Expert Review of Pharmacoeconomics & Outcomes Research

ISSN: 1473-7167 (Print) 1744-8379 (Online) Journal homepage: www.tandfonline.com/journals/ierp20

A cost-effectiveness analysis of RefluxStop against relevant therapeutic alternatives for chronic gastroesophageal reflux disease in Sweden

Sam Harper, Muralikrishnan Kartha, Stuart Mealing & Lars Lundell

To cite this article: Sam Harper, Muralikrishnan Kartha, Stuart Mealing & Lars Lundell (2025) A cost-effectiveness analysis of RefluxStop against relevant therapeutic alternatives for chronic gastroesophageal reflux disease in Sweden, Expert Review of Pharmacoeconomics & Outcomes Research, 25:3, 353-365, DOI: 10.1080/14737167.2024.2417774

To link to this article: https://doi.org/10.1080/14737167.2024.2417774

EXPERT REVIEW OF PHARMACOECONOMICS & OUTCOMES RESEARCH
2025, VOL. 25, NO. 3, 353–365
https://doi.org/10.1080/14737167.2024.2417774

Taylor & Francis
Taylor & Francis Group

ORIGINAL RESEARCH

OPEN ACCESS Check for updates

A cost-effectiveness analysis of RefluxStop against relevant therapeutic alternatives for chronic gastroesophageal reflux disease in Sweden

Sam Harper[a], Muralikrishnan Kartha[b], Stuart Mealing[a] and Lars Lundell[c,d]

[a]York Health Economics Consortium, University of York, York, UK; [b]Health Economics and Payer Evidence, Implantica, Zug, Switzerland; [c]Division of Surgery and Oncology, Karolinska Institutet, Stockholm, Sweden; [d]Department of Surgery, Odense University Hospital, Odense, Denmark

ABSTRACT

Introduction: The standard treatment for gastroesophageal reflux disease (GERD) is proton pump inhibitors (PPIs). In selected cases, Nissen fundoplication is offered as a surgical treatment option, but alternative endoscopic and minimally invasive surgical alternatives are emerging. RefluxStop is a new technology for the treatment of GERD.

Research design and methods: A cost-effectiveness analysis of RefluxStop in comparison to PPI therapy and Nissen fundoplication in the Swedish healthcare setting was conducted using a Markov model and available comprehensive population and clinical trial-based long-term data. Benefits were measured in quality-adjusted life-years (QALYs). Uncertainty was determined by deterministic and probabilistic sensitivity analyses.

Results: The base case incremental cost-effectiveness ratios (ICERs) for RefluxStop in comparison to PPIs and Nissen fundoplications were SEK 48,152 (€ 4,531) and SEK 62,966 (€ 5,925) per QALY gained, respectively. At a cost-effectiveness threshold of SEK 500,000 per QALY gained, RefluxStop has a high likelihood of being cost-effective, with probabilities of 96% and 100% against Nissen fundoplication and PPIs, respectively. The results of the model remained robust with sensitivity analysis.

Conclusions: RefluxStop may offer a highly cost-effective long-term treatment alternative for chronic GERD patients over lifelong PPI therapy, but also in comparison with laparoscopic Nissen fundoplication.

PLAIN LANGUAGE SUMMARY

Gastroesophageal reflux disease (GERD) is typically managed by proton pump inhibitor (PPI)-based medical management or antireflux surgery (i.e. Nissen fundoplication) in selected cases. However, alternative endoscopic and minimally invasive surgical alternatives have emerged. RefluxStop is a novel implantable device that aims to treat chronic GERD. We performed a cost-effectiveness analysis of RefluxStop from the perspective of the Swedish healthcare system including available treatment options in Sweden (i.e. PPI therapy and Nissen fundoplication). Benefits were measured using quality-adjusted life-years (QALYs). At the cost-effectiveness threshold of SEK 500,000 per QALY gained for Sweden, RefluxStop demonstrated a high likelihood of cost-effectiveness, with probabilities of 96% and 100% against Nissen fundoplication and PPI therapy, respectively. RefluxStop is likely to be a highly cost-effective long-term treatment alternative for chronic GERD patients as compared to lifelong PPI therapy and laparoscopic Nissen fundoplication.

ARTICLE HISTORY
Received 27 June 2024
Accepted 24 September 2024

KEYWORDS
Gastroesophageal reflux disease; cost-effectiveness; cost-utility; laparoscopic antireflux surgery; Markov model; RefluxStop; fundoplication; proton pump inhibitors

1. Introduction

Gastroesophageal reflux disease (GERD) is a disease defined by the reflux of stomach contents into the esophagus or mouth that results in troublesome symptoms and significant impairment of quality of life (QoL) [1,2]. The prevalence figures of GERD in Western societies vary between 7% and 26% [1,3–7] averaging around 10% [7]. From a public health perspective, the proportion of healthcare resource consumptions, directly and indirectly caused by GERD, are substantial [8]. Accordingly, the relative benefits and costs of various therapeutic strategies have been debated for years [3]. The costs of dyspepsia, peptic ulcer disease, and GERD in Sweden approximate $424 million (USD) or $63 (USD) per person, with direct and indirect costs of $258 million (61%) and $166 million (39%), respectively, according to an analysis published in 2002 [4]. An optimized patient journey is likely to reduce the economic burden of disease and increase productivity.

The standard treatment of GERD is proton pump inhibitors (PPIs), which in most cases offers normalization of symptoms and quality of life [9,10]. However, at least 30% of the chronic GERD patients experience insufficient effects of PPI therapy or are refractory to this treatment modality [5,6]. In those with incomplete response or refractoriness to PPI therapy, as well as in those patients who do not wish to receive long-term medication, antireflux surgery such as Nissen fundoplication should be considered [7].

CONTACT Muralikrishnan Kartha muralikrishnan.kartha@implantica.com Health Economics and Payer Evidence, Implantica, Industriestrasse 24, Zug CH-6300, Switzerland

Supplemental data for this article can be accessed online at https://doi.org/10.1080/14737167.2024.2417774

The predominant reason for the development of different surgical procedures is that the total fundic wrap technique is associated with important adverse sequelae [9–12]. Recently, a novel implantable device for surgical management of GERD has been introduced, called RefluxStop™ (Implantica, Zug, Switzerland) [13]. RefluxStop aims to restore the normal anatomy and position of the lower esophageal sphincter (LES), gastroesophageal flap valve, and angle of His with minimal postoperative complications (i.e. dysphagia and inability to belch or vomit) [13,14].

Since the relative merits of different therapeutic strategies for chronic GERD remain debatable, its relative cost-effectiveness must be introduced to reach a balanced and comprehensive view of the advantages and disadvantages of respective therapies [15–17]. Studies have shown that PPI therapy is less expensive than surgery in a limited time horizon, whereas surgery becomes the most cost-effective option after more than 5 years of follow-up [3,18,19]. With the introduction of novel therapeutic concepts, it is critical to assess the health economic impacts of wider implementation of similar devices in the long-term management of chronic GERD. The purpose of our analysis was to evaluate the cost-effectiveness of RefluxStop in relation to medical management with PPI therapy and laparoscopic Nissen fundoplication (LNF) for the treatment of GERD in Sweden. The analysis was based on data from a population in which prospectively collected, high-quality data could be retrieved.

2. Methods

A cost-effectiveness analysis was performed with the objective to compare RefluxStop with PPI-based medical management and LNF in adult patients with GERD. The economic analysis was conducted from the Swedish national healthcare system perspective over a lifetime. Only direct medical costs were included in the study, without considering societal costs (i.e. lost productivity due to absence from work). Quality-adjusted life-years (QALYs) were used as a standard measure to quantify clinical outcomes. Consistent with recent Swedish economic evaluations [20] and the recommendation of the Dental and Pharmaceutical Benefits Agency (TLV) [21], all costs and QALYs had a 3% per year discount applied. Model parameters included a cycle length of 1 month with a half cycle correction applied; thus, events that occurred in the model were assumed to take place in the middle of each month. Quality was ensured by taking into account the good practice guidelines for decision-analytic modeling in health technology assessment [22].

2.1. Model structure

A state transition (Markov) model (Excel 2023, Microsoft Corporation) was employed as the analytical framework for assessing the cost-effectiveness of RefluxStop, in which subjects went through a sequence of mutually exclusive health states to reflect possible outcomes of the management options evaluated. A recent cost-effectiveness analysis of RefluxStop in the United Kingdom was adapted to Swedish settings for the purpose of this study, consistent with model structures in published assessments of cost-effectiveness of management options for reflux disease [18,19,3,24,25]. Medical (Figure 1(a)) and surgical (Figure 1(b)) treatment options had different structures in the model as a reflection of the difference in nature of these management approaches. High-dose medical management, PPI irresponsiveness, initial surgery and reoperations, sequelae such as Barrett's esophagus and esophageal cancer, and mortality were considered in the health states of both cases. Adverse events (AEs) related to medical and surgical therapy were also included in the model structure.

