Appendix H: Full Health Economics Report

H.1 RQ4 Economic Model

H.2 General

The approach to providing health economic evidence to support decision making around a clinical review question begins with a systematic search of the literature. The aim of this is to source any published economic evaluations of relevance to the topic of interest. At this stage it may become apparent that evidence exists in the literature which exactly meets the review question criteria and therefore there is no need for original economic analysis. If this proves not to be the case it may be decided that economic modelling can generate some useful analysis. The aim is to produce a cost–utility analysis in order to weigh up the benefits and harms of comparable interventions. The extent to which this is possible will be driven by the availability of evidence upon which to parameterise the clinical pathway and disease natural history.

H.3 Proton pump inhibitors (PPIs) in the healing and maintenance of severe erosive reflux oesophagitis (RQ4)

H.3.1 Decision problem

Table 1: Research question

RQ4	What is the clinical effectiveness of PPIs in patients with severe erosive reflux disease? i) to control / reduce oesophagitis ii) as maintenance therapy

Table 2: PICO

Population	Patients with severe erosive reflux oesophagitis (LA grades C & D or equivalent)
Intervention	Proton-pump inhibitor drugs of varied dosages.
Comparator	Alternative PPIs &/or dosages.
Outcomes	A cost-utility analysis was constructed based on the quality of life (in quality adjusted life years[QALYs]) and costs of healing of oesophagitis.

H.3.2 Systematic review of published cost–utility analyses

H.3.2.1 Methods

Inclusion and exclusion criteria

The economic literature review aimed to identify economic evaluations in the form of cost–utility analyses exploring the costs and effects of different PPI treatments used in the healing or maintenance treatment of patients with severe erosive reflux oesophagitis.

Search strategy

The search strategy was based on that used to identify clinical evidence for this question, with the RCT filter removed and a standard economic filter applied (see appendix C).

H.3 Results

Study identification

The search returned 1864 studies; after title and abstract screening, we ordered the full texts of 37 studies. On perusal of the retrieved papers, no cost–utility analyses comparing PPI therapy in patients with severe erosive reflux oesophagitis could be included.

H.3.2.3 Discussion

Due to the lack of published economic evaluations to provide guidance to answer the review question, a de novo health economic model was proposed. The GDG identified that this was a high priority area for original health economic analysis.

H.3.3 Original cost–utility model – methods

H.3.3.1 Overview of the model

Table 3: Modelled population(s) and intervention(s)

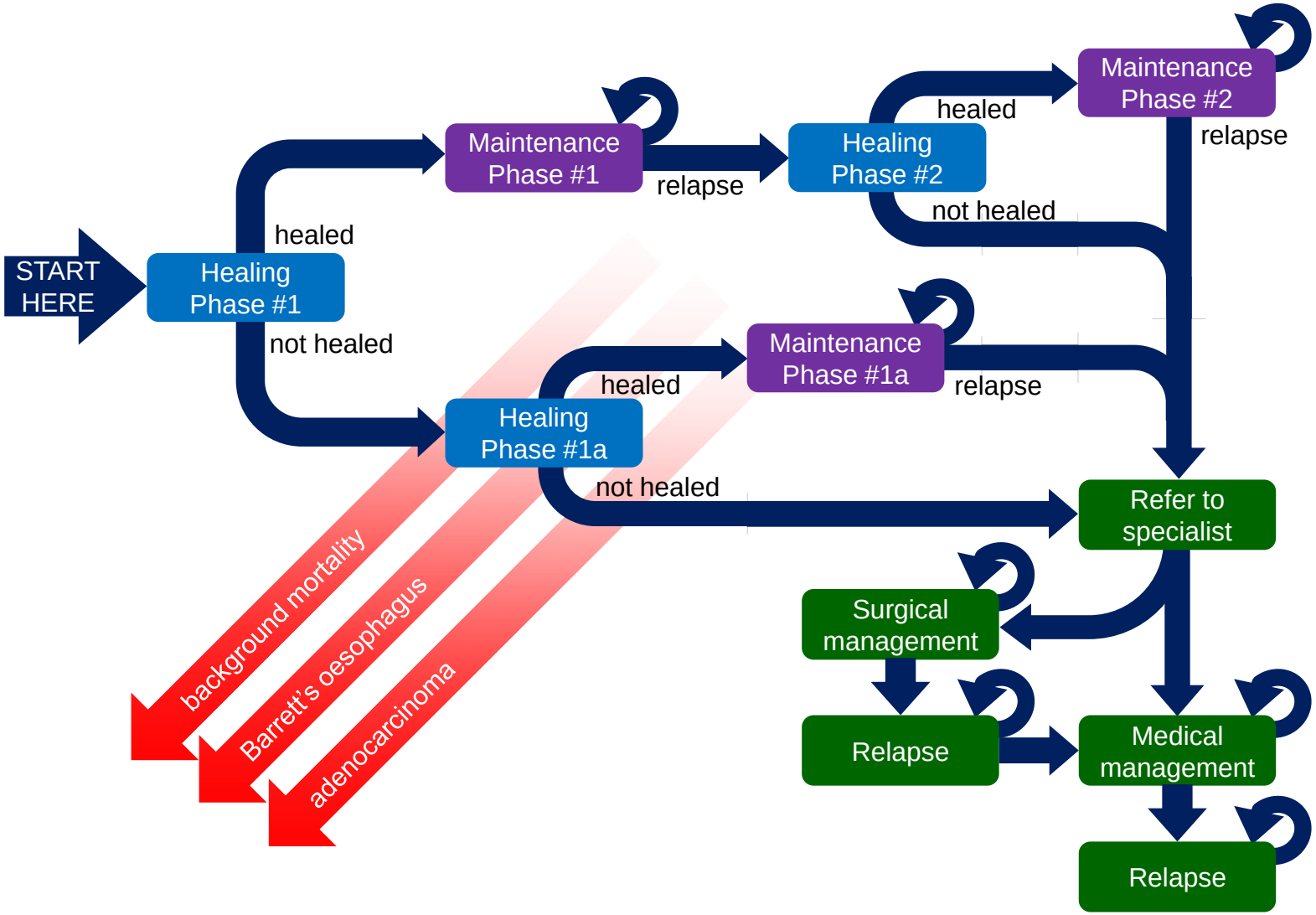
Population	Patients with severe erosive reflux oesophagitis (LA grades C & D or equivalent). Cohort modelled is 60% male with an average age of 50.
Intervention	Proton-pump inhibitor drugs of varied dosages.
Comparator	Alternative PPIs &/or dosages.
Outcomes	A cost-utility analysis was constructed based on the quality of life (in quality adjusted life years[QALYs]) and costs of healing of oesophagitis.

We built a Markov model with monthly cycles and a life-time horizon. The Markov structure allows costs and utilities to be accrued for each month spent in a series of health states.

The PPI drugs and doses included within the model, both for healing and maintenance treatments, are limited to those in which clinical evidence was available in the literature.

The model uses a patient perspective for outcomes and an NHS perspective for costs, in line with the Guidelines Manual (2012).

Figure 1 provides a schematic depiction of the model structure.



National Institute for Health and Care Excellence 2014.

Figure 1: Structure of the original cost-utility model

Upon entering the model, the cohort all have confirmed severe oesophagitis. The first stage models the probability of a selected PPI, dose and duration, healing the oesophagitis. Those patients who have their oesophagitis healed are placed on maintenance therapy of a selected PPI, dose and duration. Patients can then either remain in this health state or have an oesophagitis relapse where they are given another healing regimen. Those who are healed return to maintenance therapy and those who fail to be healed are referred to secondary care.

Patients who fail to heal with first-line therapy progress to healing phase 1a. Failure of second-line therapy leads to a referral to secondary care. Healed patients are put onto a maintenance therapy dose, on which they remain, until they relapse, when they too are referred to secondary care.

