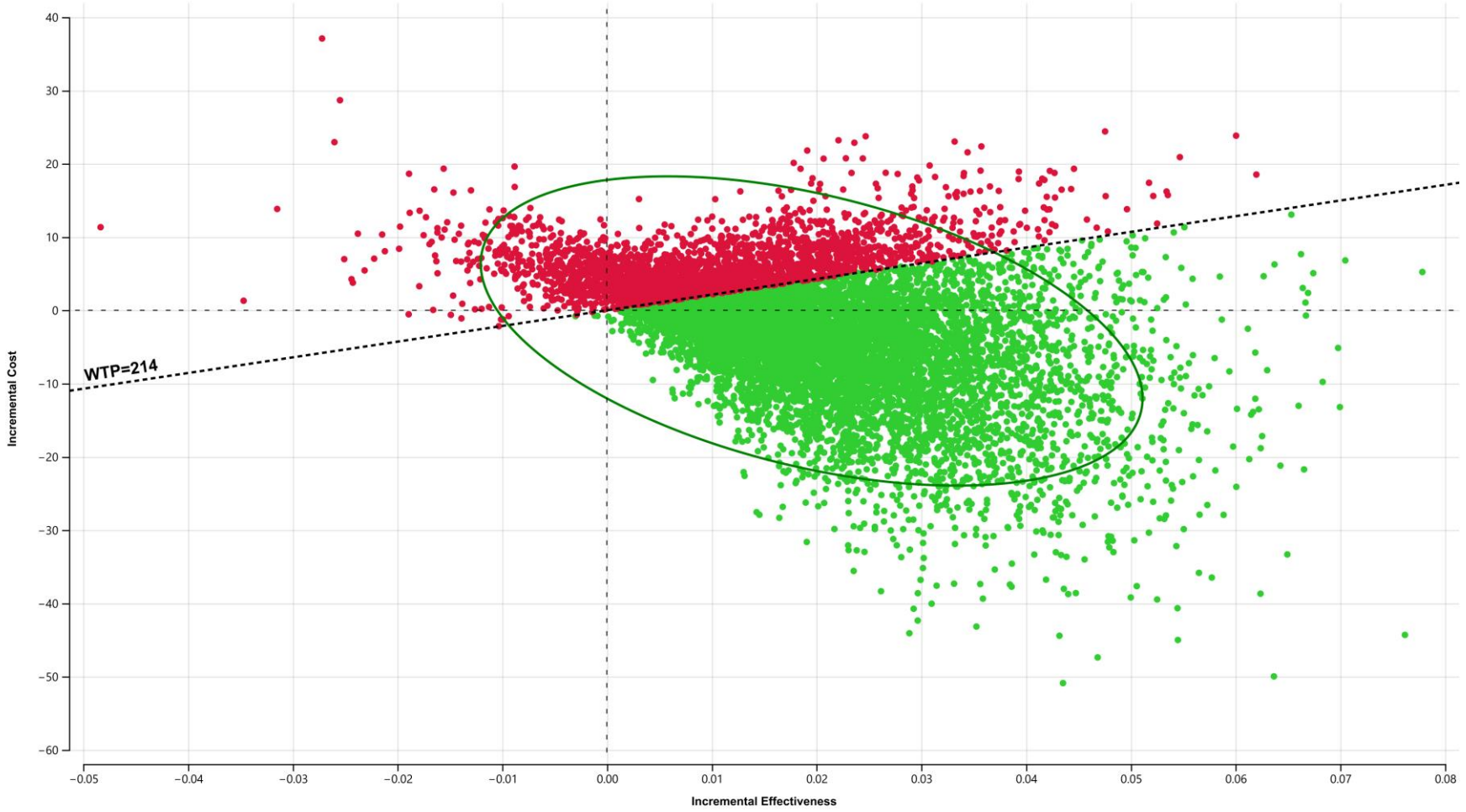
Appendix Figure A9.10 Incremental cost-effectiveness scatterplot Triclosan-coated Sutures versus Usual Care India Contaminated-Dirty (Cost per DALY averted approach)



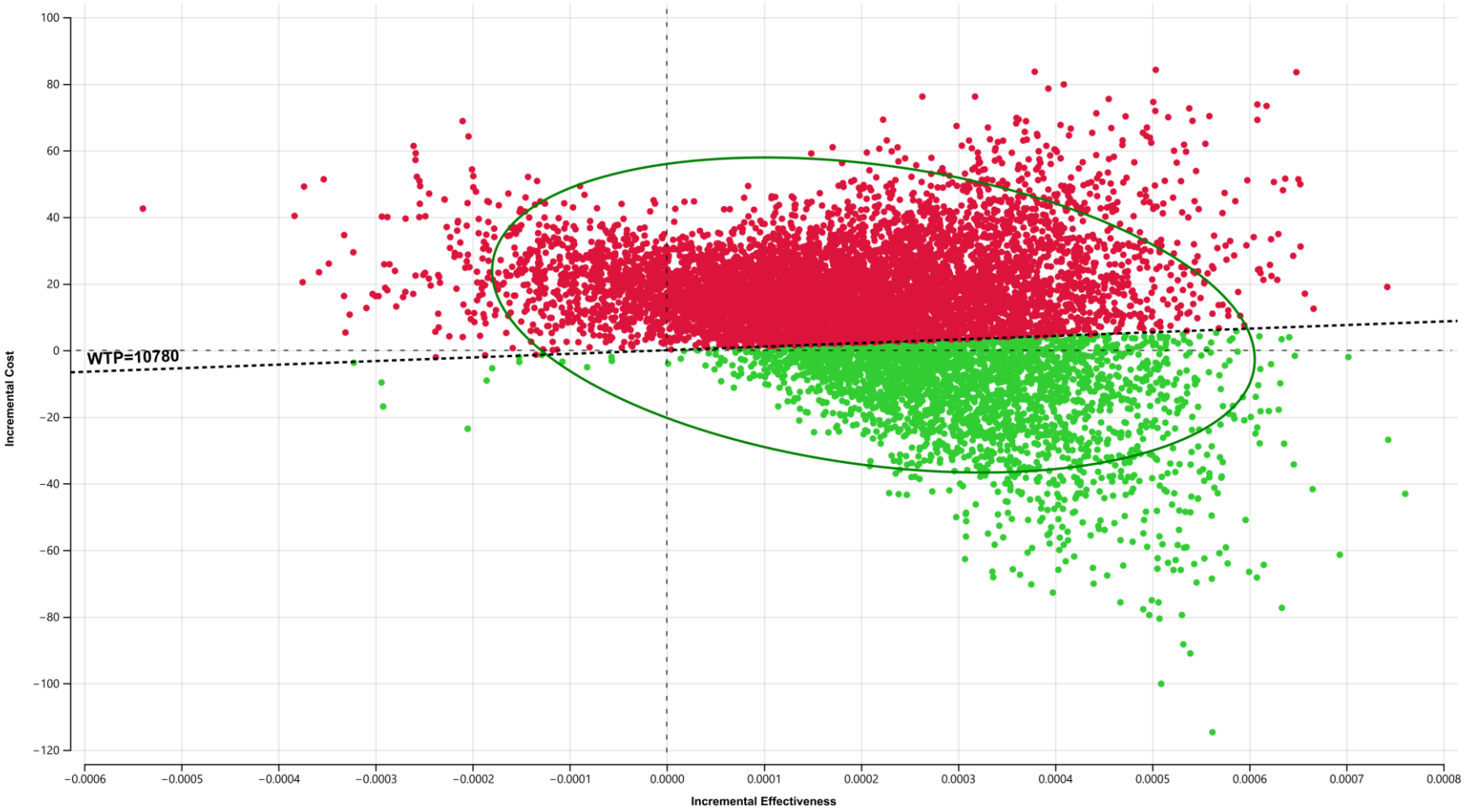
Appendix Figure A9.11 Incremental cost-effectiveness scatterplot Triclosan-coated Sutures versus Alcoholic Chlorhexidine India Contaminated-Dirty (Cost per DALY averted approach)