Subjects in the medical management arm (Figure 1(a)) were presumed to receive PPI therapy at a standard-dose as a first-line option (i.e. 'Medical management well' state). The risk of GERD symptom relapse or incomplete response was applied each month. In cases of incomplete symptom control, patients received twice the dose of PPIs (i.e. 'Medical management relapse' state) with subsequent options of either returning to standard-dose PPIs (i.e. 'Medical management well' state) or undergo antireflux surgery. The surgical treatment arm was restricted to LNF in our analysis, consistent with several international practice guidelines, including the NICE recommendations for GERD standard of care [7]. As magnetic sphincter augmentation (MSA) is not an approved option in Sweden, it was not included in the model. Health states after surgery were described as successful (i.e. 'Surgery well') or unsuccessful (i.e. 'Surgery fail') outcomes. Those with unsuccessful surgery would require reoperation (i.e. Surgery re-op') or receive twice the dose of PPIs (i.e. 'Medical management high dose') with the assumption that double-dose PPIs were continued for the remainder of the patient's life. Similarly, patients with failed reoperation went on to receive lifelong double-dose PPI therapy. All subjects entered the model at initial operation for the surgical arms. Pertaining to reoperations, those requiring reoperation received the same type of procedure as the initial operation, and those with reoperation failure would receive standard-dose PPI therapy. The risk of Barrett's esophagus was applicable to all subjects notwithstanding intervention, from which a small proportion (0.06% per month) was assumed to experience progression to esophageal carcinoma. Furthermore, mortality for the Swedish general population and mortality-associated specific health states were included from the following sources. Clinical efficacy data were obtained from publications in the literature, nationwide complete Swedish registries [26,27] retrieved from the Swedish Patient Registry, the Causes of Death Registry, and the Prescribed Drug Registry, as well as from randomized controlled clinical outcome studies with long-term follow-up. To address the actual outcome of antireflux surgery in the country under investigation, we pooled data from several randomized controlled trials (RCTs) with long-term follow-up (i.e. ≥10 years) [28–33].

2.2. Model inputs

2.2.1. Clinical and quality of life inputs

One thousand patients with a starting age of 52 years were followed in a hypothetical cohort, of which 44% were female. This was used to provide consistency with the RefluxStop CE

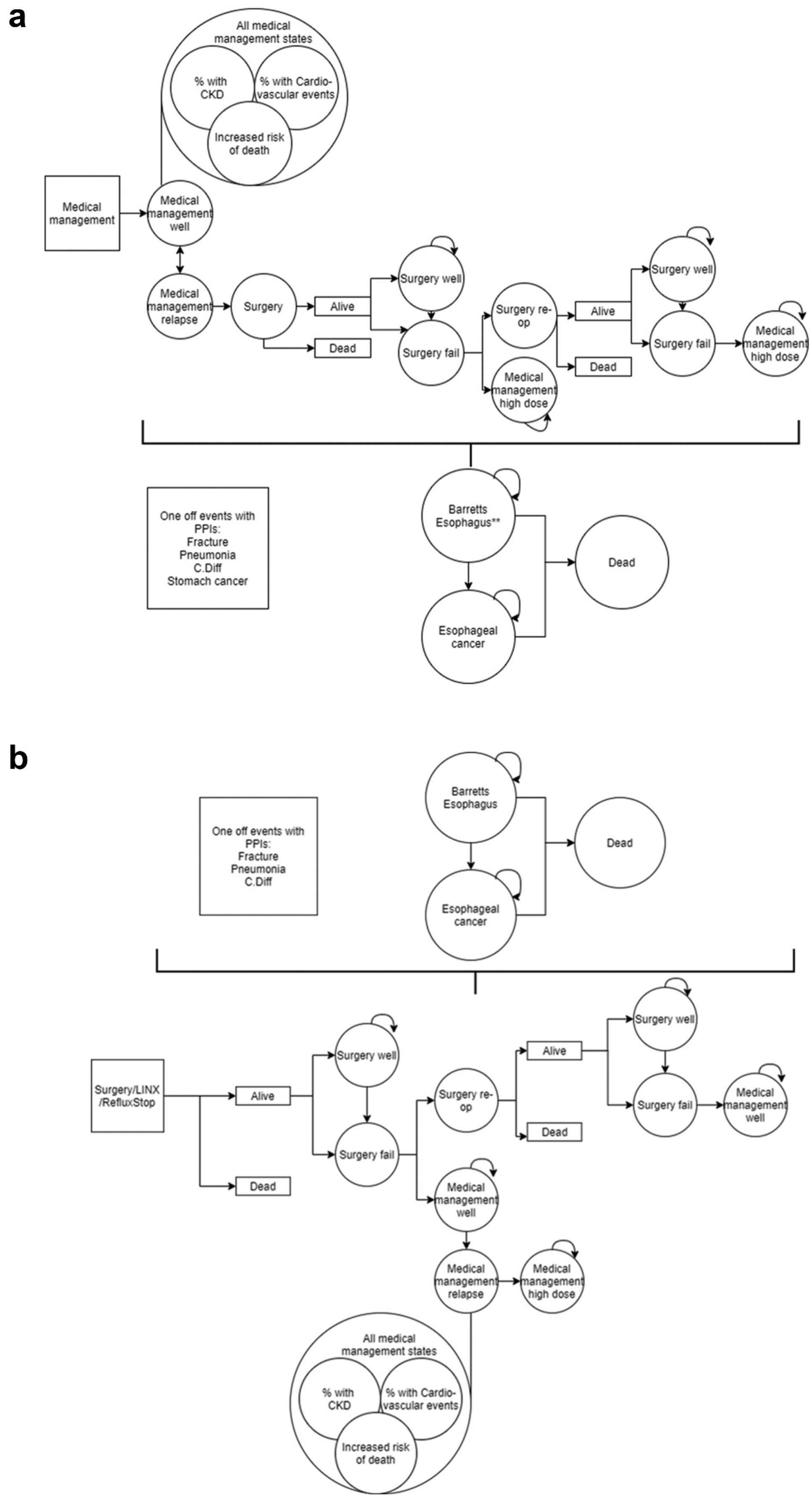

Figure 1. Model structure applied to medical management (panel a) and surgical treatment options (panel b).

C.Diff, *Clostridium difficile*; CKD, chronic kidney disease; PPI, proton pump inhibitor; reop, reoperation.

mark trial [13]. Similarly, these patient attributes broadly apply to other larger studies of GERD treatments, such as the UK REFLUX trial [34], the recent US trial comparing treatment options (i.e. medical and surgical) for refractory GERD [6] and the LOTUS trial which recruited Swedish patients [35]. The clinical parameters in the Swedish cost-effectiveness model used a systematic review of RCTs [27] that included Swedish RCTs. For scenario analysis, we exclusively used the pooled data extracted from Sweden-specific publications. Pooled estimates from the Swedish studies in the systematic review of the long-term outcomes of LNF [28–33] were also used to conduct the analysis. All estimates utilized in the base case model are displayed in Table 1 and Supplementary files (i.e. scenario estimates). Clinical and quality-of-life inputs included in the model are summarized here.

The efficacy and safety inputs for RefluxStop that informs the analysis were obtained from the CE mark trial [13], with addition of 3-year data yet-to-be published [36]. Recently available publications were sourced for pertinent data related to medical management and LNF. The probability of treatment failure (i.e. in the surgery arms) per month was divided into two periods (i.e. up to 1-year postoperatively and >1 year postoperatively) to reflect the reporting styles in studies for each intervention.

Cost-effectiveness analyses consider the lifetime journey of patients and important clinical events are required for analysis inclusion in a similar manner for all comparative treatment arms. Regardless of whether initial surgery or reoperation, intraoperative complications and postoperative AEs were included in the model, with a recent review on LNF outcomes used to delineate events to be considered [27]. Medical management states incurred the risk of AEs related to long-term PPI therapy, such as *Clostridium difficile* (C.Diff) infection [54], osteoporotic fracture [55], gastric cancer [56], community-acquired pneumonia [57], chronic kidney disease (CKD) [58], and cardiovascular (CV) events [59]. Pneumonia, gastric cancer, and C.Diff infection were modeled as one-off events, while CKD and CV events were modeled using the proportion in state method (i.e. assumption that at any given time, a proportion of patients in medical management states experienced CKD or CV events). The rate of mortality from CV and CKD events was assumed to be identical to the rate at which PPI users experienced these complications. Such rates were included for comparative arms based on the proportion of patients receiving PPI therapy consistent with individual patient journey pathways.

Long-term sequelae of GERD include Barrett's esophagus and cancer of the esophagus [60]. The probability of Barrett's esophagus development on a monthly basis has been estimated at 0.083% based on the data used to develop the UK-NICE recommendations for dyspepsia and GERD [23], which was applied to all treatment arms of our model. Furthermore, the monthly risk of progression to esophageal carcinoma from a systematic review and meta-analysis was 0.06% [61].

The analysis included excess mortality associated with surgery, esophageal carcinoma, and AEs associated with chronic PPI use in addition to mortality in the general population, which defined the mortality for each arm. A very small risk of intraoperative mortality (0.05%) was applied to initial procedures for all surgical arms, which doubled in cases of reoperation. A monthly mortality risk of 3.4 was assumed for patients developing esophageal carcinoma [24]. A relative mortality risk of 1.57 was applied to reflect the elevated risk of mortality associated with AEs of chronic PPI therapy in medical management states, regardless of arm, as described in a recent systematic review [38]. Thus, no treatment arm was favored for mortality estimation in the analysis.

Utility decrements were used to describe health-related quality of life (HRQoL) decline due to transient AEs during the treatment course. The proportion of patients with refractory dysphagia, a possible AE of relevant procedures, was used as the basis for utility decrements of successful surgery. A utility decrement value of 0.24 was applicable for 1 month after all initial procedures and reoperations. This value was extrapolated from laparoscopic cholecystectomy due to a similar approach and quality-of-life impact [18]. Utility decrements for those receiving PPI therapy were based on a cost-effectiveness analysis of PPIs and LNFs obtained from the REFLUX trial [18,34]. This trial provided another analysis informing the utility decrement related to unsuccessful LNF, also applied to RefluxStop in our study [34]. Furthermore, those suffering from Barrett's esophagus and esophageal carcinoma were applicable to pertinent utility decrements obtained from population norms in Sweden [50]. Table 1 lists all HRQoL inputs for the model.