Upon entering the secondary care element of the model the patients can be managed medically or surgically, with a probability of relapse following treatment.

During any model cycle the patient can develop Barrett's oesophagus, adenocarcinoma or die from other causes. The health states which represent Barrett's oesophagus and adenocarcinoma capture the health related quality of life and costs of each of the diseases.

Anaemia and stricture were determined as complications of relevance to unhealed oesophagitis within the modelling framework, also with associated quality of life values and costs. We assume that these complications only occur as a result of unhealed oesophagitis therefore patients in a healed health state cannot develop anaemia and stricture.

The model is flexible enough to represent the healing and maintenance of a number of sequences of treatment and can estimate a total of 1,728,000 scenarios.

Key assumptions

There are a number of assumptions built into the economic model which need to be considered when analysing the results generated. These are summarised inTable 4.

Table 4: Key assumptions of original cost–utility model

• Initial population have oesophagitis of LA Grade C or D without coexisting BO, dysplasia or malignancy.
• All health states are mutually exclusive.
• None of the patient cohort have BO at baseline (in base case; to be explored in sensitivity analysis).
• Barrett's Oesophagus is considered to be a progressive state from oesophagitis and influences the chance of progression to malignancy.
• Assume equivalent compliance & adverse event profiles for all PPIs.
• 28-day cycles.
• Recurrence of oesophagitis is at the severe grades (LA C & D or equivalent) - clinical evidence includes varied definitions of relapse.
• All-cause mortality & death from malignancy only – no direct death from other health states.

- All patients with stricture & anaemia are symptomatic and present to their GP.
- Episodes of stricture and anaemia are assumed to have quality of life detriments for six months, until symptom resolve.
- Health outcomes and costs are discounted at a rate of 3.5% in line with the NICE reference case
- Only patients with unhealed oesophagitis can develop stricture; we will assume that, as everyone in this model is already on PPI maintenance, all presenting with stricture are symptomatic & will have a dilatation.
- The utility values of healed and unhealed health states are driven by the incidence of complications only in the base case.
- A scenario analysis will be conducted in which relapse of oesophagitis will not occur beyond five years of treatment.
- Patients remain on maintenance therapy for life.
- Progression from Barrett's to adenocarcinoma incurs the cost of a GP appointment, diagnostic endoscopy and the costs of treatments for cancer.
- Any change to treatment incurs the cost of a GP visit.
- Health states are split into healing, maintenance and specialist management states and separate into healed and unhealed oesophagitis groups. The costs and utility values for each state include the probability and impact of diagnostic endoscopies, GP appointments, specialist consultations and fundoplication, complications of unhealed oesophagitis, in addition to the drugs used.
- Estimated distributions for each of the point parameter values have been applied to enable the uncertainty in each estimate to be quantified and included within estimates of cost-effectiveness.
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H.3.3.2 Parameters – general approach

Identifying sources of parameters

With the exception of the effectiveness of each PPI in the healing and maintenance of oesophagitis, which were drawn from the systematic review conducted for this research question (see below), parameters were identified through informal searches that aimed to satisfy the principle of 'saturation' (that is, to 'identify the breadth of information needs relevant to a model and sufficient information such that further efforts to identify more information would add nothing to the analysis' [Kaltenthaler et al., 2011]). We conducted searches in a variety of general databases, including Medline (via PubMed), the Cochrane Database of Systematic Reviews and GoogleScholar.

We asked the GDG to identify papers of relevance. We reviewed the sources of parameters used in the published CUAs identified in our systematic review (see H.7.2, above); during the

review, we also retrieved articles that did not meet the formal inclusion criteria, but appeared to be promising sources of evidence for our model. We studied the reference lists of articles retrieved through any of these approaches to identify any further publications of interest.

In cases where there was paucity of published literature for values essential to parameterise key aspects of the model, data were obtained from unpublished sources; further details are provided below.

Selecting parameters

Our overriding selection criteria were as follows:

- The selected studies should report outcomes that correspond as closely as possible to the health states and events simulated in the model.
- The selected studies should report a population that closely matches the UK population (ideally, they should be drawn from the UK population).
- All other things being equal, more powerful studies (based on sample size and/or number of events) were preferred.
- Where there was no reason to discriminate between multiple possible sources for a given parameter, we gave consideration to quantitative synthesis (meta-analysis), to provide a single summary estimate.
- In the absence of any published evidence for a given parameter necessary to represent the treatment pathway, the GDG provided estimates to inform the parameterisation of the model.

H.3.3.3 Parameters

Cohort characteristics

The characteristics of the cohort entering the model at baseline are loosely based on the average age and sex split of the trial populations upon which the clinical evidence is based.

Treatment effects

The effectiveness of PPI therapy in the healing and maintenance of severe erosive oesophagitis used within the model is drawn from the clinical evidence review. In order to employ this evidence on multiple drugs and doses, a network meta analysis was conducted. This enables estimates to be produced combining the evidence from multiple sources and producing estimates based on indirect comparisons of the drugs within the clinical evidence base. The network does not however, generate estimates for the drugs and doses in which no clinical trial data within the patient population of interest could be obtained.

As the effectiveness rates are pooled from the network meta-analysis of clinical evidence which includes indirect comparisons to estimate treatment effect, there is some uncertainty surrounding the effectiveness of each of the regimens as displayed in the confidence intervals.

The network meta-analysis generates estimates of relative effectiveness of each of the treatments in comparison to one another. In order to incorporate effectiveness evidence into the economic model we need an absolute estimate of effectiveness for each of the treatment options available.

The effects of healing treatments are estimated from a network meta-analysis of healing at four and eight weeks. The relative effects of each of the treatments at four and eight weeks, are applied to a baseline estimate of the effectiveness of pantoprazole 40mg, as this is the treatment at the centre of the network.

The relative effectiveness of each of the maintenance treatments is applied to the absolute combined effectiveness estimate for placebo and pantoprazole 10mg to generate an effectiveness estimate for each treatment option. Pantoprazole 10mg was deemed by the GDG as an ineffectual dose and therefore in order to produce a network in which all treatment arms could be joined up, it was assumed to be equivalent in terms of maintaining oesophagitis healing as a placebo.

For maintenance treatments, the evidence of effectiveness is only available for a maximum of twelve months. The network generates estimates of relapse after one year of treatment. As the model simulates a lifetime horizon we need to extrapolate the rate of relapse over the longer-term. We initially assumed a constant rate of relapse in each year of treatment, operationalised within the model via an exponential distribution, however the GDG raised the issue that relapse is less likely over time for patients on long-term PPI maintenance therapy. Assuming a constant rate of relapse results in an acceleration in the speed of relapses within the economic model. Kovacs et al (2009) conducted an open-label study with long-term follow-up of patients with mild oesophagitis. They found a decrease in the rate of relapse the longer a patient had been on maintenance therapy. They fitted a Weibull curve to the observations within their study which we use within our economic model to extrapolate beyond our relapse rates at twelve months. We use the shape factor directly from the Kovacs et al data and calculate the relevant scale parameter for each PPI treatment and dose using the shape factor and the estimate of effectiveness at 12 months, generated by the network meta analysis.

The distribution function for the Weibull distribution is as follows:

$$F(x; k, \lambda) = 1 - e^{-\left(\frac{x}{\lambda}\right)^k}$$

Where k=shape parameter and λ is the scale parameter.

for x ≥ 0, and F(x; k; λ) = 0 for x < 0.

The shape factor can be estimated from the Weibull curve fit to the Kovacs et al (2009) data by applying linear regression to the rearranged equation:

$$\ln(\ln(\frac{1}{1-F(x)})) = (-k(\ln(\lambda))) + k(\ln(x))$$

$$y = c + \text{mx}$$

Where c = intercept and m=slope.

The shape factor is determined by the linear regression directly. In this case the estimated shape factor used within the model is 0.737.