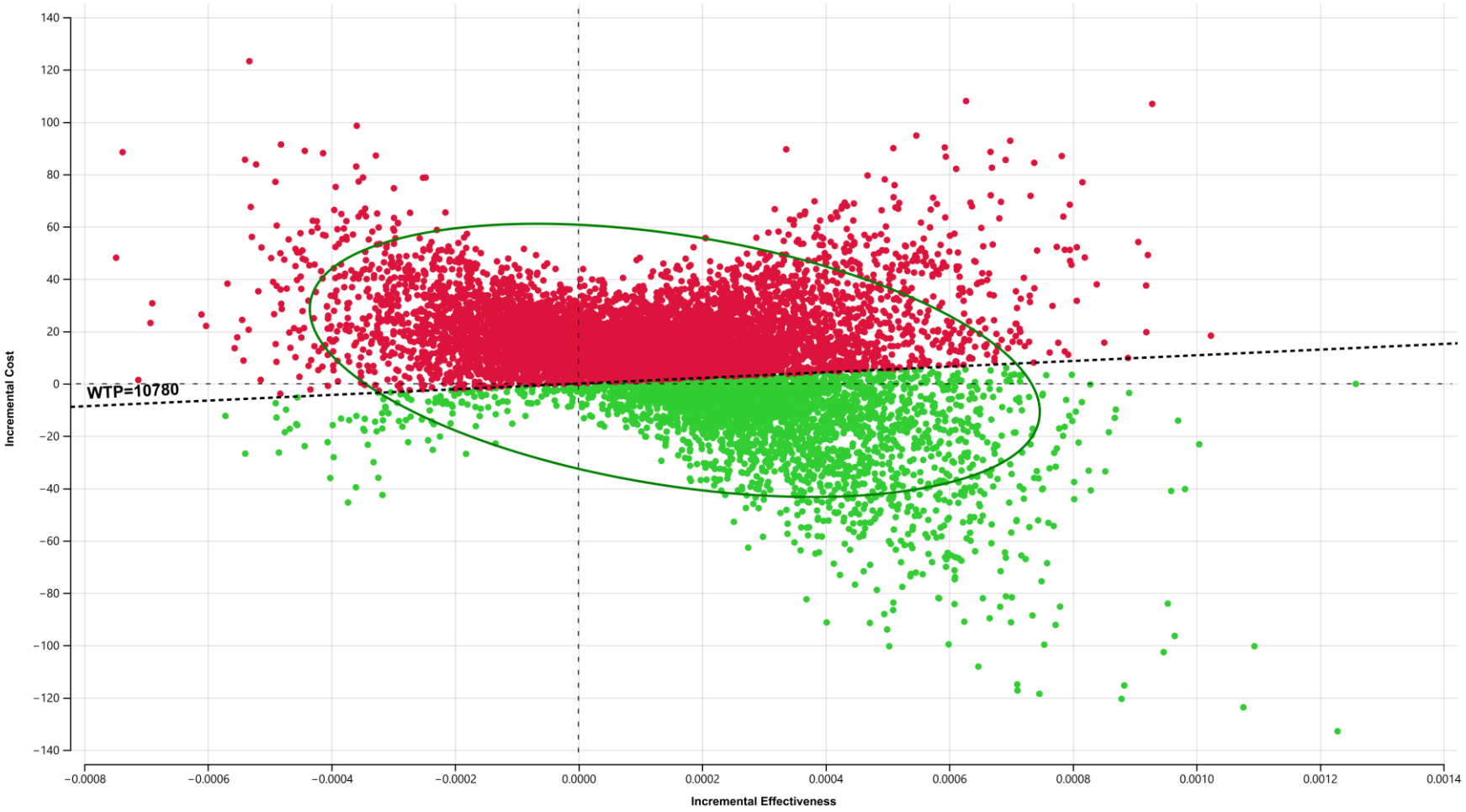
Appendix Figure A9.12 Incremental cost-effectiveness scatterplot Alcoholic Chlorhexidine versus Usual Care India Contaminated-Dirty (Cost per DALY averted approach)



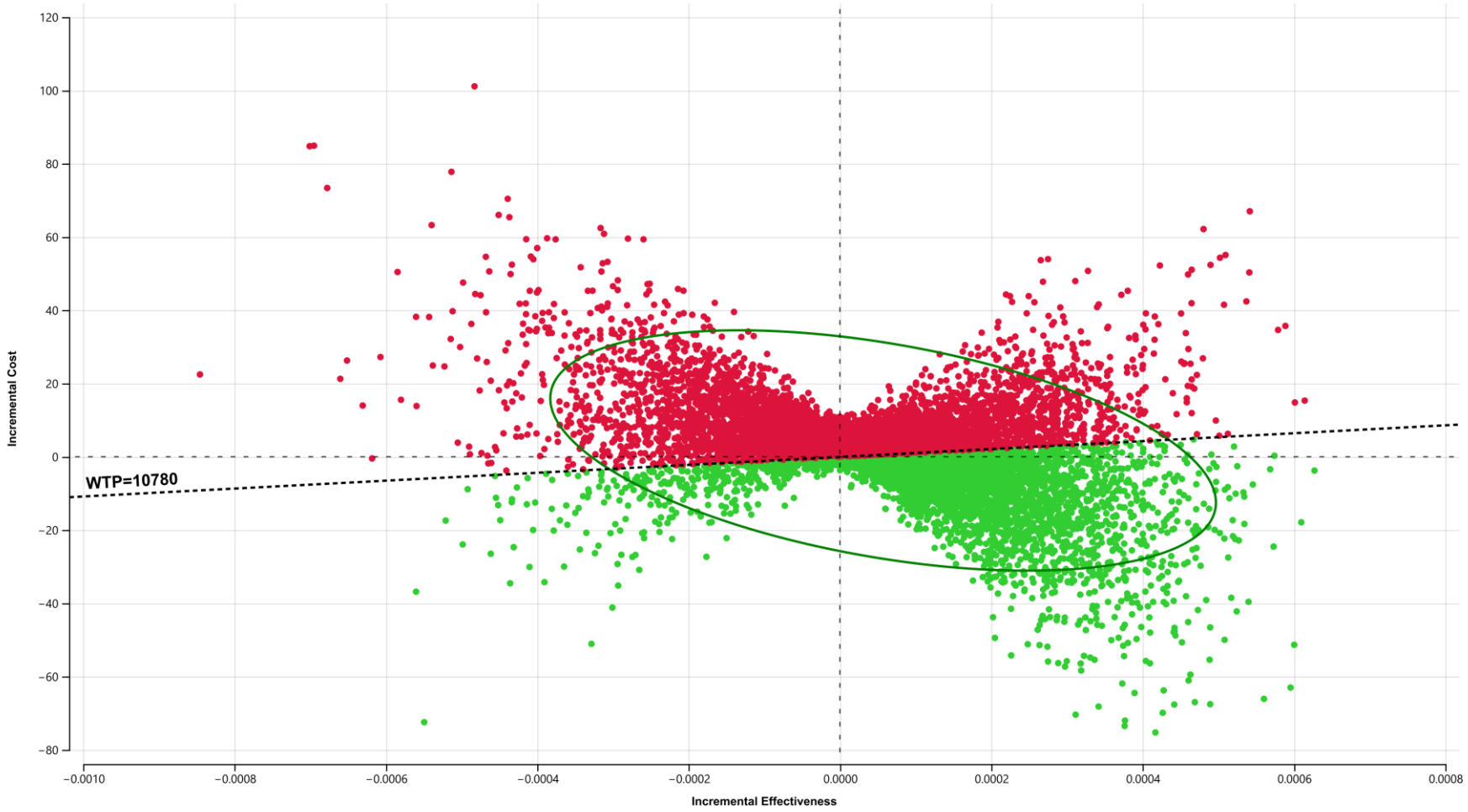
Appendix Figure A9.13 Incremental cost-effectiveness scatterplot Triclosan-coated Sutures versus Usual Care Mexico Clean-Contaminated (Cost per QALY approach)



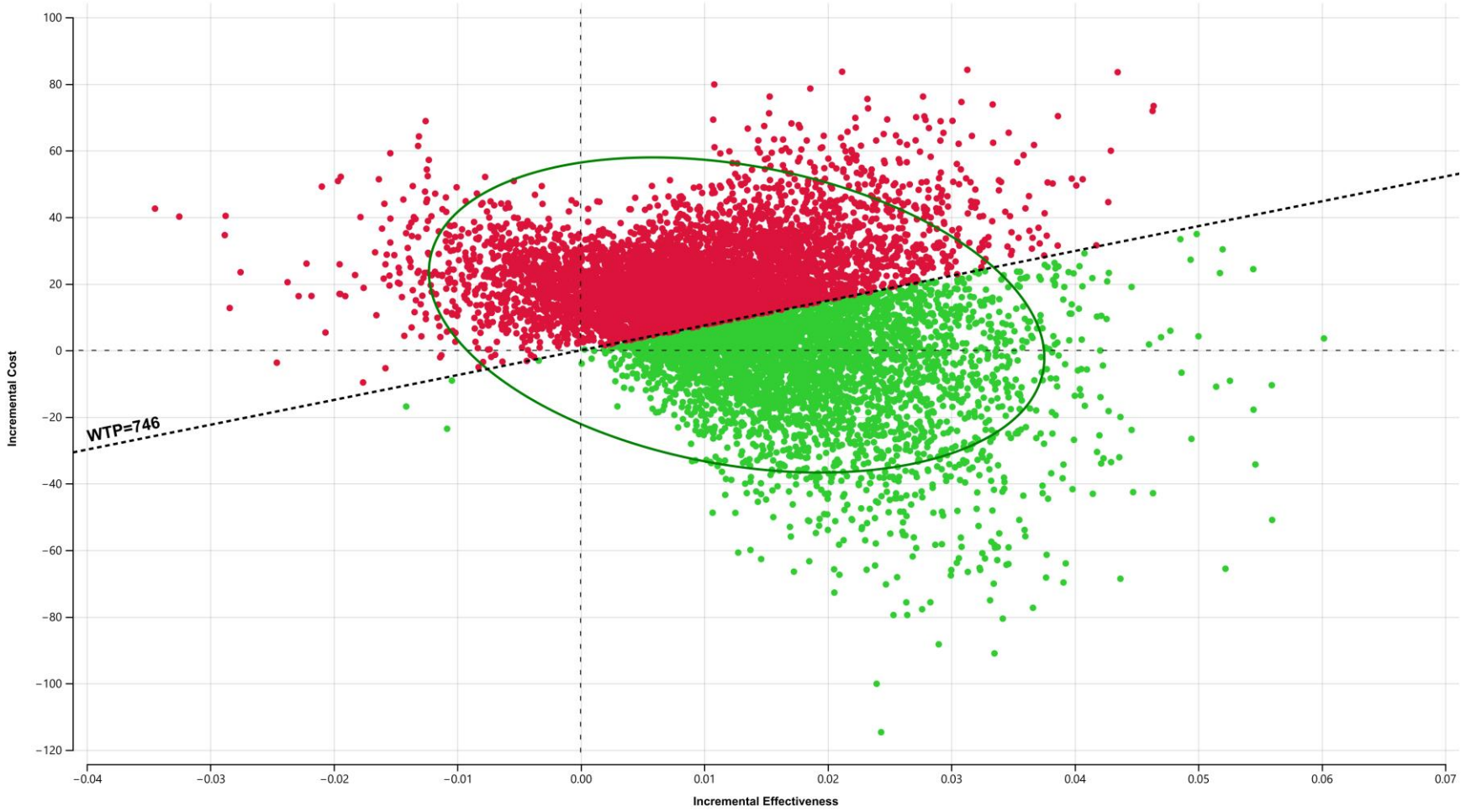
Appendix Figure A9.14 Incremental cost-effectiveness scatterplot Triclosan-coated Sutures versus Alcoholic Chlorhexidine Mexico Clean-Contaminated (Cost per QALY approach)