2.2.2. Cost inputs

Relevant costs were obtained from the Swedish Nord DRG and the published literature whenever possible [62,63]. Cost values were inflated using a web-based tool for cost conversion in cases of data obtained from older literature sources [64]. Table 2 summarizes key cost inputs informing the model.

The costs of PPI medications (i.e. omeprazole, lansoprazole, pantoprazole, rabeprazole, and esomeprazole) and antireflux procedures were considered in the model. The cost of surgery involved procedural costs, but for RefluxStop, additional costs for the device itself and training were incurred. As LNF and RefluxStop utilize similar steps for access and tool insertion, the procedural costs of LNF were assumed for both options.

Initial diagnostic and treatment costs were applied for those suffering from Barrett's esophagus, along with a monthly treatment cost consistent with patient journeys described in a cost-effectiveness evaluation of endoscopic treatment for Barrett's esophagus [53]. For these patients, diagnostic endoscopy was assumed for all and those with dysplasia (16.6%) would be managed with endoscopic mucosal ablation or radiofrequency ablation followed by PPI therapy and endoscopic monitoring every 2 years [53]. In the absence of any specific Swedish recommendations, progression of Barrett's esophagus to esophageal carcinoma incurred costs as per the pathway outlined by the NICE recommendations for dyspepsia and GERD [23], including diagnostic testing and management costs (i.e. upper endoscopy, general practitioner visits, esophagectomy, and chemotherapy), the cost of PPI therapy monthly, and the terminal care cost for relevant cases.

Table 1. Clinical and quality of life inputs used in the model.

Parameter	Input	Source
Relapse of GERD symptoms with medical management	2.65%	Bojke 2007 [18]
Reoperation following unsuccessful surgery	10.3%	
Surgery following a relapse of medical management	10.3%	Assumed to be the same as the probability in a case of reoperation
Probability of surgical failure up to 1-year post-surgery		
LNF	1.8%	Zehetner et al. Literature review and analysis: LNF [27]
RefluxStop	0.3%	Implantica data on file. RefluxStop CE mark study 3-year outcomes [36]
Probability of surgical failure ≥ 1-year post-surgery		
LNF	1.8%	Zehetner et al. Literature review and analysis: LNF [27]
RefluxStop	0.1%	Implantica data on file. RefluxStop CE mark study 3-year outcomes [36]
Probability of surgical failure for reoperation or second-line treatment		
LNF	0.31%	Calculated based on treatment failure rates up to 1 year and post 1 year provided above.
RefluxStop	0.17%	Calculated based on treatment failure rates up to 1 year and post 1 year provided above.
Monthly probability of Barrett's esophagus		
All treatment arms	0.083%	NICE model developed to support clinical guidance development in dyspepsia and GERD [23]
Risk of adverse effects of PPIs		
CV events (MI or stroke)	0.01%	Calculated based on WHO CVD risk chart working group [37] and Shiraev 2018 [38]
CKD	0.01%	Calculated based on Collins 2012 [39] and Hussain 2019 [40]
Fracture	0.02%	Calculated based on Kanis 2008 [41] and Zhou 2016 [42]
Pneumonia	0.08%	Calculated based on Sun 2019 [43] and Lambert 2015 [44]
Clostridium difficile	0.001%	Calculated based on Clostridium difficile infection: mandatory surveillance 2017/18 report [45] and Janarthanan 2012 [46]
Stomach cancer	0.002%	Brusselaers 2017 [47]
Intraoperative adverse events related to surgery		
Conversion to open surgery	RefluxStop: 2.1% LNF: 1.7%	Implantica data on file Zehetner et al. Literature review and analysis: LNF [27]
Splenic injury	RefluxStop: 0.0% LNF: 0.9%	
Gastroesophageal injury	RefluxStop: 0.0% LNF: 1.0%	
Liver injury	RefluxStop: 0.0% LNF: 1.4%	
Post-operative adverse events related to surgery		
Endoscopic esophageal dilation	RefluxStop: 0.0% LNF: 0.3%	Implantica data on file Skubleny et al [48]
Major complications requiring additional surgery	RefluxStop: 0.0% LNF: 1.4%	Bjelovic et al [13] NICE Interventional Procedures Guidance on
Endoscopic device removal	RefluxStop: 0.0% LNF: N/A	Implantica data on file Alicuben et al [49]
Utility decrement: Stable medical management	0.12	Based on Bojke 2007 [18] Swedish population norms [50]
Utility decrement: Medical management of GERD relapse	0.28	Bojke 2007 [18]
Utility decrement: Medical management high dose	0.12	Assumed equal to stable medical management
Post-surgery utility decrements (applied for 1 month)		
RefluxStop	0.24	Based on Bojke et al. [18] and originally sourced from Ainslie et al 2003 [51] using EQ-5D data
LNF	0.24	
Utility decrements applied ≥1 month following successful surgery in the 'Surgery well' state		
RefluxStop	0.00	Calculated based on utility decrement for dysphagia from Bouvy 2013 [52] and the proportion reporting dysphagia at 3 years from the RefluxStop CE mark study (Implantica data on file) [36]
LNF	0.01	Calculated based on utility decrement for dysphagia from Bouvy 2013 [52] and the proportion reporting dysphagia at 5 years from Zehetner et al [27]
Unsuccessful surgery utility decrements		
RefluxStop	0.16	Assumed equal to LNF
LNF	0.16	Based on Grant 2008 EQ-5D data [34] and Swedish population norms [50]
Utility decrements associated with Barrett's esophagus and esophageal cancer		
Barrett's esophagus	0.10	Polit 2019 [53]
Esophageal cancer	0.44	NICE model developed to support clinical guidance development in dyspepsia and GERD [23]

Abbreviations: C. Diff, *Clostridium difficile*; CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; EQ-5D, EuroQoL 5D; GERD, gastro-esophageal reflux disease; LNF, laparoscopic Nissen fundoplication; MI, myocardial infarction; NICE, National Institute for Health and Care Excellence; PPI, proton pump inhibitor; SSED, Summary of Safety and Effectiveness Data; WHO, World Health Organization.

Table 2. Key cost inputs applied in the model.

Parameter	Input	Source
Medical and surgical treatment costs		
Monthly cost of PPI medication (standard dose)	SEK 223.90	Swedish pharmaceutical costs (Apoteket) www.apoteket.se
Monthly cost of PPI medication (high dose)	SEK 228.89	Swedish pharmaceutical costs (Apoteket) www.apoteket.se
Procedure cost – all surgical treatments	SEK 96,336	Base rate SEK 67,938 multiplied by cost weight 1.418 (F12E) from NordDRG [63]
Device – RefluxStop	SEK 59,000	Implantica data on file
Training – RefluxStop	SEK 340.11	Calculated based on Chaudhary et al 2021 [76] and Palser 2018 [77]
Barrett's esophagus		
Diagnostic endoscopy	SEK 6,250.30	Base rate SEK 67,938 multiplied by cost weight 0.092 (F72O) from NordDRG [63]
Treatment (endoscopic mucosal resection (EMR) and radiofrequency ablation (RFA))	SEK 19,165.25	Calculated based on Pollit 2019 [53] and Base rate SEK 67,938 multiplied by cost weight 0.139 (EMR F67O) and 0.33 (RFA)* from NordDRG [63]
Monthly monitoring cost	SEK 499.33	Calculated based on the NICE model developed to support clinical guidance development in dyspepsia and GERD [23] and Base rate SEK 67,938 multiplied by cost weight 0.139 (F67O) from NordDRG [63]
Esophageal cancer		
Initial diagnostic and treatment	SEK 236,365.50	Calculated based on the NICE model developed to support clinical guidance development in dyspepsia and GERD [23], Base rate SEK 67,938 multiplied by cost weight 3.363 (F11E) from NordDRG [63] and Wolff et al 2020 [78]
Palliative care	SEK 81,583.78	Chaudhary et al 2021 [76]
Adverse events associated with PPIs		
CKD monthly cost (including costs of treatment, hospitalization, and end-stage renal disease)	SEK 9,996.20	Calculated based on Kerr 2012 [79], Gandjour 2002 [80], Eriksson et al 2017 [81], Kim et al 2022 [82], and Kidneyfailurerisk.com [83]
Monthly cost of CV events (MI or stroke)	SEK 5,001.20	Kim et al 2022 [82]
Fracture (event cost)	SEK 107,857.50	Borgström et al 2006 [84]
Pneumonia (event cost)	SEK 13,334.74	Calculated based on Wolff et al 2020 [78], Lambert 2015 [44], NICE quality standard for pneumonia in adults [85],
C.Diff infection (event cost)	SEK 24,920.10	Calculated based on Nordling et al 2014 [86], the *Clostridium difficile* infection: mandatory surveillance 2017/18 report [45], and costs of antibiotics as provided in www.apoteket.se
Stomach cancer (lifetime cost)	SEK 110,891.43	NICE technology appraisal of ramucirumab (TA378) [87]
Adverse events associated with surgery		
Conversion to open surgery	SEK 30,620.73	Laudicella 2016 [88]
Esophageal dilation	SEK 9,443.38	Base rate SEK 67,938 multiplied by cost weight 0.139 (F67O) from NordDRG [63]
Additional surgery for major complications	SEK 96,336	Assumed to be the same cost as the initial procedure.
Device removal	SEK 96,336	Assumed to be the same cost as the initial procedure.