The uncertainty in the shape factor is tested within the probabilistic sensitivity analysis. The range of values explored includes 1, which is equivalent to an exponential distribution therefore some iterations will have a constant rate of relapse

The scale factor is determined by estimating the line that in using the pre-defined shape factor equals the estimated rate of relapse at 12 months for each of the treatments within the model. The scale factor for each treatment arm is estimated as follows:

$$k = -\ln(Probhealed)^{\left(-\frac{1}{\lambda}\right)}$$

The Weibull function is not used within the second maintenance phase of the model as patients can enter this state during any cycle, therefore it is not possible to apply a relapse rate that is dependent on the duration of maintenance treatment.

Transition probabilities

The transition probabilities within the model have been obtained from a number of published sources, the details of which are displayed in Table 5.

The transition probabilities relevant to specialist management are sourced from the REFLUX trial (Grant et al 2008).

Mortality

There is a risk of death from adenocarcinoma represented within the model, as well as a risk of operative mortality with laparoscopic nissen fundoplication surgery. Patients within the model can also die from other causes, with the probability relevant to the average age of the cohort, within each model cycle.

Resource use

The resource use associated with complications in the model is based on published evidence, where available. However, a number of resource use elements are unavailable in the literature. The treatment of people with adenocarcinoma for example is an element of care in which the expert opinion of the GDG members has been the basis upon which to estimate the parameters.

Costs

Where resource use estimates have been obtained from the literature, NHS reference costs (2011/2012) have been allocated to represent the cost to the healthcare system. Costs derived directly from published evidence have been inflated to the same year for consistency.

Drug costs

The unit costs for each PPI at each dose were sourced from either the NHS Drugs tariff or the MIMs database depending on which reported the lowest acquisition cost.

The cost of the dosage prescribed in each study was constructed from formulations currently available in the UK, using combinations of doses where the exact dose in the study is not available. Rabeprazole 50mg in the extended release formulation that was used within the clinical trial in which the evidence was sourced, is not available in the UK. In order to be able to incorporate this evidence into the economic model we estimated the cost as two 20mg and one 10mg tablets. This is a limitation of the costing methodology as the 50mg rabeprazole in this formulation may have an entirely different cost if it were to be approved for use within the NHS.

H.3.3.4 Parameters – quality of life

We conducted a literature search to locate utility values to be applied to the health states within the economic model.

Direct evidence of the health-related quality of life impact of severe erosive reflux oesophagitis could not be sourced therefore the baseline estimates of utility were taken from the population of patients undergoing the REFLUX trial. The patient population differs from

the focus of this review question as they do not necessarily all have severe reflux oesophagitis. They are however deemed an appropriate proxy.

Utility values for the complications represented within the model were obtained from a number of sources. In the case of BO and stricture, EQ-5D estimates of utility could not be found therefore the values used are based on a time-trade-off valuation of health related quality of life.

An estimate of the impact of anaemia on quality of life could not be obtained however the GDG suggested an assumption that the decrement was equivalent to that of dysphagia (in stricture) was appropriate and would enable representation of anaemia as a complication of unhealed oesophagitis within the model.

There was insufficient evidence in the clinical review to be able to incorporate a quality of life decrement for adverse events of the PPI therapies. It is therefore assumed, for the purpose of the economic modelling, that all the PPIs included as healing and maintenance treatments for oeosphagitis carry the same side-effect profile.

A decrement in utility is assumed to apply to anyone who resides within health states which are managed in a specialist care setting. The high probability of successful healing with specialist treatment manifests itself in a paradoxical result within the model in which there is an incentive to fail treatment with PPIs. The treatment pathway, as modelled, which aims to represent an appropriate simplification of the UK practice of care, has people who fail to heal with two phases of treatment referred to a specialist. The utility decrement therefore enables decision making to be contained within the primary care sector, which is the focus of the review question. The GDG deem the decrement is a reasonable assumption to make given that the group of patients referred to specialist care are likely to be those with the most severe disease.

H.3.3.5 Parameters – summary

All parameters used in the model are summarised, with their source and distribution for probabilistic sensitivity analysis, in Table 5.

Table 5: Model Parameters

Parameter	Value (95%CI)	Ref	Distribution and parameters	Notes
Cohort characteristics				
Sex (% male)	60%	Assumption		
Mean age of cohort at start	50	Assumption		
Proportion of cohort with Barrett's at baseline	0%	Assumption		Tested in sensitivity analysis
Probability of healing (natural scale)				
4wk				
Pantoprazole - 40	0.543 (0.428, 0.655)	NMA	multivariate normal	
Esomeprazole - 20	0.438 (0.221, 0.629)			
Esomeprazole - 40	0.566 (0.337, 0.727)			
Lansoprazole - 30	0.434 (0.230, 0.610)			
Nizatidine - 300	0.058 (0.008, 0.246)			
Omeprazole - 20	0.379 (0.191, 0.560)			
Pantoprazole - 10	0.198 (0.058, 0.507)			
Pantoprazole - 20	0.479 (0.220, 0.749)			
Placebo	0.024 (0.003, 0.147)			
Rabeprazole - 20	0.639 (0.077, 0.983)			
Rabeprazole - 50 (ER)	0.594 (0.358, 0.754)			
Ranitidine - 300	0.316 (0.154, 0.500)			
Ranitidine - 600	0.034 (0.001, 0.268)			
8wk				
Pantoprazole - 40	0.698 (0.584, 0.799)	NMA	multivariate normal	

Parameter	Value (95%CI)	Ref	Distribution and parameters	Notes
Esomeprazole - 20	0.603 (0.353, 0.775)			
Esomeprazole - 40	0.717 (0.490, 0.843)			
Lansoprazole - 30	0.599 (0.359, 0.760)			
Nizatidine - 300	0.107 (0.015, 0.399)			
Omeprazole - 20	0.543 (0.309, 0.719)			
Pantoprazole - 10	0.325 (0.106, 0.676)			
Pantoprazole - 20	0.642 (0.354, 0.860)			
Placebo	0.045 (0.005, 0.250)			
Rabeprazole - 20	0.775 (0.135, 0.991)			
Rabeprazole - 50 (ER)	0.740 (0.510, 0.860)			
Ranitidine - 300	0.473 (0.261, 0.668)			
Ranitidine - 600	0.064 (0.002, 0.424)			
Probability of relapse at one year (natural scale)				
Placebo	0.827 (0.746, 0.894)	NMA	multivariate normal	
Esomeprazole - 20	0.201 (0.084, 0.417)			
Lansoprazole - 15	0.329 (0.155, 0.589)			
Lansoprazole - 30	0.183 (0.064, 0.412)			
Pantoprazole - 20	0.328 (0.193, 0.512)			
Pantoprazole - 40	0.249 (0.132, 0.423)			
Ranitidine - 300	0.786 (0.590, 0.929)			
Transition probabilities				
Adherence to maintenance therapy	81.0% (76.4%, 85.2%)	van Soest et al. (2006)	Beta: α=247.53; β=58.06	
Months between GP attendances in maintenance	9.000 (6.000, 12.000)	Remak (2004)	Normal: μ=9.000; σ=1.531	
Prob choose surgery following failure of maintenance Rx	57.6% (53.0%, 62.1%)	Grant et al (2008)	Beta: α=261; β=192	
Prob choose surgery following failure of 2 x healing Rx	80% (64%, 96%)	Gerson et al (2000)	Triangular: min=60%; mode=80%; max=100%	