Appendix Figure A9.15 Incremental cost-effectiveness scatterplot Alcoholic Chlorhexidine versus Usual Care Mexico Clean-Contaminated (Cost per QALY approach)



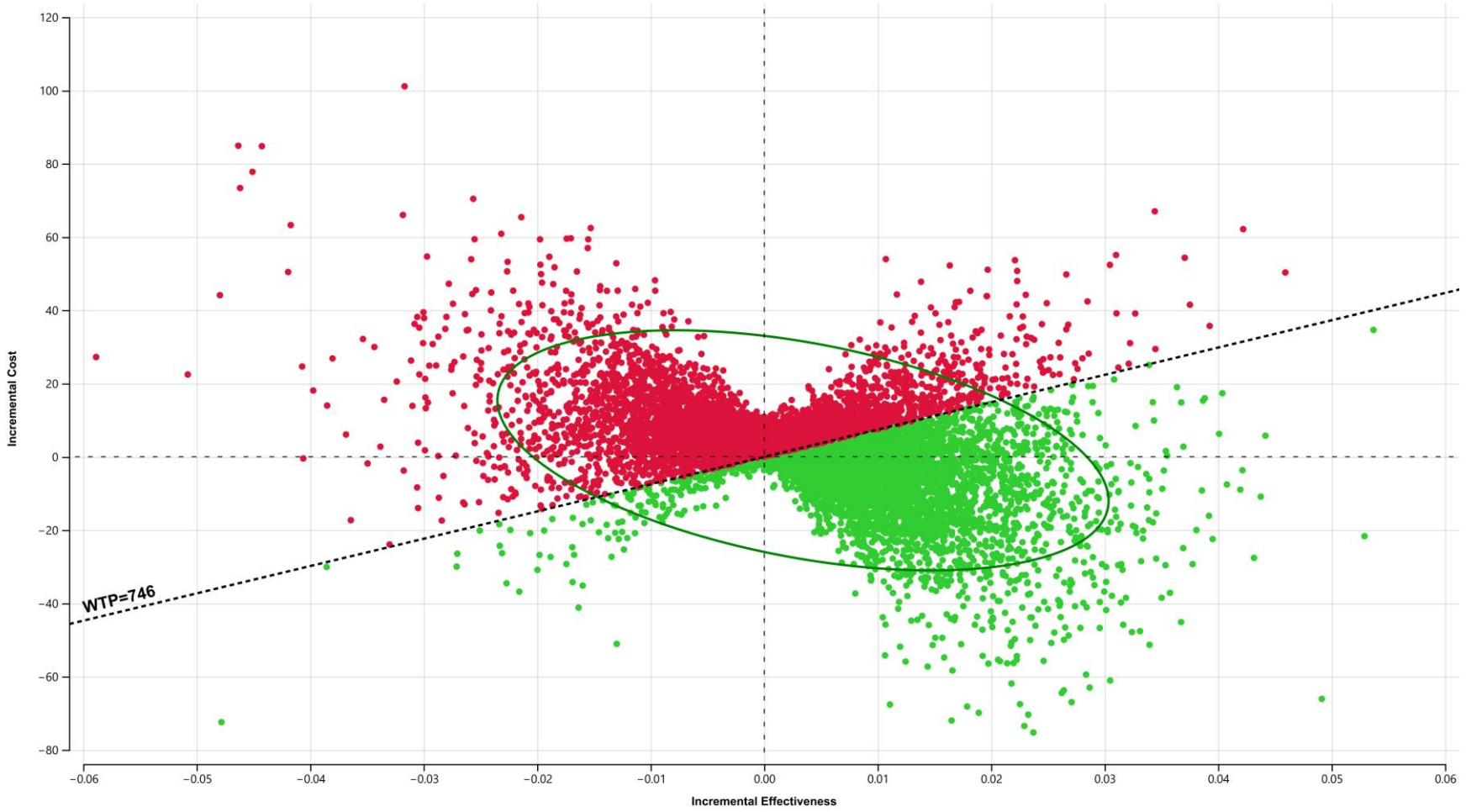
Appendix Figure A9.16 Incremental cost-effectiveness scatterplot Triclosan-coated Sutures versus Usual Care Mexico Clean-Contaminated (Cost per DALY averted approach)



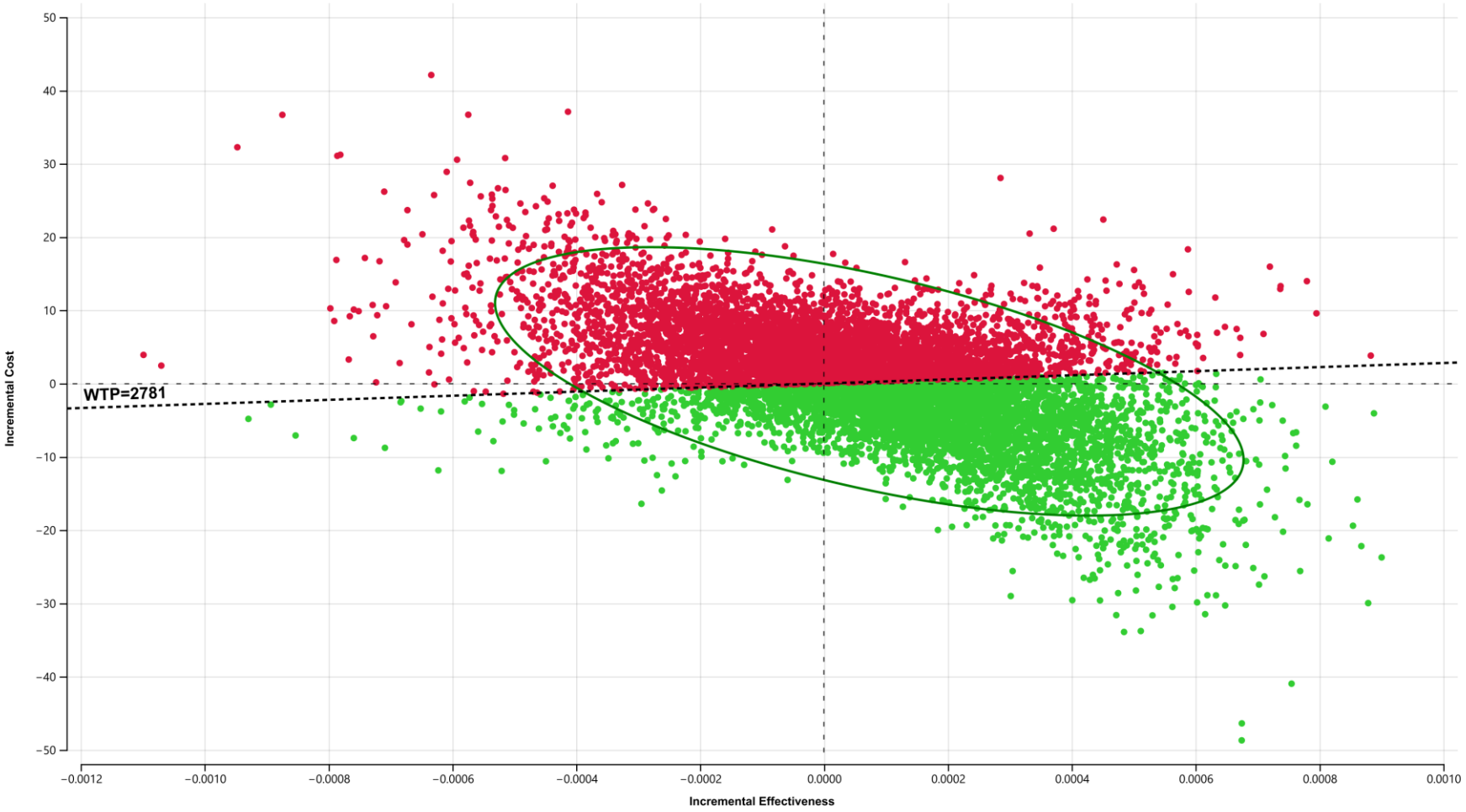
Appendix Figure A9.17 Incremental cost-effectiveness scatterplot Triclosan-coated Sutures versus Alcoholic Chlorhexidine Mexico Clean-Contaminated (Cost per DALY averted approach)