Abbreviations: C.Diff, *Clostridium difficile*; CKD, chronic kidney disease; CV, cardiovascular; GERD, gastro-esophageal reflux disease; MI, myocardial infarction; NICE, National Institute for Health and Care Excellence; PPI, proton pump inhibitor.
*DRG cost weight for RFA not available in Sweden; assumed similar to Norwegian DRG cost weight.

Monthly costs were applied to patients developing PPI-associated AEs, CKD, and CV events. One-off costs attributable to PPI-related AEs included osteoporotic fractures, C.Diff infection, and pneumonia. Furthermore, lifetime costs of supportive care and chemotherapy were included for patients with gastric malignancy.

Surgery-related AEs incurred costs of conversion to open surgery, major surgical complications, device removal, and esophageal dilation. Injuries occurring intraoperatively (i.e. splenic, liver, or gastroesophageal) were presumed embedded in the those of the procedure itself.

2.3. Economic analysis

Estimates pertaining to per patient QALYs, total costs, life-years (LYs), and life expectancy were generated for each model arm. Furthermore, incremental differences were generated between each treatment arm. The following measures were utilized to compare treatment arms: 1) incremental cost-effectiveness ratio (ICER), representing the cost per QALY gained; 2) incremental net health benefit (NHB), calculated as incremental gain in QALYs – (incremental cost/opportunity cost threshold), representing the impact of introducing a new intervention on population health (i.e. NHB assumes that 'lost health' is estimated as an 'opportunity cost' as an indicator of health that is foregone elsewhere, due to funding allocation for a new intervention); and 3) incremental net monetary benefit (NMB), calculated as incremental QALYs by the threshold – (incremental cost), representing the value of an intervention in monetary terms when the threshold for willingness to pay for a benefit unit (e.g. health outcome or QALY) is known. No specific cost-effectiveness threshold is officially established in Sweden, but as a reference, the Swedish National Board of Health and Welfare considers a cost per QALY gained between SEK 100,000 and SEK 500,000 as moderate [20,65]. Calculations for NMB and NHB were performed using a Swedish cost-effectiveness threshold of SEK 500,000. Positive values for NMB and NHB indicated that a management option would provide benefits for the healthcare system at the applied cost-effectiveness threshold value. Greater benefits were indicated by larger magnitudes in the NMB and NHB values.

The base case analysis described above was supplemented by deterministic sensitivity analyses. Their purpose was to evaluate the inherent uncertainty related to analytical results. Individual model inputs were varied one at a time in deterministic sensitivity analyses, and effects on analysis results were documented to identify inputs that were most influential. Confidence intervals (CIs) were the foundation for the variation of individual inputs, and in cases where CIs were not available, assumptions were made. The analysis inputs that were pertinent to uncertainty were simultaneously sampled

Table 3. Clinical outcome estimates in the base-case analysis (per 1,000 patients unless otherwise stated).

Clinical outcomes (per patient)	RefluxStop	Medical management	Incremental vs Medical management	LNF	Incremental vs LNF
Number of people developing BE	0.26	0.25	0.01	0.26	0.01
Number of people developing esophageal cancer	0.03	0.03	0.00	0.03	0.00
Number of surgeries	1.03	0.53	0.49	1.05	−0.02
Number of surgical failures	0.26	0.25	0.01	0.51	−0.25
Number of endoscopic dilations	0.00	0.30	−0.30	0.85	−0.85
Number of device removals	0.00	0.00	0.00	0.00	0.00
Average life expectancy, years (per patient)	35.73	33.91	1.82	34.82	0.91

BE, Barrett's esophagus; LNF, laparoscopic Nissen fundoplication.

Table 4. Cost-effectiveness outcomes estimated in the base case analysis, per patient.

Summary results	RefluxStop	Medical management	Incremental RS vs MM	Nissen fundoplication	Incremental RS vs LNF	Incremental LNF vs MM
Cost per patient	SEK 187,782	SEK 101,098	SEK 86,684	SEK 145,259	SEK 42,523	SEK 44,161
QALYs per patient	15.20	13.40	1.80	14.52	0.68	1.12
Life years per patient (undiscounted)	30.80	29.39	1.41	30.20	0.61	0.81
Life years per patient (discounted)	19.63	18.99	0.64	19.38	0.25	0.39
Incremental cost-effectiveness ratio (ICER)		SEK 48,152 (€ 4,531)*		SEK 62,966 (€ 5,925)*		SEK 39,429 (€ 3,710)*
Net monetary benefit (NMB)		SEK 813,432 (€ 76544)*		SEK 295,144 (€ 27773)*		SEK 515,839 (€ 48540)*
Net health benefit (NHB)		1.63		0.59		1.03

ICER, incremental cost-effectiveness ratio; LNF, laparoscopic Nissen fundoplication; MM, medical management; NHB, net health benefit; NMB, net monetary benefit; QALY, quality-adjusted life-year; RS, RefluxStop.
*Conversion rate (2022) Swedish Krona to Euros (0.0941).

from distributions of plausibility and the model was executed for over 1,000 iterations in probabilistic sensitivity analyses, with every iteration using a different set of inputs. Reported CIs were used wherever possible to derive the standard errors for generation of probabilistic values. The standard error was assumed to be equal to 10% of the mean value when unavailable.

Additional analysis was pursued to determine whether uncertainties regarding variably reported risks of PPI-related AEs, progression to Barrett's esophagus, and further progression to esophageal adenocarcinoma affected the findings of our analysis. The three scenarios explored were: 1) no risk of PPI-associated AEs in all comparison arms; 2) no risk of progression to Barrett's esophagus in all comparison arms; and 3) no risk of progression of Barrett's esophagus to esophageal adenocarcinoma in all comparator arms.

3. Results

3.1. Base case results

In terms of surgical outcomes, RefluxStop compared favorably against LNF for number of surgeries, surgical failures, and endoscopic dilations (Table 3). Our model estimated a higher life expectancy in the RefluxStop arm compared to all comparator arms, with differences of 0.91 to 1.82 years in favor of RefluxStop (Table 3). In the RefluxStop arm, patients accrued between 0.68 and 1.80 more QALYs than patients in the LNF and PPI-based medical management arms, respectively (Table 4).

At the Swedish cost-effectiveness threshold of SEK 500,000 per QALY gained, RefluxStop demonstrated cost-effectiveness against PPI-based management and Nissen fundoplication. LNF was effective against medical management (Table 4). The ICER value for RefluxStop was SEK 48,152 (€ 4,531) per QALY gained against PPI-based medical management and SEK 62,966 (€ 5,925) per QALY gained against LNF. The ICER value for LNF against medical management was SEK 39,429 (€3,710) per QALY gained. The NHB and NMB values of RefluxStop against all assessed comparators were positive.

Somewhat offsetting the costs of RefluxStop, PPI therapy offers lower costs (savings of SEK 29,017.65 and SEK 8,172.59 vs. medical management and LNF, respectively) and costs for treatment of PPI-related events (i.e. savings of SEK 4,421.55 and SEK 1,216.08 vs. medical management and LNF, respectively). In comparison to LNF, RefluxStop provided per-patient lifetime savings for surgical outcomes and complications (i.e. savings of SEK 1,347.87 for events occurring intraoperatively and complications necessitating surgery and SEK 5,296 for endoscopic dilation).

3.2. Sensitivity analyses

Surgical failure with RefluxStop and the probability of surgery following medical relapse were the most influential model inputs in deterministic sensitivity analyses (Suplementary Figure S1). Results were resistant to variation of isolated input parameters. With individual variation, no parameters (with the exception of the monthly surgical failure rate with RefluxStop as compared with LNF) altered the direction of results. Exploration of different estimates of cost and risk of AEs did not significantly affect the long-term cost-effectiveness.