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Parameter	Value (95%CI)	Ref	Distribution and parameters	Notes
Operative mortality	0.0012 (0.0003, 0.0026)	Grant et al (2008)	Gamma: α=4.0000; β=0.0003	
5-yr prob of relapse in surgical arm	0.125 (0.076, 0.184)	Lundell et al (2001)	Beta: α=18; β=126	
5-yr prob of relapse in medical arm	0.130 (0.082, 0.187)	Lundell et al (2001)	Beta: α=20; β=134	
Drift from surgical to medical management (5 yrs)	0.309 (0.243, 0.379)	Grant et al (2008)	Beta: α=55; β=123	
Annual rate of GP attendances in specialist (surgical)	2.10 (2.01, 2.20)	Grant et al (2008)	Lognormal: μ=0.74; σ=0.02	
Annual rate of GP attendances in specialist (medical)	2.21 (2.11, 2.31)	Grant et al (2008)	Lognormal: μ=0.79; σ=0.02	
Annual rate of day admissions in specialist (surgical)	0.10 (0.08, 0.12)	Grant et al (2008)	Lognormal: μ=-2.33; σ=0.11	
Annual rate of day admissions in specialist (medical)	0.13 (0.10, 0.15)	Grant et al (2008)	Lognormal: μ=-2.08; σ=0.09	
Annual rate of overnight admissions in specialist (surgical)	0.03 (0.02, 0.04)	Grant et al (2008)	Lognormal: μ=-3.57; σ=0.20	
Annual rate of overnight admissions in specialist (medical)	0.05 (0.04, 0.07)	Grant et al (2008)	Lognormal: μ=-2.91; σ=0.14	
Probability of repeat endoscopy in maintenance phases				
Rate of re-scope per patient-year	0.077 (0.059, 0.101)	Lundell et al (2001)	Lognormal: μ=-3; σ=0	
Prob of developing Barrett's oesophagus:				
Rate of Barrett's in GORD population (per patient-yr)	0.010 (0.006, 0.014)	Ronkainen et al (2011)	Beta: α=23; β=2300	
RRR unhealed -v- healed	5.200 (1.190, 22.716)	Ronkainen et al (2011)	Lognormal: μ=1.65; σ=0.75	
Probability of developing cancer:				
Annual probability of cancer (with BO)	0.0013 (0.0011, 0.0016)	Bhat 2011	Lognormal: μ=-6.63; σ=0.11	
Annual probability of cancer (no BO)	0.0000 (0.0000, 0.0013)	Assumption	Uniform: min=0.0000; max=0.0013	
Cancer mortality (oesophageal cancer):				
1-year survival-rate (men)	0.402 (0.396, 0.409)	ONS	Lognormal: μ=-0.911; σ=0.008	

Parameter	Value (95%CI)	Ref	Distribution and parameters	Notes
1-year survival-rate (women)	0.399 (0.389, 0.409)	ONS	Lognormal: μ=-0.919; σ=0.013	
Diagnosed cancer				
Proportion of diagnosed adenocarcinomas (with surveillance)	97.8% (96.1%, 99.6%)	Garside et al (2006)	Cosine: min=95.6%; max=100.0%	
Proportion of diagnosed adenocarcinomas (no surveillance)	2.1% (0.4%, 3.8%)	Garside et al (2006)	Cosine: min=0.0%; max=4.3%	
Proportion of diagnosed adenocarcinomas inoperable	1.2% (0.0%, 14.7%)	Inadomi et al (2003)	Beta: α=0.04; β=3.70	assumed SE of 0.1
RR presymptomatic operable adenocarcinomas surgery -v- RFA	1.00 (0.50, 2.00)	Assumption	Lognormal: μ=0.000; σ=0.354	
Proportion of symptomatic adenocarcinomas inoperable	75.0% (53.1%, 91.6%)	Assumption	Beta: α=1331.3%; β=443.8%	Calculated using an assumed 50:50 split from GDG for those patients who are operable receiving either RFA or surgery
RR symptomatic operable adenocarcinomas surgery -v- RFA	3.00 (0.75, 12.00)	Assumption	Lognormal: μ=1.099; σ=0.707	Calculated using an assumed 50:50 split from GDG for those patients who are operable receiving either RFA or surgery
BO surveillance				
Proportion of BO cohort undergoing surveillance	70.0% (51.0%, 89.0%)	Assumption	Uniform: min=50.0%; max=90.0%	
Frequency of BO surveillance (yrs)	2 (1, 3)	Assumption	Triangular: min=1; mode=2; max=3	
Proportion of BO- adenocarcinomas diagnosed	2.1% (0.4%, 3.8%)	Garside et al (2006)	Cosine: min=0.0%; max=4.3%	
Annual probability of developing high-grade dysplasia in BO	0.0029 (0.0024, 0.0035)	Inadomi et al (2003)	Lognormal: μ=-5.840; σ=0.093	Only used to estimate costs of RFA; otherwise HGD not modelled separately

Parameter	Value (95%CI)	Ref	Distribution and parameters	Notes
Complications:				
% with unhealed oesophagitis developing anaemia over lifetime	11.00% (2.46%, 19.54%)	Gerson et al (2012)	Triangular: min=0%; mode=11%; max=22%	
% with unhealed oesophagitis developing stricture over lifetime	6.60% (1.48%, 11.72%)	Gerson et al (2012)	Triangular: min=0.0%; mode=6.6%; max=13.2%	
Correlation between healing and symptoms (optional scenario)				
p(symptomatic|healed)	0.083 (0.050, 0.122)	Bate & Richardson (1993)	Beta: α=18; β=200	
p(symptomatic|unhealed)	0.242 (0.162, 0.333)	Bate & Richardson (1993)	Beta: α=23; β=72	
p(healed|symptomatic)	0.897 (0.854, 0.933)	Bate & Richardson (1993)	Beta: α=200; β=23	
p(healed|asymptomatic)	0.200 (0.124, 0.288)	Bate & Richardson (1993)	Beta: α=18; β=72	
Costs				
Drug costs (per cycle)				
Healing				
Pantoprazole - 40	£1.62 (not varied in PSA)	MIMS		
Esomeprazole - 20	£6.18 (not varied in PSA)	NHS Drug tariff		
Esomeprazole - 40	£7.93 (not varied in PSA)	NHS Drug tariff		
Lansoprazole - 30	£1.76 (not varied in PSA)	MIMS		
Omeprazole - 20	£1.34 (not varied in PSA)	MIMS		
Pantoprazole - 10	£1.24 (not varied in PSA)	MIMS		
Pantoprazole - 20	£1.24 (not varied in PSA)	MIMS		
Placebo	£0.00 (not varied in PSA)	MIMS		
Rabeprazole - 20	£4.26 (not varied in PSA)	MIMS		
Rabeprazole - 50 (ER)	£11.53 (not varied in PSA)	MIMS		

Parameter	Value (95%CI)	Ref	Distribution and parameters	Notes
Maintenance				
Placebo	£0.00 (not varied in PSA)	MIMS		
Esomeprazole - 20	£5.01 (not varied in PSA)	NHS Drug tariff		
Lansoprazole - 15	£1.04 (not varied in PSA)	MIMS		
Lansoprazole - 30	£1.43 (not varied in PSA)	MIMS		
Pantoprazole - 20	£1.00 (not varied in PSA)	MIMS		
Pantoprazole - 40	£1.31 (not varied in PSA)	MIMS		
Fundoplication (NHS reference costs)	£4,137.81 (£4,010.59, £4,265.40)	NHS Ref Costs	weighted average of multiple categories from NHS reference costs, each subject to a separate gamma distribution	
Fundoplication (REFLUX trial)	£2,281.32 (£2,184.67, £2,380.03)	Grant et al (2008)	Gamma: α=2095.18; β=1.09	Inflated to 2011/12
Endoscopy	£448.01 (£433.24, £463.44)	NHS Ref Costs	weighted average of multiple categories from NHS reference costs, each subject to a separate gamma distribution	
First consultant appointment	£162.04 (£152.81, £170.89)	NHS Ref Costs	weighted average of multiple categories from NHS reference costs, each subject to a separate gamma distribution	
Anaemia				
Unit cost of ferrous sulfate 200mg (28-tablet pack)	£1.02 (not varied in PSA)	MIMS		
No. of ferrous sulfate 200mg tablets in a course	168 (125, 211)	BNF	Triangular: min=112.00; mode=168.00; max=224.00	
Cost of diagnostic colonoscopy	£548.83 (£533.17, £563.40)	NHS Ref Costs	weighted average of multiple categories from NHS reference costs, each subject to a separate gamma distribution	
Proportion of people with anaemia undergoing colonoscopy	75.0% (55.6%, 94.4%)	Assumption	Triangular: min=50.0%; mode=75.0%; max=100.0%	