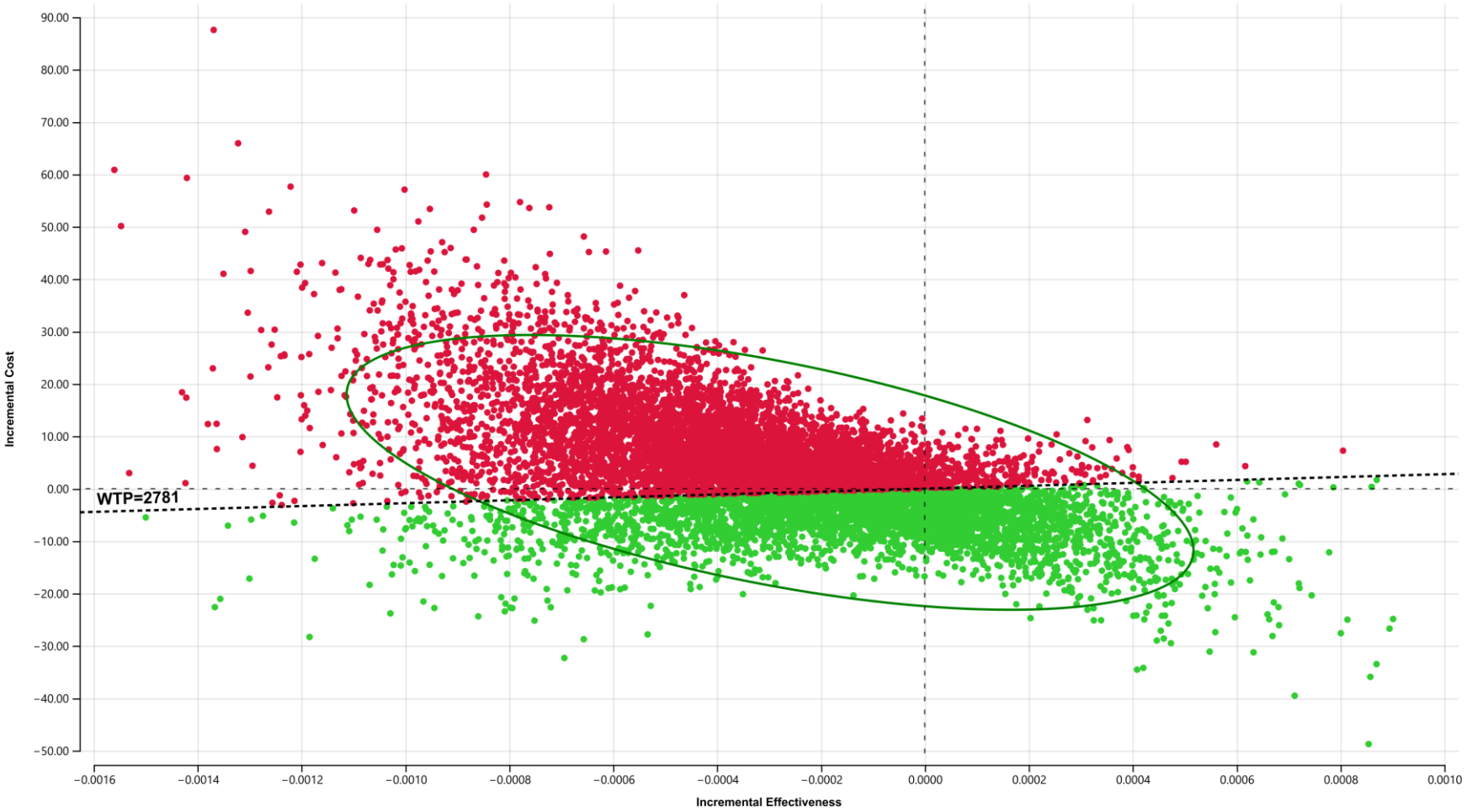
Appendix Figure A9.18 Incremental cost-effectiveness scatterplot Alcoholic Chlorhexidine versus Usual Care Mexico Clean-Contaminated (Cost per DALY averted approach)



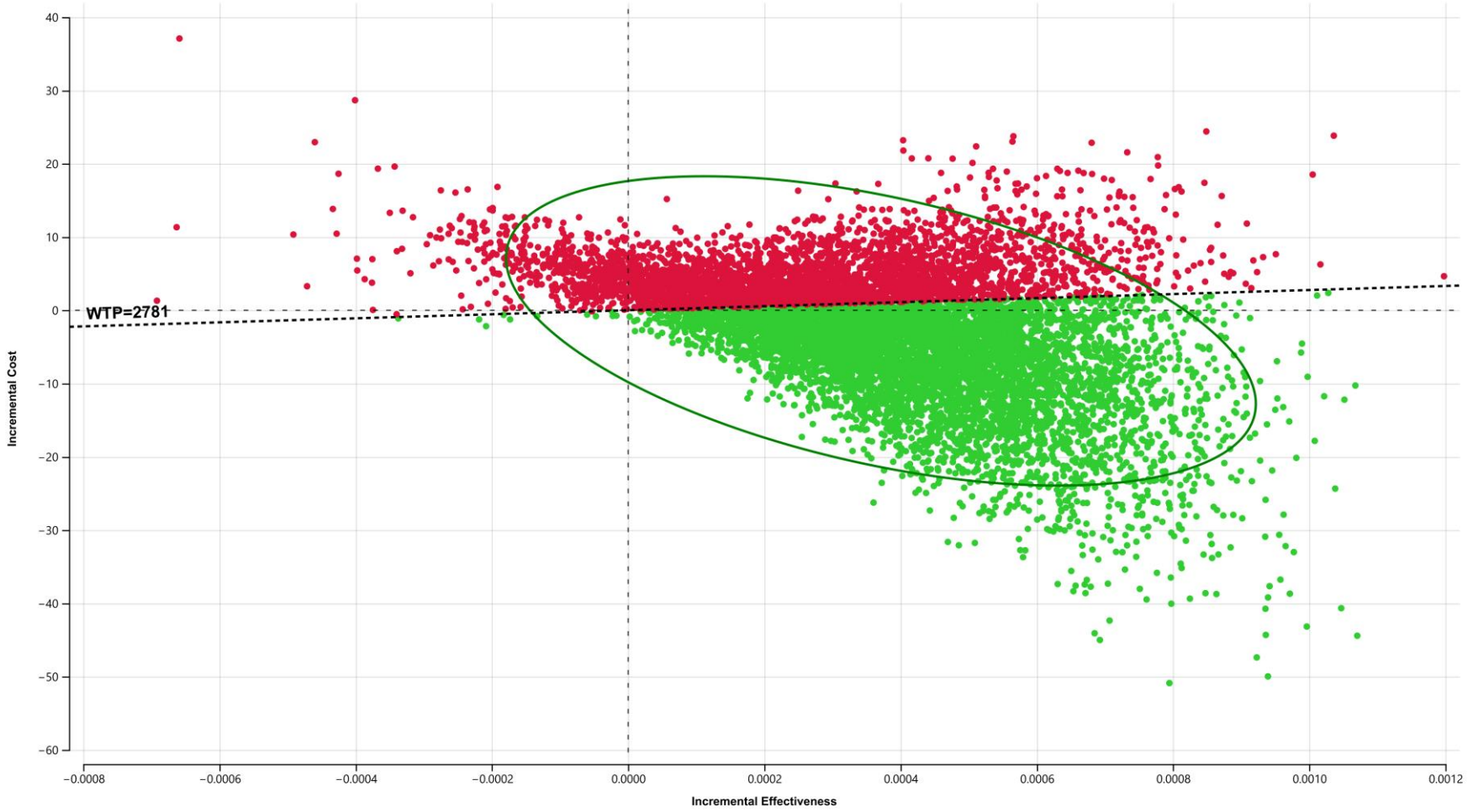
Appendix Figure A9.19 Incremental cost-effectiveness scatterplot Triclosan-coated Sutures versus Usual Care Ghana Contaminated-Dirty (Cost per QALY approach)



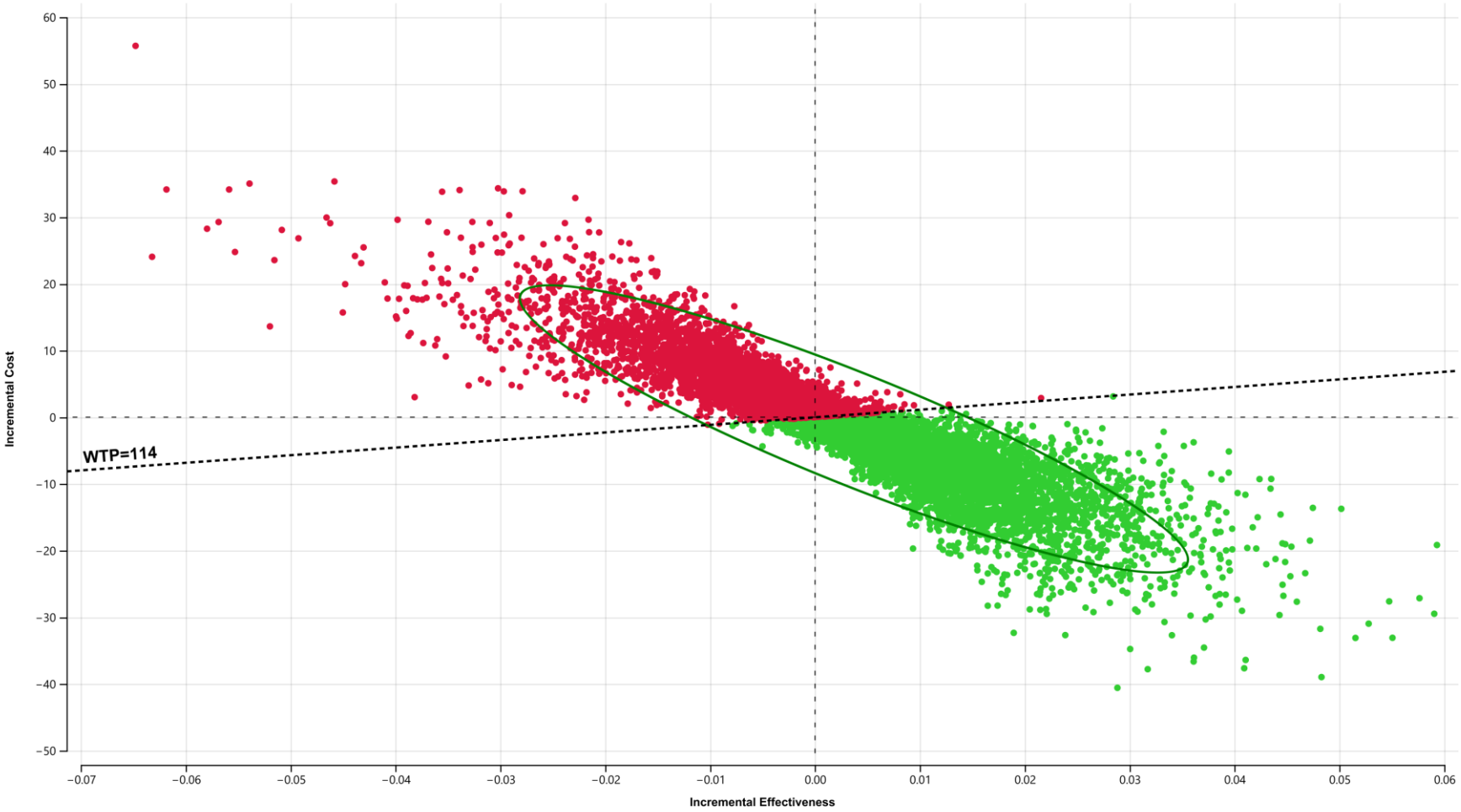
Appendix Figure A9.20 Incremental cost-effectiveness scatterplot Triclosan-coated Sutures versus Alcoholic Chlorhexidine Ghana Contaminated-Dirty (Cost per QALY approach)