RefluxStop had a high probability of being cost-effective in probabilistic analyses at a Swedish cost-effectiveness threshold of SEK 500,000, with probabilities of 100% and 96% against PPI-based medical management and Nissen fundoplication, respectively. Iterations of probabilistic sensitivity

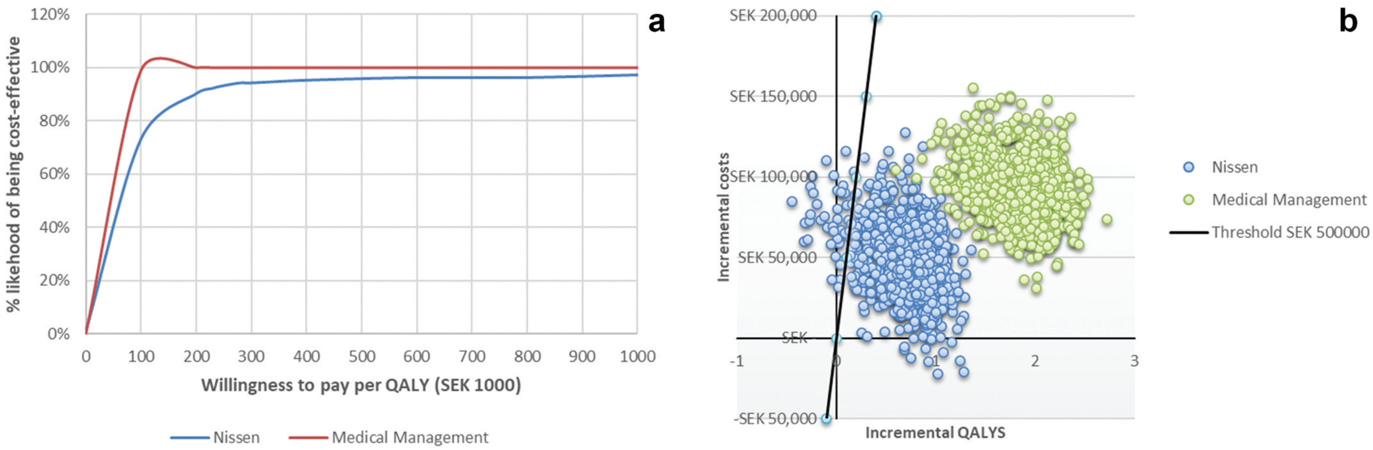

Figure 2. Results of the probabilistic sensitivity analyses of RefluxStop against the two comparators presented as cost-effectiveness acceptability curves (panel A) and as a cost-effectiveness plane showing the spread of the individual iterations (panel B). The black line in panel B indicates the Swedish cost-effectiveness threshold of SEK 500,000 per QALY. The points lying to the right of this line indicate iterations in which RefluxStop was cost-effective vs. the assessed comparator (marked by the color of the individual points) and the points lying to the left of the black line indicate those iterations in which RefluxStop was not cost-effective. *QALY, quality-adjusted life year.*

analysis were mostly found below the threshold of cost-effectiveness (Figure 2(b)). In comparison to PPI-based medical management and LNF, the average ICERs obtained from 1,000 iterations of probabilistic analyses were SEK 51,052.52 per QALY gained and SEK 69,853.12 per QALY gained, respectively. Thus, they were like the base case ICERs against each of the comparators.

3.3. Scenario analysis

We completed the analysis by introducing the following scenarios: 1) no PPI-induced AEs for all comparison arms; 2) no risk of Barrett's esophagus for all comparison arms; 3) no risk of esophageal adenocarcinoma in all comparison arms; and 4) no risk of intraoperative events in all comparison arms. As seen in Table A1 (see Supplementary Appendix), none of these scenarios exhibited significant impact on cost-effectiveness. Also seen in this table, when exclusively utilizing Swedish RCT-based data, there was a significant impact on the cost-effectiveness ratio compared to LNF, but significantly below the Swedish cost-effectiveness threshold of SEK 500,000.

4. Discussion

In the present study, RefluxStop was found to exert a positive impact on life expectancy that continued when quality of life was considered, as expressed by incremental differences in QALYs and LYs in comparison to the other assessed management strategies (i.e. lifelong PPI therapy and LNF). Our model demonstrated that RefluxStop was a cost-effective treatment alternative for chronic GERD when compared to the currently available management options. The base case ICER estimates were all significantly below the Swedish cost-effectiveness threshold of SEK 500,000 per QALY gained, as specified by Swedish authorities. This analysis is particularly helpful for health technology assessment bodies in Sweden like Tandvårds- och Läkemedelsförmånsverket (TLV), as standard cost-effectiveness methods using QALYs are considered for pricing and reimbursement of health technologies [66]. These estimates were robust, as suggested by sensitivity and scenario analyses, and were not subjected to variation of model inputs. In fact, the ICER and probabilistic sensitivity analysis showed comfortable cost-effectiveness at the more stringent threshold of SEK 100,000 [65]. Ultimately, these estimates suggest that RefluxStop offers a cost-effective technology in which the additional upfront cost carried by the insertion of the device is balanced by its long-term health benefits.

The results of our study expand on the literature already exploring the cost-effectiveness of various management strategies for GERD. Although there are some conflicting data, there is a slight skew in favor of antireflux procedures as compared with medical therapy in GERD management [3]. Using a Markov model to assess the cost utility of long-term PPI treatment versus laparoscopic fundoplication, PPI therapy was estimated to be less expensive within the 5-year time horizon, whereas others claim cost saving between the two strategies after about 10 years [15–17]. Other studies, applying modeling and/or retrospective methodological approaches, have favored surgical treatment reaching a cost saving point after a shorter time of comparison [3,15–19]. Accordingly, most studies (even prospective controlled studies) comparing the cost-effectiveness of modern therapies for GERD have concluded that surgery is the most cost-effective approach in the long-term perspective; these conclusions are also confirmed by our present results.

A potential weakness of the study, as well as with most previous modeling and/or retrospective studies, is the focus on direct medical costs. The relative costs of operation and medication have a paramount impact on the outcome. In this approach, other cost items (i.e. indirect costs) are marginalized. Ignoring the loss of productivity due to absence from work may give rise to a considerable underestimation of the cost burden for society [3,67]. On the other hand, remarkably small differences emerge between surgical and medical management strategies for GERD with a longer time perspective [35]. In this context, it needs to be pointed out that chronic GERD may be associated with significant health burdens for society in terms of absence from work due to illness, sleep disturbances, and other disease-specific AEs, which hitherto have been incompletely elucidated [68]. Another consideration is that comparison between the costs of medical and surgical treatments for GERD will, by necessity, vary from one country to another and likely from one time to another [3]. Observations lend support to the hypothesis that the costs of medical treatment are relatively constant over time whereas those of surgical treatment are associated with an enormous initial investment followed by low annual costs, eventually resulting in surgical treatment becoming less expensive over time provided that the cost of medication does not dramatically change [18,19,69]. Another dimension that should be considered is related to the costs associated with the actual operation and its profound impact on the subsequent direct medical costs in totality. About 40% and 70% of the total hospital costs for open and laparoscopic treatment, respectively, are caused by expenses related to the operative procedure and what happens within the operating theater [67]. For instance, the disposable materials used for laparoscopic fundoplication could entirely explain the differences in cost between open and minimally invasive procedures. Since the current use of disposable material for any surgical or endoscopic procedure in chronic GERD treatment remains the standard of care, the additional costs of a device such as RefluxStop should not be looked upon as a significant obstacle for its future clinical implementation.

Although evidence shows the benefit of RefluxStop from the Swedish payer's perspective, disseminating surgical innovation may be difficult in praxis, requiring additional strides beyond evidence presentation. To the best of our knowledge, a protocol for the adoption of surgical innovation similar to that developed by the Royal College of Surgeons does not exist in many other countries [70]. Surgeon training is also paramount to the adoption of novel surgical interventions that rely on diligent execution for their benefit to be widely observed [70]. RefluxStop surgery is subject to specific training factors, such as appropriate placement of the device anatomically and adherence of the esophagus to the fundus in the creation of the device platform [13]. These critical steps are important for ensuring the effectiveness of the intervention.

The results of our analysis indicate that broader use of RefluxStop is likely to provide benefits for those in Sweden suffering from GERD. The explanation for the apparent advantage of RefluxStop over LNF in health economic terms needs to be considered. In patients with GERD undergoing an antireflux procedure, side effects do often occur at varying degrees, particularly so when a total fundoplication is created. These side effects include dysphagia, inability to belch or vomit, postprandial fullness, bloating, pain, and socially embarrassing flatus [9–12,28,71,72]. Previous studies have shown that a total wrap is more frequently followed by mechanical side effects than a partial anterior or posterior wrap; it is likely that RefluxStop can accordingly minimize these side effects associated with LNF. By utilizing this approach, these differences also disseminate through the assessment of HRQoL to provide clinical benefit [73]. Possible mechanisms for these differences include distinct effects by respective procedures on important reflux-preventing mechanisms, such as LES tone, ability of the LES to relax in response to proper stimuli, and the frequency of transient LES relaxations [74]. It seems, therefore, that a total fundoplication might in fact 'overcorrect' the mechanical deficiencies of the gastroesophageal junction in patients with GERD, eliciting a super competent cardia [75]. Regarding the potentially advantageous effects of RefluxStop, the standardization and simplification of this surgical intervention (causing potentially fewer intraoperative events) may well have a bearing on the ensuing health economic variables presently assessed.

Accuracy is a problem in many health economic assessments, especially since charges and diagnosis-related group (DRG) estimates are often mere approximations of the true cost and cannot be regarded as an entirely valid representation of reality. The profound effect of the cost of surgery on direct medical costs has the implication that if a computer- or office-based model is used to assess costs, detailed knowledge of the real costs of surgery is required. Most hospitals can provide this type of information. However, the computer-based approach in assessing the costs of surgery for GERD has some obvious limitations. Accuracy is a problem in many health economic assessments, especially since charges and DRG estimates are often mere approximations of the true cost. However, DRGs were originally developed as a tool to classify and standardize hospital cases into groups that are clinically coherent and homogenous in terms of the resources they consume. This classification system allows for a systematic way to compare hospital services and expenditures across different patients, also taking clinical realities and cost variations into account. The uncertainties in using these estimates are assessed through our sensitivity analyses.