Parameter	Value (95%CI)	Ref	Distribution and parameters	Notes
Stricture				
Unit cost of balloon dilatation	£563.07 (£540.96, £584.68)	NHS Ref Costs	weighted average of multiple categories from NHS reference costs, each subject to a separate gamma distribution	
Proportion experiencing perforation due to dilatation	0.5% (0.0%, 1.0%)	Assumption	Uniform: min=0.0%; max=1.0%	
Proportion undergoing surgery due to perforation	68.0% (50.9%, 85.1%)	Stal et al (1998)	Uniform: min=50.0%; max=86.0%	
Cost of oesophagectomy for adenocarcinoma	£11,464.67 (£10,773.10, £12,182.98)	NHS Ref Costs	weighted average of multiple categories from NHS reference costs, each subject to a separate gamma distribution	
Cost of palliative care (without stenting) for people with inoperable adenocarcinoma	£4,987.26 (£4,005.64, £6,209.43)	Shenfine 2005	Lognormal: μ=8.51; σ=0.11	Inflated to 2011/12
Cost of palliative care (including stenting) for people with inoperable adenocarcinoma	£5,348.88 (£4,541.49, £6,299.80)	Shenfine 2005	Lognormal: μ=8.58; σ=0.08	Inflated to 2011/12
Proportion of people receiving stenting	50.0% (2.5%, 97.5%)	Assumption	Uniform: min=0.0%; max=100.0%	
Cost of 1 session endoscopic therapy for adenocarcinoma	£1,886.72 (£1,794.94, £1,975.53)	NHS Ref Costs	weighted average of multiple categories from NHS reference costs, each subject to a separate gamma distribution	
Number of sessions of RFA	2 (1, 3)	Assumption	weighted average of multiple categories from NHS reference costs, each subject to a separate gamma distribution	
Proportion receiving both EMR & RFA	85.0% (80.3%, 89.8%)	Assumption	Uniform: min=80.0%; max=90.0%	
Cost of definitive chemoradiotherapy	£4,836.29 (£4,467.93, £4,833.48)	NHS Ref Costs	weighted average of multiple categories from NHS reference costs, each subject to a	

Parameter	Value (95%CI)	Ref	Distribution and parameters	Notes
			separate gamma distribution	
Proportion of unresectable receiving chemoradiotherapy	25.0% (10.8%, 39.3%)	Assumption	Uniform: min=10.0%; max=40.0%	
Proportion of surgical undergoing neoadjuvant chemotherapy	75.0% (51.3%, 98.8%)	Assumption	Uniform: min=50.0%; max=100.0%	
Cost of neoadjuvant chemotherapy	£1,149.53 (£897.42, £980.22)	NHS Ref Costs	weighted average of multiple categories from NHS reference costs, each subject to a separate gamma distribution	
Unit cost of GP attendances	£43.00 (not varied in PSA)	PSSRU		
Unit cost of day admissions	£352.03 (£329.40, £376.14)	NHS Ref Costs	weighted average of multiple categories from NHS reference costs, each subject to a separate gamma distribution	
Unit cost of overnight admissions	£1,353.25 (£1,322.29, £1,384.78)	NHS Ref Costs	weighted average of multiple categories from NHS reference costs, each subject to a separate gamma distribution	
Utilities				
Medical arm at baseline	0.72 (0.68, 0.76)	Grant et al (2008)	Gamma: α=1484.6976; β=0.0005	
Surgical arm at baseline	0.71 (0.67, 0.75)	Grant et al (2008)	Gamma: α=1327.3639; β=0.0005	
Medical arm at 12mo	0.71 (0.67, 0.75)	Grant et al (2008)	Gamma: α=1230.8615; β=0.0006	
Surgical arm at 12mo	0.75 (0.71, 0.79)	Grant et al (2008)	Gamma: α=1611.0000; β=0.0005	
Implied utility decrement from baseline for surgery (1mo)	0.100 (0.035, 0.226)		Lognormal: μ=-2.414; σ=0.472	Calculated from surgical utility at baseline minus utility for month of surgery

Parameter	Value (95%CI)	Ref	Distribution and parameters	Notes
Symptomatic	0.56 (0.46, 0.67)	Grant et al (2008)	Gamma: α=100.0000; β=0.0056	Inflated to 2011/12
Decrement for specialist care states	0.05 (0.01, 0.09)	Assumption	Triangular: min=0.00; mode=0.05; max=0.10	
TTO utility for Barrett's	0.91 (0.53, 1.00)	Gerson et al (2007)	Beta: α=3.50; β=0.35	
Population SG utility for adenocarcinoma	0.40 (0.31, 0.48)	Garside et al (2006)	Beta: α=53.12; β=81.36	
Days of QoL life lost per endoscopy	1.00 (0.22, 1.78)	Assumption	Triangular: min=0.00; mode=1.00; max=2.00	
TTO dysphagia	0.950 (0.907, 0.980)	Stal et al (1998)	Beta: α=124.050; β=6.529	
TTO healed dysphagia	0.998 (0.993, 1.000)	Stal et al (1998)	Beta: α=497.004; β=0.996	
assumed duration of stricture decrement (months)	6 (2, 10)	Assumption	Triangular: min=1; mode=6; max=11	
assumed duration of anaemia decrement (months)	6 (2, 10)	Assumption	Triangular: min=1; mode=6; max=11	

H.3.3.6 Deterministic sensitivity analyses

One-way sensitivity analysis

One-way sensitivity analysis was conducted to examine the factors which have an influence on the cost-effectiveness of the treatment regimens. In this form of analysis the value for one parameter is varied while the values for all other parameters remain constant. This enables us to decipher the impact of each parameter on the results of the model.

The analysis was conducted for all variables within the model for both healing and maintenance analysis. The diagrams show only a section of the results, but include all the variables for which the value has a significant impact upon the cost-effectiveness results. Varying the estimates of the parameters (towards the bottom of the figure, or not shown) within plausible ranges, does not alter the decision on which treatment in the most cost-effective. Their inclusion in the model does however provide face validity in the representation of the clinical decision problem.

The results of the analysis for healing treatments are presented in Figure 2.