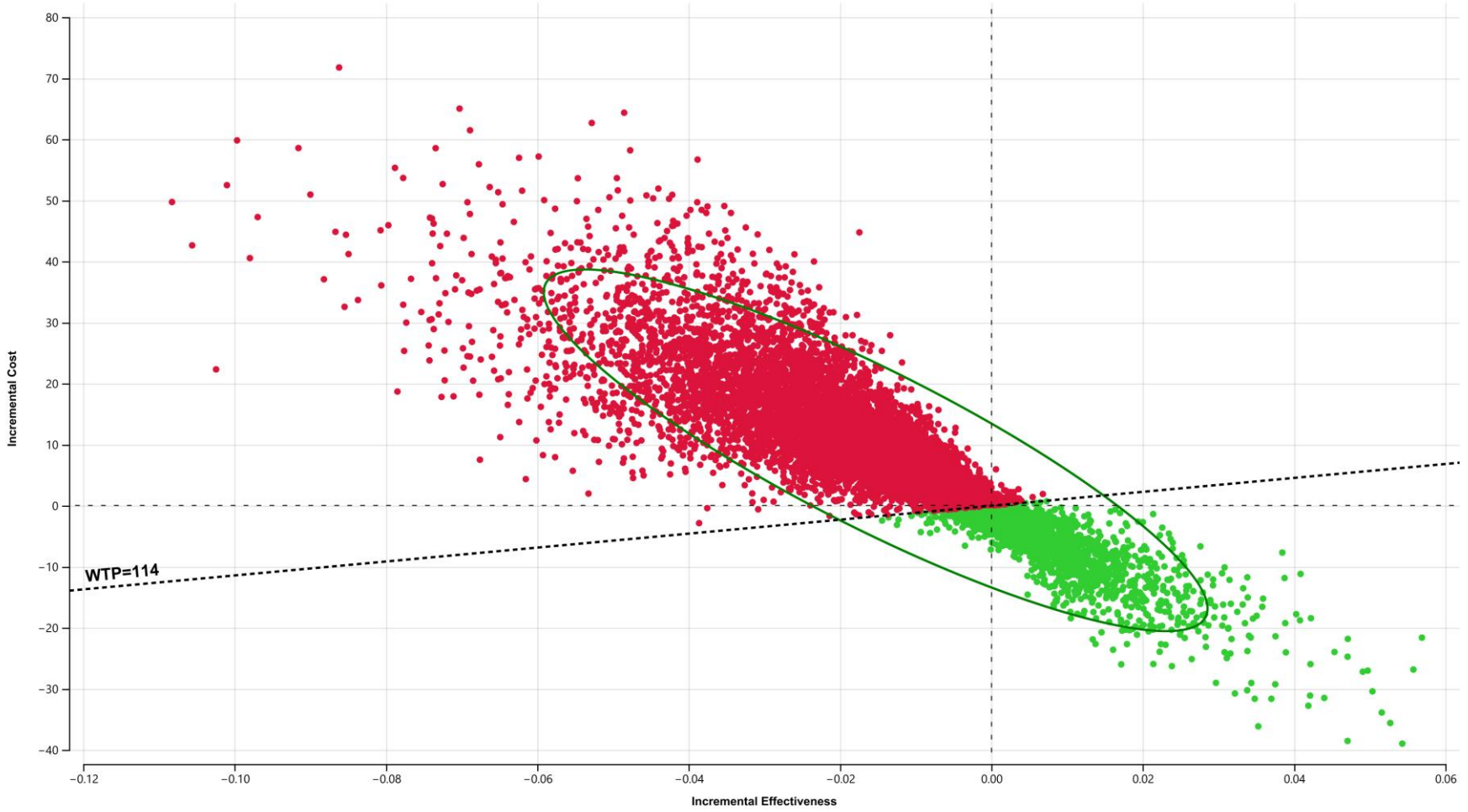
Appendix Figure A9.21 Incremental cost-effectiveness scatterplot Alcoholic Chlorhexidine versus Usual Care Ghana Contaminated-Dirty (Cost per QALY approach)



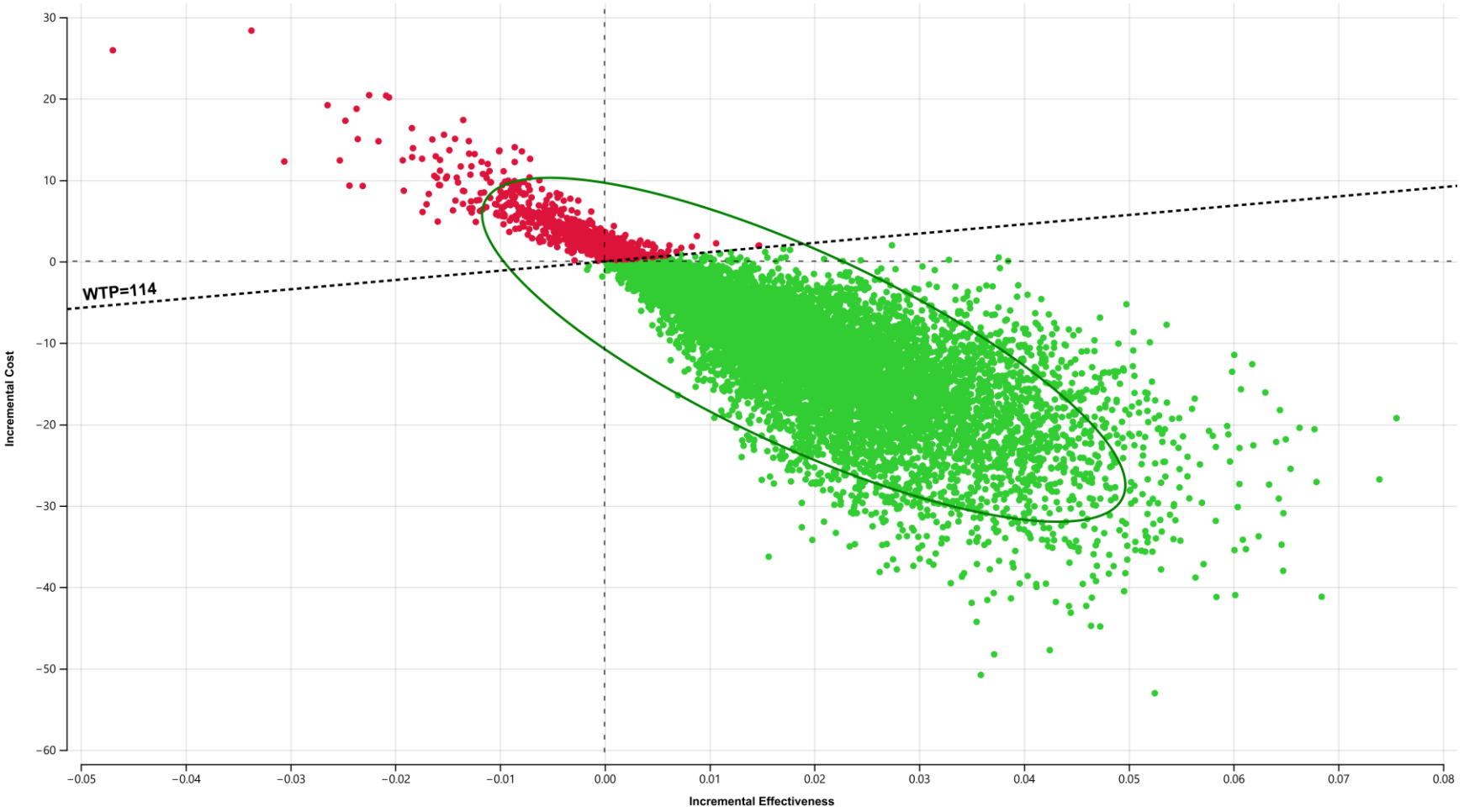
Appendix Figure A9.22 Incremental cost-effectiveness scatterplot Triclosan-coated Sutures versus Usual Care Ghana Contaminated-Dirty (Cost per DALY averted approach)