Another factor which was effectively controlled for in the present study was the outcome of antireflux surgery both on a nationwide level and in the context of the quality of surgery. In the surgical management of GERD, the volume–quality relationship is well-documented, and our model incorporated the highly relevant outcomes of LNF when carried out in high-volume expert centers. When the pooled outcome analyses were accordingly adjusted for, the final outcomes were only marginally affected without clinical significance. An additional strength of our study was the derivation of RefluxStop data from the recently collected 3-year data of the CE mark trial [36] in addition to the previously published 1-year results [13]. However, these data should be interpreted with some caution as the corresponding datasets are continuously expanding. Data on safety and efficacy for comparator arms were derived from the literature, somewhat based on heterogeneous populations and outcome measures when juxtaposed with the RefluxStop CE mark trial (e.g. surgical failure definitions). Thus, the results of our analysis represent a naïve comparison, subject to consideration when interpreting the data. This is a source of uncertainty related to the model results, which were largely balanced by the robustness of model estimates (i.e. variation of inputs in sensitivity analyses) in the case of our analysis. Further analyses were pursued to elucidate whether uncertainties pertaining to the variably reported risks of PPI-associated AEs, progression to Barrett's esophagus, and further progression to esophageal adenocarcinoma affected the results of the cost-effectiveness analysis. Three scenarios were explored with zero risk: 1) no risk of PPI-associated AEs in all comparison arms; 2) no risk of progression to Barrett's esophagus in all comparison arms; and 3) no risk of progression from Barrett's esophagus to esophageal adenocarcinoma in all comparison arms. In all scenarios, a marginal difference in ICER values was observed that remained significantly below the Swedish cost-effectiveness threshold. Currently, the RCT of RefluxStop against the surgical standard of care (i.e. LNF) will soon be launched to provide additional data regarding the role of this device as a long-term treatment for GERD patients.

5. Conclusion

According to our results, RefluxStop offers a highly cost-effective long-term treatment alternative for chronic GERD patients over lifelong PPI therapy, but also when compared to LNF, in the Swedish healthcare setting.

Funding

This paper was not funded.

Declaration of interest

S Harper and S Mealing are employed by a consultancy company that was commissioned by Implantica to develop the model. M Kartha is an employee of Implantica. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Author contributions

S Harper, M Kartha, and S Mealing designed and developed the model. L Lundell contributed to the design of the model and validated the results from a clinical perspective. All authors contributed to the drafting and revision of the manuscript.

Previous presentations

The data described in the manuscript was partially presented at ISPOR Europe 2023.

Data availability statement

The economic model predominantly uses data from published literature, and if any data is indicated as on file, it is available from the authors on reasonable request.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. El-Serag HB, Sweet S, Winchester CC, et al. Update on the epidemiology of gastro-oesophageal reflux disease: a systematic review. Gut. 2014;63(6):871–880. doi: 10.1136/gutjnl-2012-304269
2. Richter JE, Rubenstein JH. Presentation and epidemiology of gastroesophageal reflux disease. Gastroenterology. 2018;154 (2):267–276. doi: 10.1053/j.gastro.2017.07.045
3. Myrvold HE, Lundell L, Miettinen P, et al. The cost of long term therapy for gastro-oesophageal reflux disease: a randomised trial comparing omeprazole and open antireflux surgery. Gut. 2001;49 (4):488–494. doi: 10.1136/gut.49.4.488
   - **This reference provides additional health economic context that is elaborated on in the Discussion section.**
4. Agréus L, Borgquist L. The cost of Gastro-oesophageal reflux disease, dyspepsia and peptic ulcer disease in Sweden. Pharmacoeconomics. 2002;20(5):347–355. doi: 10.2165/00019053-200220050-00006
5. Rettura F, Bronzini F, Campigotto M, et al. Refractory gastroesophageal reflux disease: a management update. Front Med (Lausanne). 2021;8:765061. doi: 10.3389/fmed.2021.765061
6. Spechler SJ, Hunter JG, Jones KM, et al. Randomized trial of medical versus surgical treatment for refractory heartburn. N Engl J Med. 2019;381(16):1513–1523. doi: 10.1056/NEJMoa1811424
7. National Institute for Health and Care Excellence. Clinical guideline [CG184]: gastro-oesophageal reflux disease and dyspepsia in adults: investigation and management. London: National Institute for Health and Care Excellence (NICE); 2019.
8. Ronkainen J, Aro P, Storskrubb T, et al. High prevalence of gastroesophageal reflux symptoms and esophagitis with or without symptoms in the general adult Swedish population: a kalixanda study report. Scand J Gastroenterol. 2005;40(3):275–285. doi: 10.1080/00365520510011579
9. Katkhouda N, Khalil MR, Manhas S, et al. André Toupet: surgeon technician par excellence. Annals Surgery. 2002;235(4):591–599. doi: 10.1097/00000658-200204000-00019
   - **This reference provides additional health economic context that is elaborated on in the Discussion section.**
10. Stylopoulos N, Bunker CJ, Rattner DW. Development of achalasia secondary to laparoscopic Nissen fundoplication. J Gastrointest Surg. 2002;6(3):368–376; discussion 77-78. doi: 10.1016/S1091-255X(02)00019-7
    - **This reference provides additional health economic context that is elaborated on in the Discussion section.**
11. Anvari M, Allen C. Postprandial bloating after laparoscopic Nissen fundoplication. Can J Surg. 2001;44(6):440–444.
    - **This reference provides additional health economic context that is elaborated on in the Discussion section.**
12. Walle KV, Funk LM, Xu Y, et al. Persistent dysphagia rate after antireflux surgery is similar for nissen fundoplication and partial fundoplication. J Surg Res. 2019;235:52–57. doi: 10.1016/j.jss.2018.09.036
    - **This reference provides additional health economic context that is elaborated on in the Discussion section.**
13. Bjelović M, Harsányi L, Altorjay Á, et al. Non-active implantable device treating acid reflux with a new dynamic treatment approach: 1-year results. BMC Surg. 2020;20(1):159. doi: 10.1186/s12893-020-00794-9
    - •• **This reference directly informs the Markov model of this cost-effectiveness analysis.**
14. Nguyen N, Thosani N, Canto M, et al. The american foregut society white paper on the endoscopic classification of esophagogastric junction integrity. Foregut: The J Am Foregut Soc. 2022;2 (4):339–348. doi: 10.1177/26345161221126961
15. Heudebert GR, Marks R, Wilcox CM, et al. Choice of long-term strategy for the management of patients with severe esophagitis: a cost-utility analysis. Gastroenterology. 1997;112(4):1078–1086. doi: 10.1016/S0016-5085(97)70118-5
    - **This reference provides additional health economic context that is elaborated on in the Discussion section.**
16. Viljakka M, Nevalainen J, Isolauri J. Lifetime costs of surgical versus medical treatment of severe gastro-oesophageal reflux disease in Finland. Scand J Gastroenterol. 1997;32(8):766–772. doi: 10.3109/00365529708996532
    - **This reference provides additional health economic context that is elaborated on in the Discussion section.**
17. Weinstein MC, Stason WB. Foundations of cost-effectiveness analysis for health and medical practices. N Engl J Med. 1977;296 (13):716–721. doi: 10.1056/NEJM197703312961304

- **This reference provides additional health economic context that is elaborated on in the Discussion section.**

18. Bojke L, Hornby E, Sculpher M. A comparison of the cost effectiveness of pharmacotherapy or surgery (laparoscopic fundoplication) in the treatment of GORD. Pharmacoeconomics. 2007;25(10):829–841. doi: 10.2165/00019053-200725100-00003

- •• **This reference directly informs the Markov model of this cost-effectiveness analysis.**

19. Epstein D, Bojke L, Sculpher MJ. Laparoscopic fundoplication compared with medical management for gastro-oesophageal reflux disease: cost effectiveness study. BMJ. 2009;339(jul14 2):b2576. doi: 10.1136/bmj.b2576

- **This reference provides additional health economic context that is elaborated on in the Discussion section.**

20. Vrouchou PS, Heimbürger O, Ademi Z, et al. Cost-effectiveness analysis of Patiromer in combination with renin–angiotensin–aldosterone system inhibitors for chronic kidney disease in Sweden. Pharmacoeconomics. 2020;38(7):747–764. doi: 10.1007/s40273-020-00902-w
21. The Pharmaceutical Benefits Board. General guidelines for economic evaluations from the pharmaceutical benefits board (LFNAR 2003: 2). 2003. Available from: https://www.tlv.se/download/18.2e53241415e842ce95514e9/1510316396792/Guidelines-for-economicevaluations-LFNAR-2003-2.pdf
22. Philips Z, Bojke L, Sculpher M, et al. Good practice guidelines for decision-analytic modelling in health technology assessment: a review and consolidation of quality assessment. Pharmacoeconomics. 2006;24(4):355–371. doi: 10.2165/00019053-200624040-00006
23. National Institute for Health and Care Excellence (NICE). Dyspepsia and gastro-oesophageal reflux disease. Appendix H: full health economics report. 2014. Available from: https://www.nice.org.uk/guidance/cg184/evidence/appendix-h-full-health-economics-report-pdf-6955335252

- •• **This reference directly informs the Markov model of this cost-effectiveness analysis.**

24. Harper S, Grodzicki L, Mealing S, et al. Cost-effectiveness of a novel, non-active implantable device as a treatment for refractory gastro-esophageal reflux disease. J Med Econ. 2023;26(1):603–613. doi: 10.1080/13696998.2023.2201063
25. Wahlqvist P, Junghard O, Higgins A, et al. Cost effectiveness of proton pump inhibitors in gastro-oesophageal reflux disease without oesophagitis: comparison of on-demand esomeprazole with conventional omeprazole strategies. Pharmacoeconomics. 2002;20(4):267–277. doi: 10.2165/00019053-200220040-00005
26. Maret-Ouda J, Wahlin K, El-Serag HB, et al. Association between laparoscopic antireflux surgery and recurrence of gastroesophageal reflux. JAMA. 2017;318(10):939–946. doi: 10.1001/jama.2017.10981
27. Zehetner J, Hoffsten J, Das S, et al. Looking back to a 'gold standard': a systematic literature review of laparoscopic Nissen fundoplication as an anti-reflux treatment option. Eur Surg. 2024. doi: 10.1007/s10353-024-00836-z