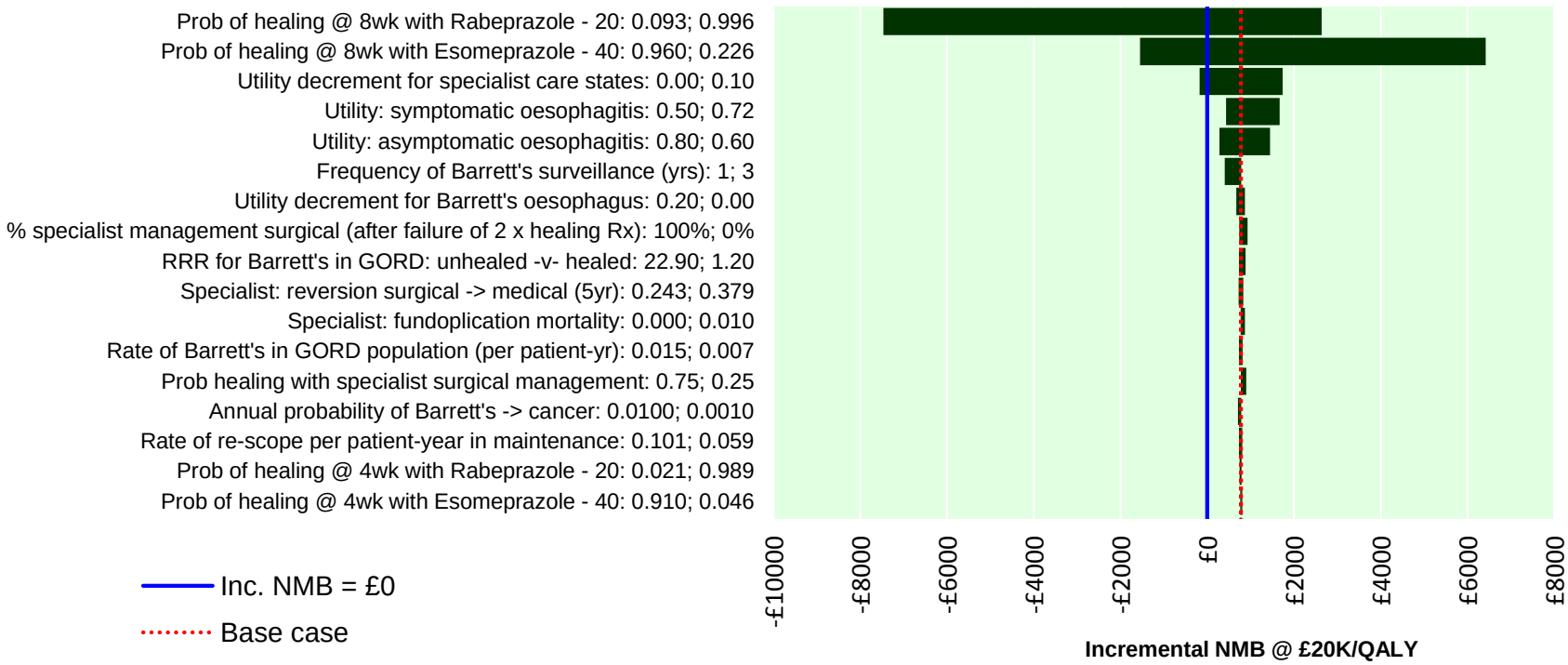


Figure 2: One-way sensitivity analysis of healing treatments for severe erosive reflux oesophagitis

The two variables at the top of the tornado diagram are the probability of healing with rabeprazole (20mg) and esomeprazole (40mg). This demonstrates that our uncertainty in the estimates of healing effectiveness are what is driving our uncertainty in our estimates of cost-effectiveness.

The only other variable to have a significant influence on the cost-effectiveness is the estimate of the impact being managed in a specialist care setting has on patient quality of life. This highlights the importance of this variable in a model with the aim of guiding a decision on the optimum treatments for patients within a primary care setting. If the value of the utility decrement is set to zero then the treatments with the lowest probability of healing the oesophagitis, have the highest probability of being the most cost-effective options.

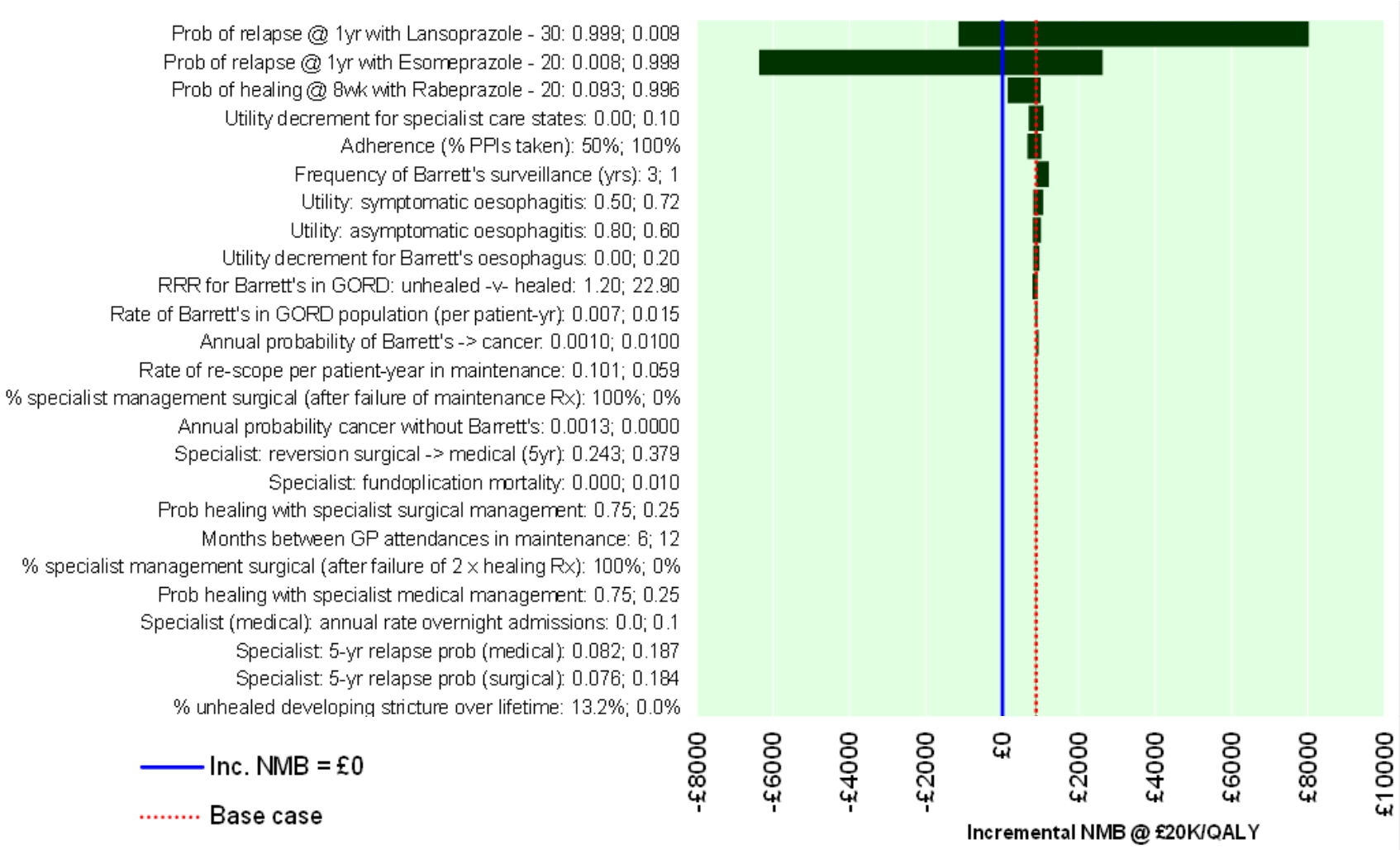


Figure 3: One-way sensitivity analysis of maintenance treatments for severe erosive reflux oesophagitis

National Institute for Health and Care Excellence 2014.

As with the model for healing of oesophagitis, the uncertainty in the clinical effectiveness of the PPI maintenance therapies is the driver of our uncertainty in the treatment that is likely to be the most cost-effective.

H.3.3.7 Probabilistic sensitivity analyses

We configured the models to perform probabilistic sensitivity analysis to quantify uncertainty in the true values of input parameters.

Probability distributions were estimated for all input variables with the exception of the direct (drug) costs of the PPIs. Distribution parameters were sourced from the study in which the value was obtained, where possible, or were estimated based on the usual properties of data of that type.

The distribution for each of the parameters used within the probabilistic sensitivity analysis is driven by the variable type and the availability of reported information. Beta distributions are used for variables denoting a probability, as bounded between 0 and 1, where data are reported to estimate the standard error, otherwise a triangular distribution is estimated. A beta distribution is also estimated for the utility values, which also traditionally confined to values between 0 and 1.

The proportion of patients using each element of resource use is also estimated to follow a beta distribution. The variables which denote a number of events, are estimated to follow a normal distribution. Triangular distributions are estimated where the GDG have generated a range of values to be tested in sensitivity analysis.