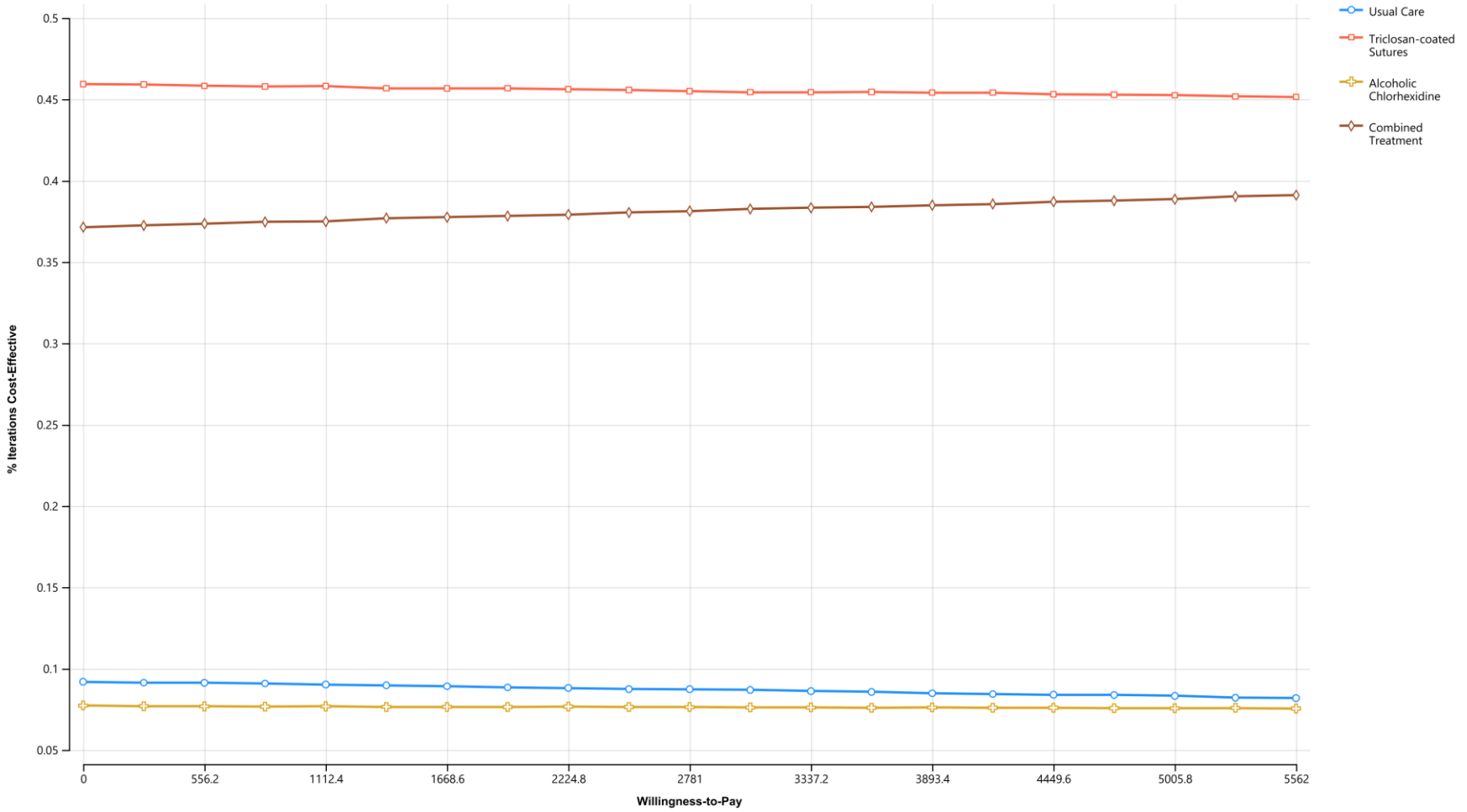
Appendix Figure A9.23 Incremental cost-effectiveness scatterplot Triclosan-coated Sutures versus Alcoholic Chlorhexidine Ghana Contaminated-Dirty (Cost per DALY averted approach)



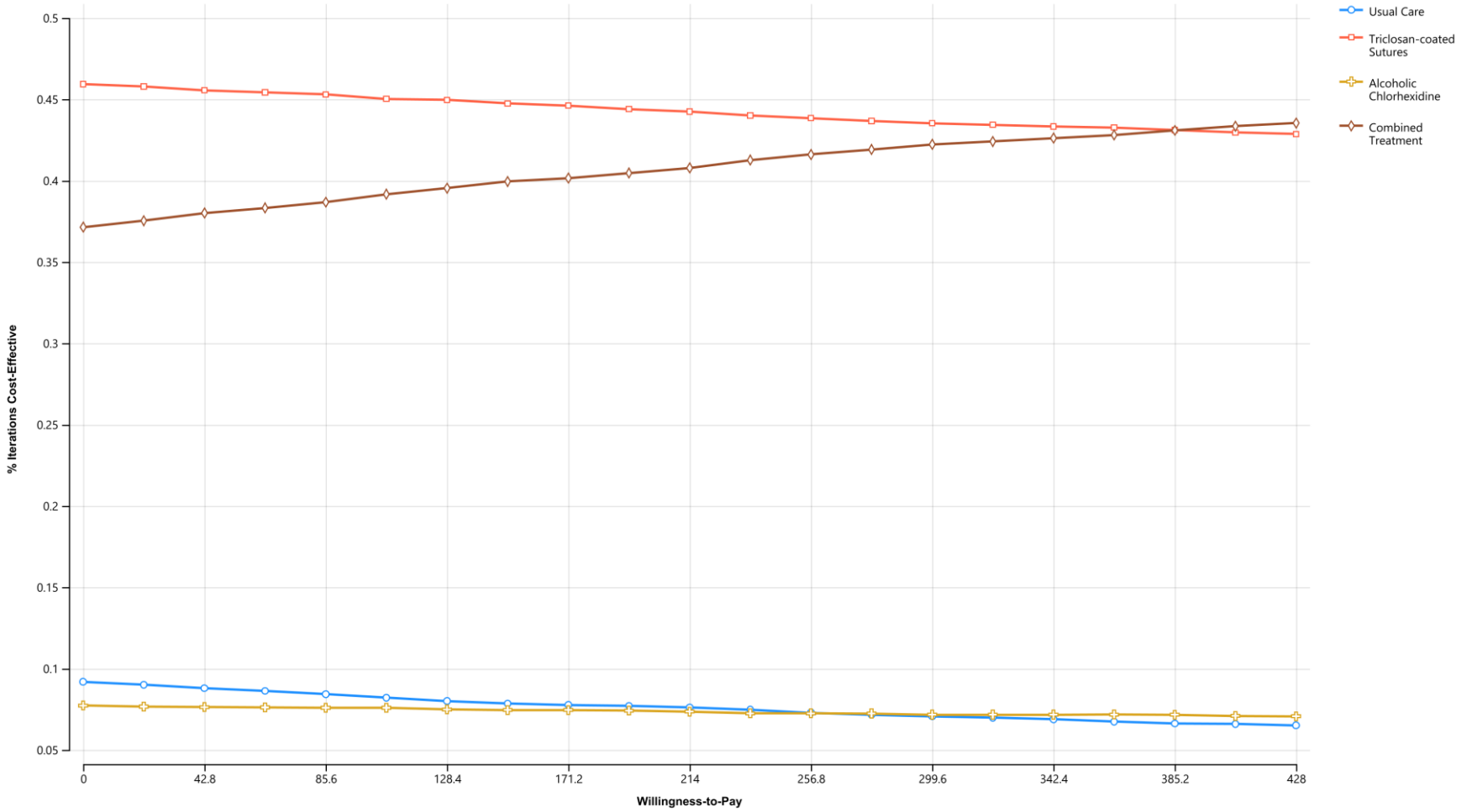
Appendix Figure A9.24 Incremental cost-effectiveness scatterplot Alcoholic Chlorhexidine versus Usual Care Ghana Contaminated-Dirty (Cost per DALY averted approach)