- •• **This reference directly informs the Markov model of this cost-effectiveness analysis.**

28. Analatos A, Håkanson BS, Ansorge C, et al. Clinical outcomes of a laparoscopic total vs a 270° posterior partial fundoplication in chronic gastroesophageal reflux disease: a randomized clinical trial. JAMA Surg. 2022;157(6):473–480. doi: 10.1001/jamasurg.2022.0805
29. Analatos A, Håkanson BS, Lundell L, et al. Tension-free mesh versus suture-alone cruroplasty in antireflux surgery: a randomized, double-blind clinical trial. Br J Surg. 2020;107(13):1731–1740. doi: 10.1002/bjs.11917
30. Blomqvist A, Dalenbäck J, Hagedorn C, et al. Impact of complete gastric fundus mobilization on outcome after laparoscopic total fundoplication. J Gastrointest Surg. 2000;4(5):493–500. doi: 10.1016/S1091-255X(00)80092-X
31. Håkanson BS, Lundell L, Bylund A, et al. Comparison of Laparoscopic 270° posterior partial fundoplication vs total fundoplication for the treatment of gastroesophageal reflux disease: a randomized clinical trial. JAMA Surg. 2019;154(6):479–486. doi: 10.1001/jamasurg.2019.0047
32. Mardani J, Lundell L, Engström C. Total or posterior partial fundoplication in the treatment of GERD: results of a randomized trial after 2 decades of follow-up. Ann Surg. 2011;253(5):875–878. doi: 10.1097/SLA.0b013e3182171c48
33. Mardani J, Lundell L, Lönroth H, et al. Ten-year results of a randomized clinical trial of laparoscopic total fundoplication with or without division of the short gastric vessels. Br J Surg. 2009;96(1):61–65. doi: 10.1002/bjs.6393
34. Grant A, Wileman S, Ramsay C, et al. The effectiveness and cost-effectiveness of minimal access surgery amongst people with gastro-oesophageal reflux disease – a UK collaborative study. The REFLUX trial. The REFLUX Trial Health Technol Assess. 2008;12(31):1–181, iii–iv. doi: 10.3310/hta12310
35. Galmiche JP, Hatlebakk J, Attwood S, et al. Laparoscopic antireflux surgery vs esomeprazole treatment for chronic GERD: the LOTUS randomized clinical trial. JAMA. 2011;305(19):1969–1977. doi: 10.1001/jama.2011.626

- **This reference provides additional health economic context that is elaborated on in the Discussion section.**

36. Implantica. RefluxStop CE mark trial - 3-year data. Data on file [Unpublished but currently in peer-review]. 2022.

- •• **This reference directly informs the Markov model of this cost-effectiveness analysis.**

37. Kaptoge S, Pennells L, De Bacquer D, et al. World Health Organization cardiovascular disease risk charts: revised models to estimate risk in 21 global regions. Lancet Glob Health. 2019;7(10):e1332–e45. doi: 10.1016/S2214-109X(19)30318-3

- •• **This reference directly informs the Markov model of this cost-effectiveness analysis.**

38. Shiraev TP, Bullen A. Proton pump inhibitors and cardiovascular events: a systematic review. Heart Lung Circ. 2018;27(4):443–450. doi: 10.1016/j.hlc.2017.10.020

- •• **This reference directly informs the Markov model of this cost-effectiveness analysis.**

39. Collins G, Altman D. Predicting the risk of chronic kidney disease in the UK: an evaluation of QKidney® scores using a primary care database. Br J Gen Pract. 2012;62(597):e243–50. doi: 10.3399/bjgp12X636065

- •• **This reference directly informs the Markov model of this cost-effectiveness analysis.**

40. Hussain SS, Habib A, Najmi AK. Proton pump inhibitors use and risk of chronic kidney disease: evidence-based meta-analysis of observational studies. Clin Epidemiol Global Health. 2019;7(1):46–52. doi: 10.1016/j.cegh.2017.12.008

- •• **This reference directly informs the Markov model of this cost-effectiveness analysis.**

41. Kanis JA, Johnell O, Oden A, et al. FRAX™ and the assessment of fracture probability in men and women from the UK. Osteoporos Int. 2008;19(4):385–397. doi: 10.1007/s00198-007-0543-5

- •• **This reference directly informs the Markov model of this cost-effectiveness analysis.**

42. Zhou B, Huang Y, Li H, et al. Proton-pump inhibitors and risk of fractures: an update meta-analysis. Osteoporos Int. 2016;27(1):339–347. doi: 10.1007/s00198-015-3365-x

- •• **This reference directly informs the Markov model of this cost-effectiveness analysis.**

43. Sun X, Douiri A, Gulliford M. Pneumonia incidence trends in UK primary care from 2002 to 2017: population-based cohort study. Epidemiol Infect. 2019;147:e263.

- •• **This reference directly informs the Markov model of this cost-effectiveness analysis.**

44. Lambert AA, Lam JO, Paik JJ, et al. Risk of community-acquired pneumonia with outpatient proton-pump inhibitor therapy: a systematic review and meta-analysis. PLoS One. 2015;10(6):e0128004. doi: 10.1371/journal.pone.0128004

- •• **This reference directly informs the Markov model of this cost-effectiveness analysis.**