H.3.3.8 Scenario analyses

Of all the possible scenarios that the model is capable of providing estimates, we ran the 64,000 most plausible, to check that there were no unexpected interactions. No such anomalous results appeared to be present therefore the results presented are for scenarios in which a single healing treatment and maintenance treatment is selected and reused in sequential treatment phases.

In addition to the treatment-related scenarios, three additional scenarios are examined:

- No relapse after 5 years
    - In the base case modelled the probability of relapse whilst on maintenance therapy is the same in each cycle. If after five years the oesophagitis remains healed, we assume, in this scenario, that this will continue to be the case indefinitely, therefore no further relapses will occur.
- % in initial cohort with BO
    - In the base case none of the cohort have oesophagitis at the start of the period modelled, to reflect the population in which the clinical evidence has been based. In this scenario we include a proportion of individuals with BO to explore how this may impact upon the cost-effectiveness of PPI treatment.
- Symptoms are correlated with oesophagitis
    - In the base case the likelihood of having symptoms does not depend on the presence of oesophagitis. We test this assumption using evidence from a study in a population with all oesophagitis severity

levels (Bate & Richardson 1993) and assume the same relationship is apparent in patients with severe disease.

H.3.4 Original cost–utility model – healing results

H.3.4.1 Clinical outcomes from the model – healing

Strategy	Progress to		Drug costs		Specialist
	Barrett's	Adenocarcinoma	Healing	Maintenance	
Rabe20(8wk)->Lanso30	30.58%	0.75%	£14.00	£238.26	£1792.11
Rabe50 (ER)(8wk)->Lanso30	30.12%	0.74%	£38.46	£225.86	£1971.10
Esome40(8wk)->Lanso30	29.91%	0.73%	£26.62	£220.23	£2051.67
Panto40(8wk)->Lanso30	29.84%	0.73%	£5.45	£218.37	£2078.24
Panto20(8wk)->Lanso30	29.32%	0.71%	£4.24	£203.74	£2286.06
Esome20(8wk)->Lanso30	29.02%	0.70%	£21.30	£194.88	£2411.04
Lanso30(8wk)->Lanso30	28.86%	0.70%	£6.09	£190.28	£2475.49
Ome20(8wk)->Lanso30	28.51%	0.69%	£4.69	£179.63	£2624.40
Panto10(8wk)->Lanso30	26.47%	0.62%	£4.58	£113.83	£3528.32
Placebo(8wk)->Lanso30	23.81%	0.52%	£0.00	£16.86	£4825.50

H.3.4.2 Base-case cost–utility result

Healing treatment duration

In order to demonstrate whether 4 weeks or 8 weeks of healing treatment is the most likely to be cost-effective, each PPI treatment is presented with comparative analysis of treatment for both treatment periods.

Figure 4 shows the results of each of the pairwise analyses on the cost-effectiveness plane. 4-week treatment is dominated in each case by treatment for 8 weeks therefore the treatment scenarios modelled in the remainder of the results contain healing regimens of 8 weeks duration in every case.

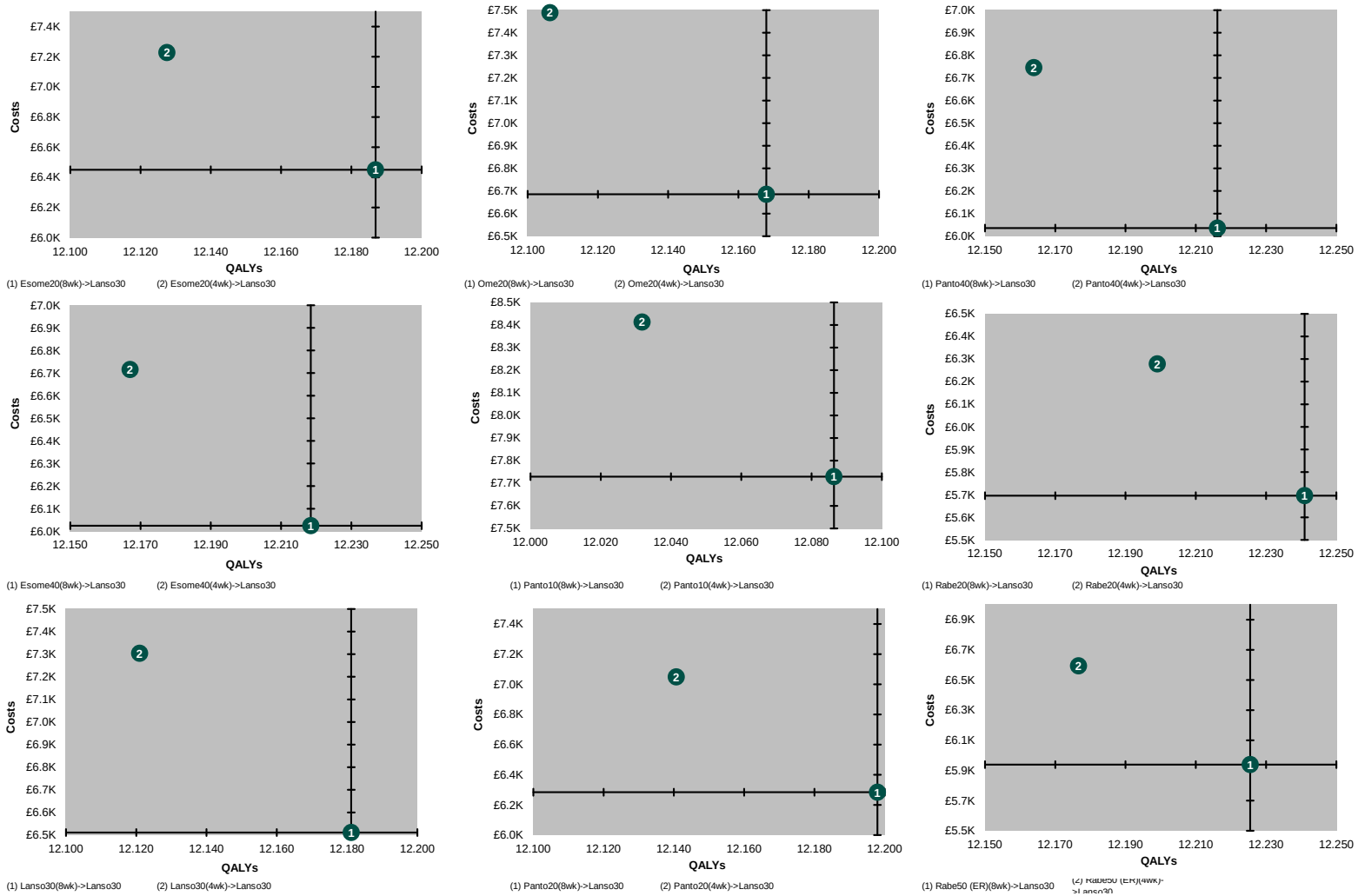


Figure 4: Pairwise comparisons of PPIs for healing with treatment lengths of 4 & 8 weeks
National Institute for Health and Care Excellence 2014.

PPIs for healing

The analysis for healing of oesophagitis includes each PPI healing treatment option available within the clinical evidence base with a common maintenance treatment to enable a fair comparison to be made.