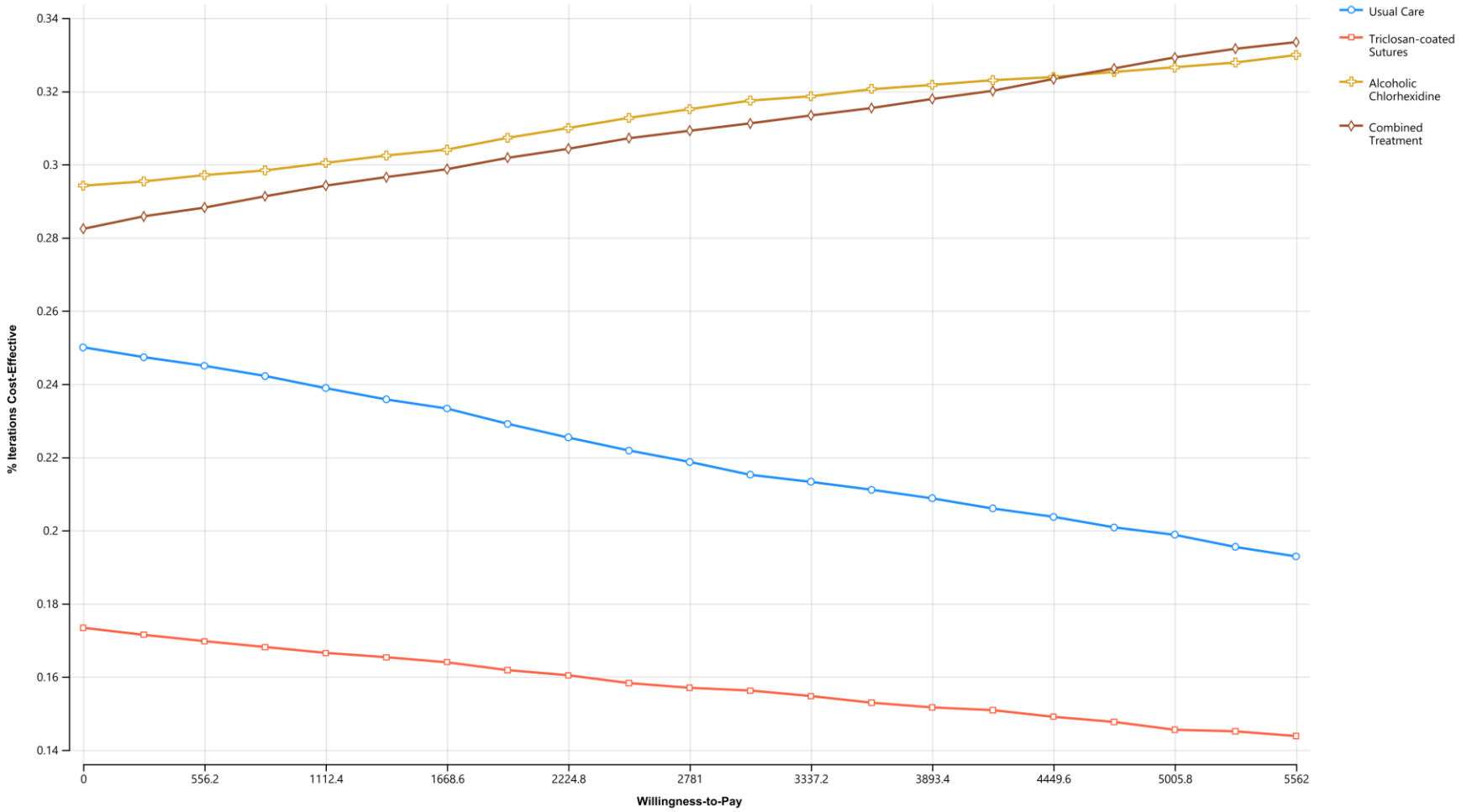
Appendix Figure A9.25 Cost-effectiveness acceptability curve Combined Treatment India Clean-Contaminated (Cost per QALY approach)



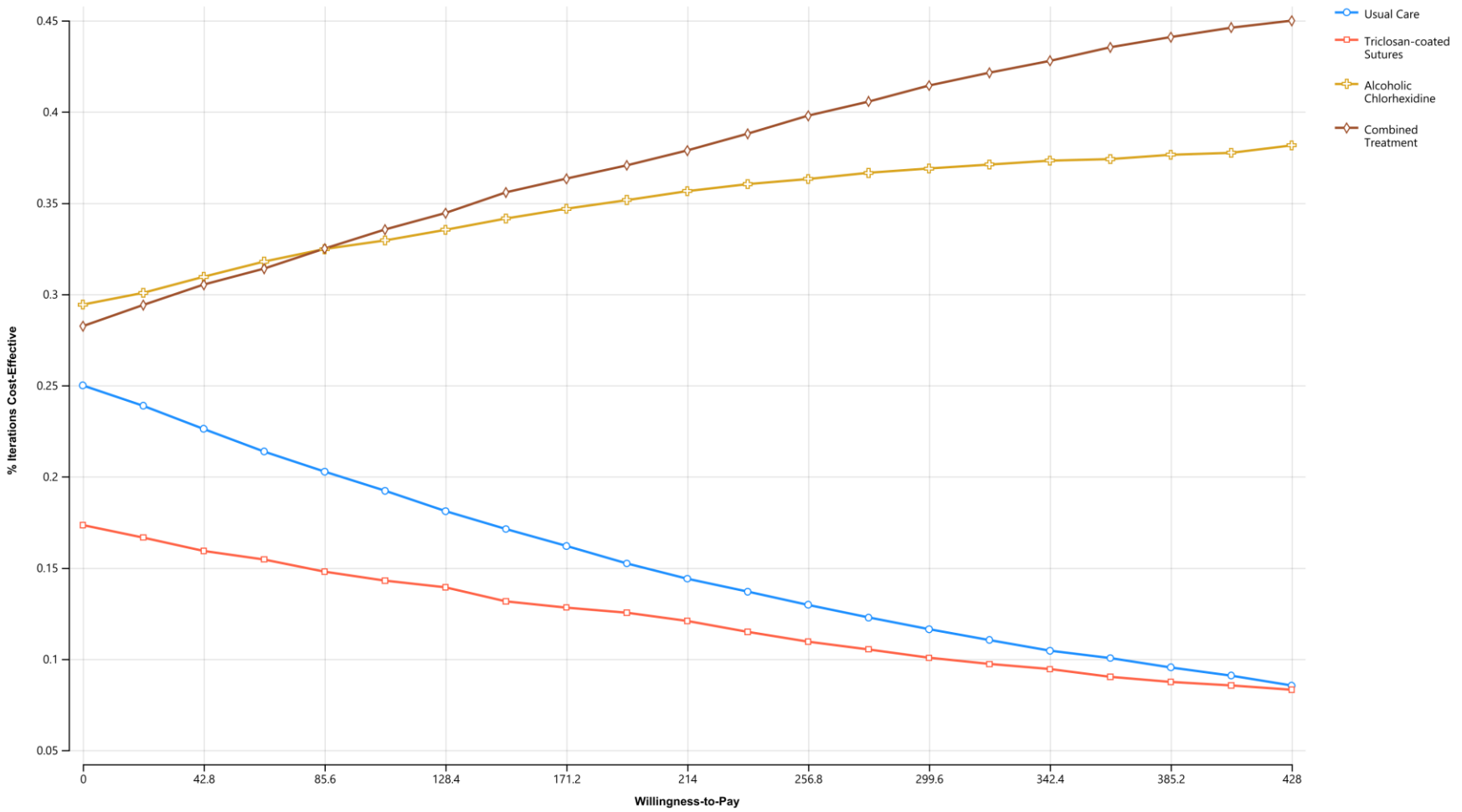
Appendix Figure A9.26 Cost-effectiveness acceptability curve Combined Treatment India Clean-Contaminated (Cost per DALY averted approach)



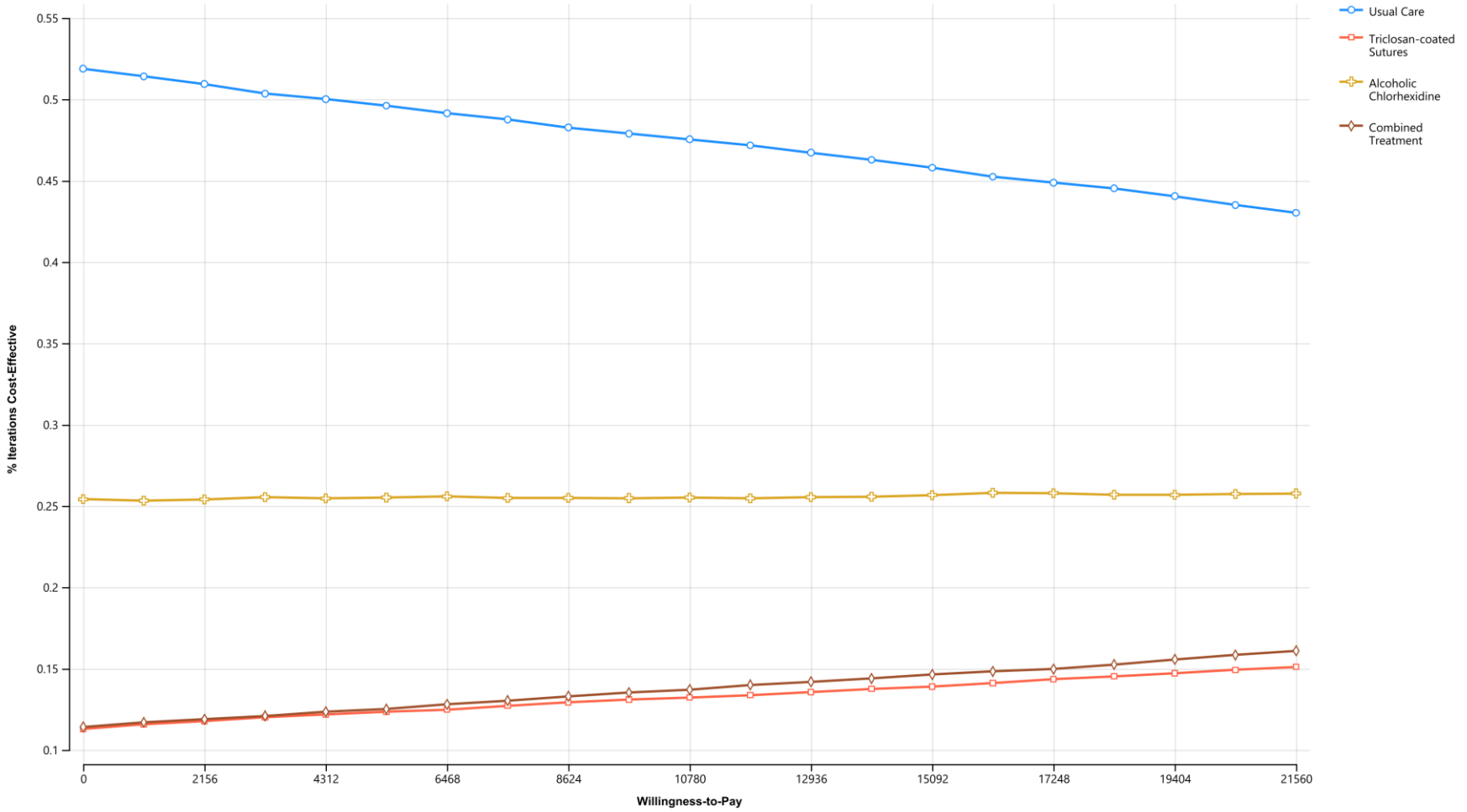
Appendix Figure A9.27 Cost-effectiveness acceptability curve Combined Treatment India Contaminated-Dirty (Cost per QALY approach)