45. Public Health England. *Clostridium difficile* infection: mandatory surveillance 2017/18 2018. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/724368/CDI_summary_2018.pdf
- •• **This reference directly informs the Markov model of this cost-effectiveness analysis.**
46. Janarthanan S, Ditah I, Adler DG, et al. Clostridium difficile-associated diarrhea and proton pump inhibitor therapy: a meta-analysis. Am J Gastroenterol. 2012;107(7):1001–1010. doi: 10.1038/ajg.2012.179
- •• **This reference directly informs the Markov model of this cost-effectiveness analysis.**
47. Brusselaers N, Wahlin K, Engstrand L, et al. Maintenance therapy with proton pump inhibitors and risk of gastric cancer: a nationwide population-based cohort study in Sweden. BMJ Open. 2017;7(10):e017739. doi: 10.1136/bmjopen-2017-017739
- •• **This reference directly informs the Markov model of this cost-effectiveness analysis.**
48. Skubleny D, Switzer NJ, Dang J, et al. LINX® magnetic esophageal sphincter augmentation versus Nissen fundoplication for gastroesophageal reflux disease: a systematic review and meta-analysis. Surg Endosc. 2017;31(8):3078–3084. doi: 10.1007/s00464-016-5370-3
- •• **This reference directly informs the Markov model of this cost-effectiveness analysis.**
49. Alicuben ET, Bell RCW, Jobe BA, et al. Worldwide experience with erosion of the magnetic sphincter augmentation device. J Gastrointest Surg. 2018;22(8):1442–1447. doi: 10.1007/s11605-018-3775-0
- •• **This reference directly informs the Markov model of this cost-effectiveness analysis.**
50. Szende A, Janssen B, Cabases J, editors. Self-reported population health: an international perspective based on EQ-5D. 1 ed. Dordrecht (NL): Springer; 2014.
- •• **This reference directly informs the Markov model of this cost-effectiveness analysis.**
51. Ainslie WG, Catton JA, Davides D, et al. Micropuncture cholecystectomy vs conventional laparoscopic cholecystectomy: a randomized controlled trial. Surgical Endoscopy. 2003;17(5):766–772. doi: 10.1007/s00464-002-8568-5
- •• **This reference directly informs the Markov model of this cost-effectiveness analysis.**
52. Bouvy JC, Ebbers HC, Schellekens H, et al. The cost-effectiveness of periodic safety update reports for biologicals in Europe. Clin Pharmacol Ther. 2013;93(5):433–442. doi: 10.1038/clpt.2013.13
- •• **This reference directly informs the Markov model of this cost-effectiveness analysis.**
53. Pollit V, Graham D, Leonard C, et al. A cost-effectiveness analysis of endoscopic eradication therapy for management of dysplasia arising in patients with Barrett's oesophagus in the United Kingdom. Curr Med Res Opin. 2019;35(5):805–815. doi: 10.1080/03007995.2018.1552407
- •• **This reference directly informs the Markov model of this cost-effectiveness analysis.**
54. Trifan A, Stanciu C, Girleanu I, et al. Proton pump inhibitors therapy and risk of Clostridium difficile infection: systematic review and meta-analysis. World J Gastroenterol. 2017;23(35):6500–6515. doi: 10.3748/wjg.v23.i35.6500
55. Nassar Y, Richter S. Proton-pump inhibitor use and fracture risk: an updated systematic review and meta-analysis. J Bone Metab. 2018;25(3):141–151. doi: 10.11005/jbm.2018.25.3.141
56. Poly TN, Lin MC, Syed-Abdul S, et al. Proton pump inhibitor use and risk of gastric cancer: current evidence from epidemiological studies and critical appraisal. Cancers (Basel). 2022;14(13):14. doi: 10.3390/cancers14133052
57. Nguyen PA, Islam M, Galvin CJ, et al. Meta-analysis of proton pump inhibitors induced risk of community-acquired pneumonia. Int J Qual Health Care. 2020;32(5):292–299. doi: 10.1093/intqhc/mzaa041
58. Nochaiwong S, Ruengorn C, Awiphan R, et al. The association between proton pump inhibitor use and the risk of adverse kidney outcomes: a systematic review and meta-analysis. Nephrol Dial Transplant. 2018;33(2):331–342. doi: 10.1093/ndt/gfw470
59. Batchelor R, Kumar R, Gilmartin-Thomas JFM, et al. Systematic review with meta-analysis: risk of adverse cardiovascular events with proton pump inhibitors independent of clopidogrel. Aliment Pharmacol Ther. 2018;48(8):780–796. doi: 10.1111/apt.14955
60. Shaheen N, Ransohoff DF. Gastroesophageal reflux, barrett esophagus, and esophageal cancer: scientific review. JAMA. 2002;287(15):1972–1981. doi: 10.1001/jama.287.15.1972
61. Yousef F, Cardwell C, Cantwell MM, et al. The incidence of esophageal cancer and high-grade dysplasia in Barrett's esophagus: a systematic review and meta-analysis. Am J Epidemiol. 2008;168(3):237–249. doi: 10.1093/aje/kwn121
62. NHS England. National cost collection data publication. 2019/20. Available from: https://www.england.nhs.uk/publication/2019-20-national-cost-collection-data-publication/
63. Nord DRG. 2022 Available from: https://www.socialstyrelsen.se/statistik-och-data/klassifikationer-och-koder/drg/viktlistor
- •• **This reference directly informs the Markov model of this cost-effectiveness analysis.**
64. Shemilt I, Thomas J, Morciano M. A web-based tool for adjusting costs to a specific target currency and price year. Evidence & Policy A J Res Debate And Pract. 2010;6(1):51–60. doi: 10.1332/174426410X482999
65. Hambraeus J, Pulkki-Brannstrom AM, Lindholm L. Cost-effectiveness of radiofrequency denervation for zygapophyseal joint pain. Pain Physician. 2021;24(8):E1205–e18.
- • **This reference provides additional health economic context that is elaborated on in the Discussion section.**
66. TLV - How should we assess and pay? 2021 [cited 2024 Aug 23]. Available from: https://www.tlv.se/download/18.2f080b7e182629be22dd4e3c/1660743327830/rapport_rupm_atmp_eng.pdf
- • **This reference provides additional health economic context that is elaborated on in the Discussion section.**
67. Blomqvist AM, Lönroth H, Dalenbäck J, et al. Laparoscopic or open fundoplication? A complete cost analysis. Surg Endosc. 1998;12(10):1209–1212. doi: 10.1007/s004649900822
- • **This reference provides additional health economic context that is elaborated on in the Discussion section.**
68. Toghanian S, Johnson DA, Stålhammar NO, et al. Burden of gastro-oesophageal reflux disease in patients with persistent and intense symptoms despite proton pump inhibitor therapy: a post hoc analysis of the 2007 national health and wellness survey. Clin Drug Investig. 2011;31(10):703–715. doi: 10.2165/11595480-000000000-00000
- • **This reference provides additional health economic context that is elaborated on in the Discussion section.**
69. Kleppe KL, Xu Y, Funk LM, et al. Healthcare spending and utilization following antireflux surgery: examining costs and reasons for readmission. Surg Endosc. 2020;34(1):240–248. doi: 10.1007/s00464-019-06758-2
- • **This reference provides additional health economic context that is elaborated on in the Discussion section.**
70. The Royal College of Surgeons of England. From innovation to adoption. Successfully spreading surgical innovation 2014 Available from: https://www.rcseng.ac.uk/-/media/files/rcs/library-and-publications/non-journal-publications/rcs_innovation_to_adoption_2014_web-(1).pdf
- • **This reference provides additional health economic context that is elaborated on in the Discussion section.**
71. Broeders JA, Mauritz FA, Ahmed Ali U, et al. Systematic review and meta-analysis of laparoscopic Nissen (posterior total) versus toupet (posterior partial) fundoplication for gastro-oesophageal reflux disease. British Journal Of Surgery. 2010;97(9):1318–1330. doi: 10.1002/bjs.7174
- • **This reference provides additional health economic context that is elaborated on in the Discussion section.**
72. Lundell L, Abrahamsson H, Ruth M, et al. Long-term results of a prospective randomized comparison of total fundic wrap (Nissen-Rossetti) or semifundoplication (toupet) for gastro-oesophageal reflux. J British Surgery. 1996;83(6):830–835. doi: 10.1002/bjs.1800830633

- **This reference provides additional health economic context that is elaborated on in the Discussion section.**

73. Analatos A, Lindblad M, Ansorge C, et al. Total versus partial posterior fundoplication in the surgical repair of para-oesophageal hernias: randomized clinical trial. BJS Open. 2022;6(3):6. doi: 10.1093/bjsopen/zrac034
- **This reference provides additional health economic context that is elaborated on in the Discussion section.**

74. Rydberg L, Ruth M, Lundell L. Mechanism of action of antireflux procedures. Br J Surg. 1999;86(3):405–410. doi: 10.1046/j.1365-2168.1999.01025.x
- **This reference provides additional health economic context that is elaborated on in the Discussion section.**

75. Implantica CE Reflux Ltd. Instructions for use PMIM001 rev 06 - English version. 2022.
- **This reference provides additional health economic context that is elaborated on in the Discussion section.**

76. Chaudhary MA, Holmberg C, Lakhdari K, et al. Cost-effectiveness of nivolumab in squamous and non-squamous non-small cell lung cancer in Canada and Sweden: an update with 5-year data. J Med Econ. 2021;24(1):607–619. doi: 10.1080/13696998.2021.1917139
- •• **This reference directly informs the Markov model of this cost-effectiveness analysis.**

77. Palser TR, Ceney A, Navarro A, et al. Variation in laparoscopic anti-reflux surgery across England: a 5-year review. Surg Endosc. 2018;32(7):3208–3214. doi: 10.1007/s00464-018-6038-y
- •• **This reference directly informs the Markov model of this cost-effectiveness analysis.**

78. Wolff E, Storsaeter J, Örtqvist Å, et al. Cost-effectiveness of pneumococcal vaccination for elderly in Sweden. Vaccine. 2020;38(32):4988–4995. doi: 10.1016/j.vaccine.2020.05.072
- •• **This reference directly informs the Markov model of this cost-effectiveness analysis.**

79. Kerr M, Bray B, Medcalf J, et al. Estimating the financial cost of chronic kidney disease to the NHS in England. Nephrol Dial Transplant. 2012;27 Suppl 3(Suppl 3):iii73–80. doi: 10.1093/ndt/gfs269
- •• **This reference directly informs the Markov model of this cost-effectiveness analysis.**

80. Gandjour A, Kleinschmit F, Lauterbach KW. European comparison of costs and quality in the treatment of acute myocardial infarction (2000–2001). European Heart Journal. 2002;23(11):858–868. doi: 10.1053/euhj.2001.3080
- •• **This reference directly informs the Markov model of this cost-effectiveness analysis.**

81. Eriksson D, Karlsson L, Eklund O, et al. Real-world costs of autosomal dominant polycystic kidney disease in the nordics. BMC Health Serv Res. 2017;17(1):560. doi: 10.1186/s12913-017-2513-8
- •• **This reference directly informs the Markov model of this cost-effectiveness analysis.**

82. Kim K, Fagerström J, Chen G, et al. Cost effectiveness of sodium zirconium cyclosilicate for the treatment of hyperkalaemia in patients with CKD in Norway and Sweden. BMC Nephrol. 2022;23(1):281. doi: 10.1186/s12882-022-02903-7
- •• **This reference directly informs the Markov model of this cost-effectiveness analysis.**

83. Kidneyfailurerisk.com. The kidney failure risk equation. Available from: https://kidneyfailurerisk.com/
- •• **This reference directly informs the Markov model of this cost-effectiveness analysis.**

84. Borgström F, Zethraeus N, Johnell O, et al. Costs and quality of life associated with osteoporosis-related fractures in Sweden. Osteoporos Int. 2006;17(5):637–650. doi: 10.1007/s00198-005-0015-8
- •• **This reference directly informs the Markov model of this cost-effectiveness analysis.**

85. National Institute for Health and Care Excellence. Quality standard [QS110]: Pneumonia in adults 2016. Available from: https://www.nice.org.uk/guidance/qs110
- •• **This reference directly informs the Markov model of this cost-effectiveness analysis.**

86. Nordling S, Anttila VJ, Norén T, et al. The burden of clostridium difficile (CDI) infection in hospitals, in Denmark, Finland, Norway and Sweden. Value Health. 2014;17(7):A670. doi: 10.1016/j.jval.2014.08.2480
- •• **This reference directly informs the Markov model of this cost-effectiveness analysis.**

87. National Institute for Health and Care Excellence (NICE). Technology appraisal guidance [TA378]: ramucirumab for treating advanced gastric cancer or gastro-oesophageal junction adenocarcinoma previously treated with chemotherapy 2016. Available from: https://www.nice.org.uk/guidance/ta378
- •• **This reference directly informs the Markov model of this cost-effectiveness analysis.**

88. Laudicella M, Walsh B, Munasinghe A, et al. Impact of laparoscopic versus open surgery on hospital costs for colon cancer: a population-based retrospective cohort study. BMJ Open. 2016;6(11):e012977. doi: 10.1136/bmjopen-2016-012977
- •• **This reference directly informs the Markov model of this cost-effectiveness analysis.**