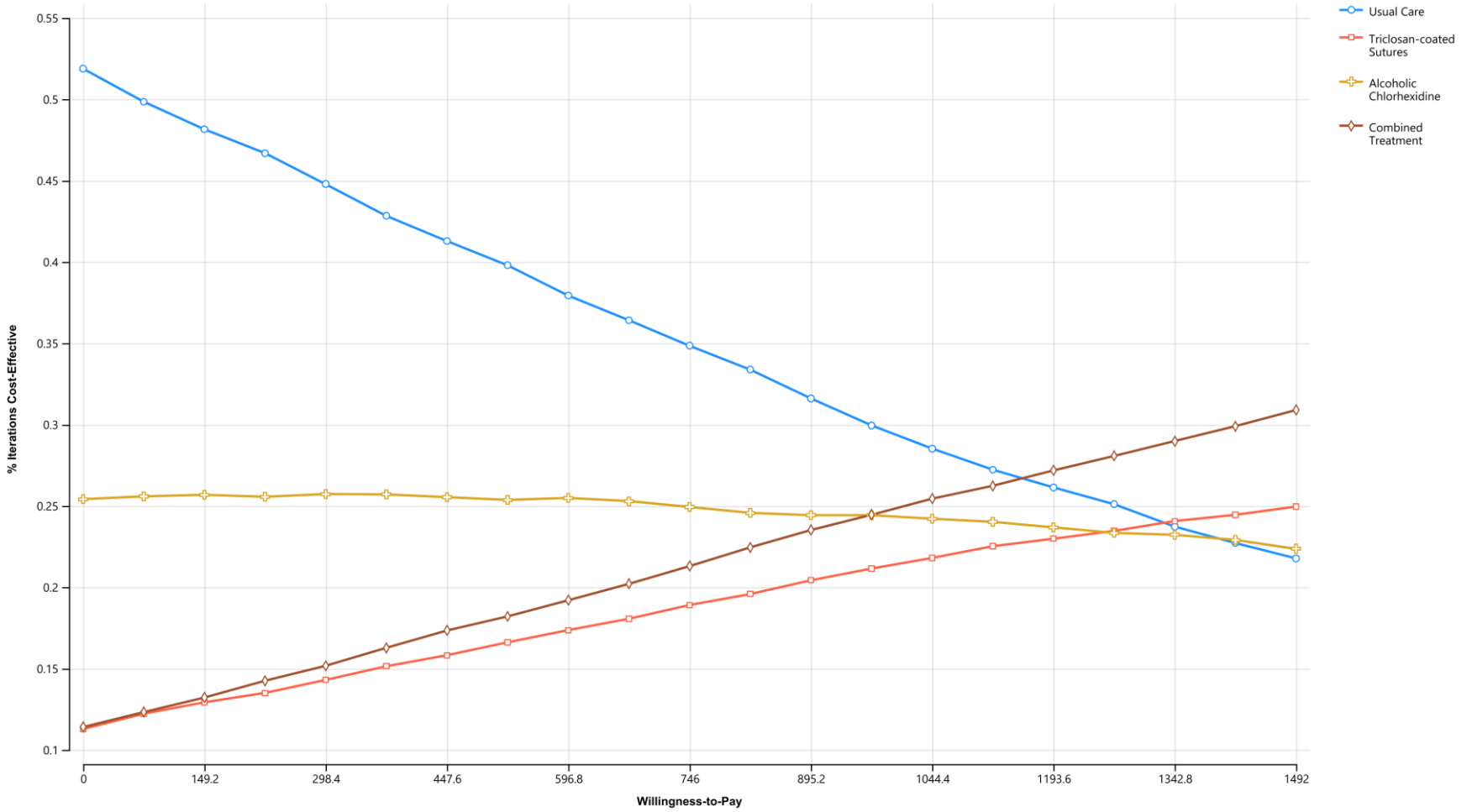
Appendix Figure A9.28 Cost-effectiveness Acceptability Curve Combined Treatment India Contaminated-Dirty (Cost per DALY averted approach)



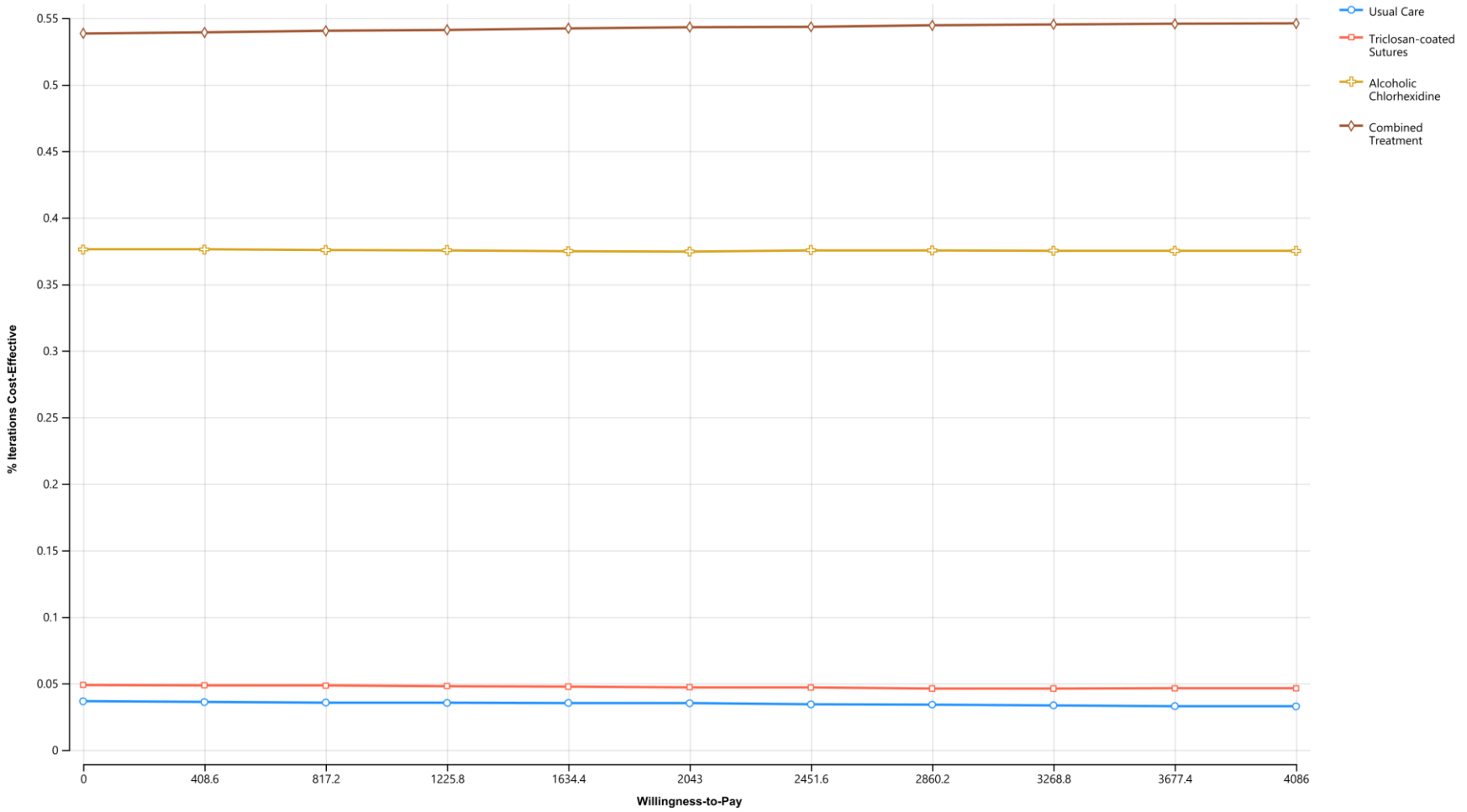
Appendix Figure A9.29 Cost-effectiveness Acceptability Curve Combined Treatment Mexico Clean-Contaminated (Cost per QALY approach)



Appendix Figure A9.30 Cost-effectiveness acceptability curve Combined Treatment Mexico Clean-Contaminated (Cost per DALY averted approach)



Appendix Figure A9.31 QALYs Cost-effectiveness Acceptability Curve Combined Treatment Ghana Contaminated-Dirty (Cost per QALY approach)



Appendix Figure A9.32 Cost-effectiveness Acceptability Curve Combined Treatment Ghana Contaminated-Dirty (Cost per DALY averted approach)