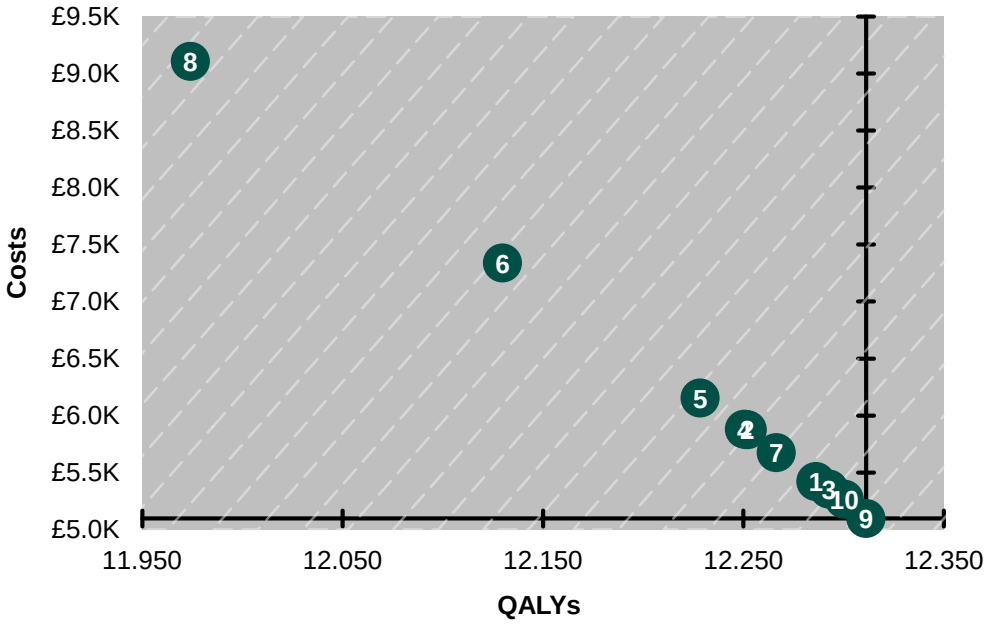


Figure 5: Healing: incremental cost–utility results - Base-case deterministic analysis (RE)

(1) Panto40(8wk)->Lanso30
(2) Esome20(8wk)->Lanso30
(3) Esome40(8wk)->Lanso30
(4) Lanso30(8wk)->Lanso30
(5) Ome20(8wk)->Lanso30
(6) Panto10(8wk)->Lanso30
(7) Panto20(8wk)->Lanso30
(8) Placebo(8wk)->Lanso30
(9) Rabe20(8wk)->Lanso30
(10) Rabe50 (ER)(8wk)->Lanso30

The figure above shows that where the costs of treatment are similar, the estimates of cost-effectiveness are driven almost entirely by the estimates of healing.

Fenwick et al (2001) propose that when the distribution of incremental net benefit is positively skewed, which is likely to be the case here as there is substantial uncertainty in the estimates of healing, the cost-effectiveness of treatment options should be represented by a cost-effectiveness acceptability frontier. It allows a quantification of the variation in value for each of the model iterations. If for example those iterations where a given treatment is the most cost-effective it is so by a large amount, we are less concerned with how often the treatment is the most cost-effective but, on balance, which treatment provides the best value at any given threshold. We present the results of this analysis based on this approach.

The cost effectiveness acceptability frontier is generated from the mean results of the PSA as shown in Figure 6.

Table 6: Incremental cost–utility results - Based on means of probabilistic analysis (RE)

	Absolute		Incremental			Absolute Net Monetary Benefit
Name	Costs	QALYs	Costs		ICER	£20K/QALY
Rabe50ER(8wk)→Lanso30	£5639	12.184				£238,047
Panto40(8wk)→Lanso30	£5668	12.180	£29	-0.004	dominated	£237,940
Esome40(8wk)→Lanso30	£5692	12.180	£53	-0.005	dominated	£237,899
Rabe20(8wk)→Lanso30	£5752	12.172	£113	-0.012	dominated	£237,691
Panto20(8wk)→Lanso30	£5950	12.160	£310	-0.024	dominated	£237,247
Esome20(8wk)→Lanso30	£6045	12.153	£406	-0.032	dominated	£237,005
Lanso30(8wk)→Lanso30	£6090	12.149	£451	-0.036	dominated	£236,885
Ome20(8wk)→Lanso30	£6226	12.139	£586	-0.045	dominated	£236,553
Panto10(8wk)→Lanso30	£7180	12.065	£1541	-0.119	dominated	£234,123
Placebo(8wk)→Lanso30	£8842	11.929	£3203	-0.256	dominated	£229,728

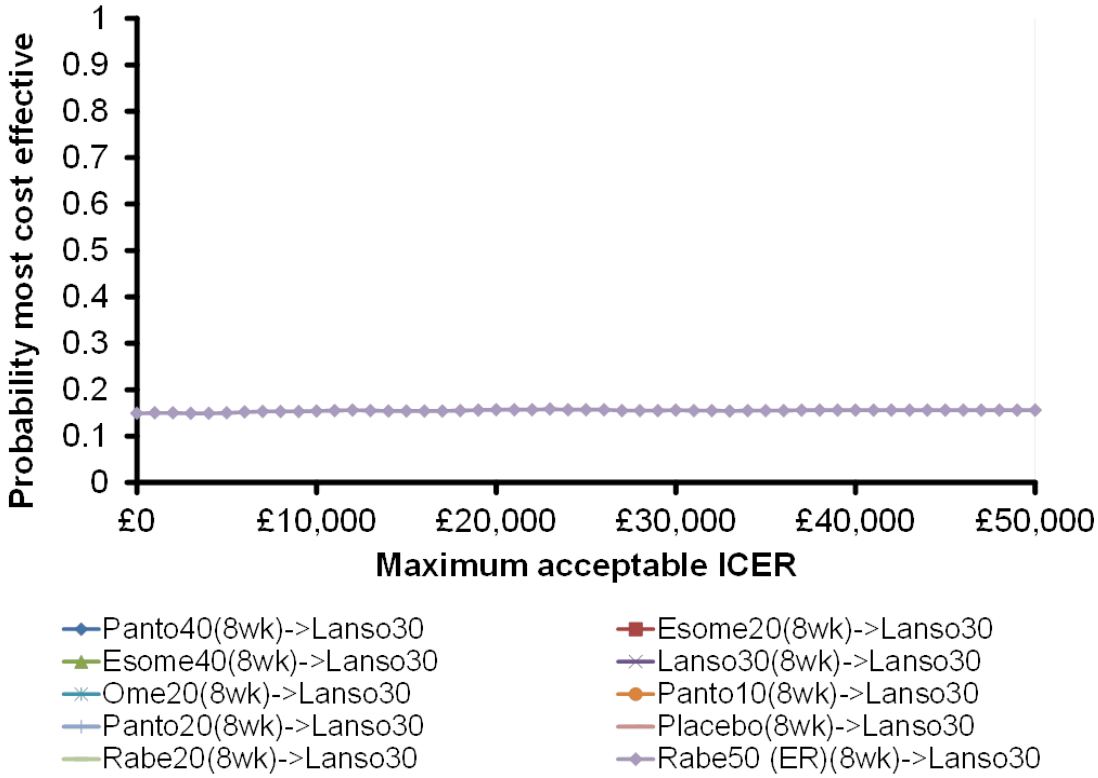


Figure 6: Healing: cost–utility results – PSA (RE) Cost-effectiveness acceptability frontier (CEAF)

The treatment that is the most likely to be cost-effective when the uncertainty in the effectiveness estimates is taken into account is Rabeprazole 50mg.

PPIs for maintenance

H.3.4.3 Clinical outcomes from the model

	Progress to		Drug costs		
Strategy	Barrett's	Adenocarcinoma	Healing	Maintenance	Specialist
Rabe20(8wk)→Lanso30	27.09%	0.64%	£13.35	£262.54	£1364.86
Rabe20(8wk)→Panto40	29.05%	0.70%	£13.74	£228.95	£1603.67
Rabe20(8wk)→Panto20	30.42%	0.75%	£14.02	£166.86	£1810.55

Strategy	Progress to		Drug costs		Specialist
	Barrett's	Adenocarcinoma	Healing	Maintenance	
Rabe20(8wk)→Lanso15	30.43%	0.75%	£14.03	£173.51	£1812.55
Rabe20(8wk)→Esome20	27.75%	0.66%	£13.48	£906.66	£1439.72
Rabe20(8wk)→Placebo	32.74%	0.85%	£14.58	–	£2316.24

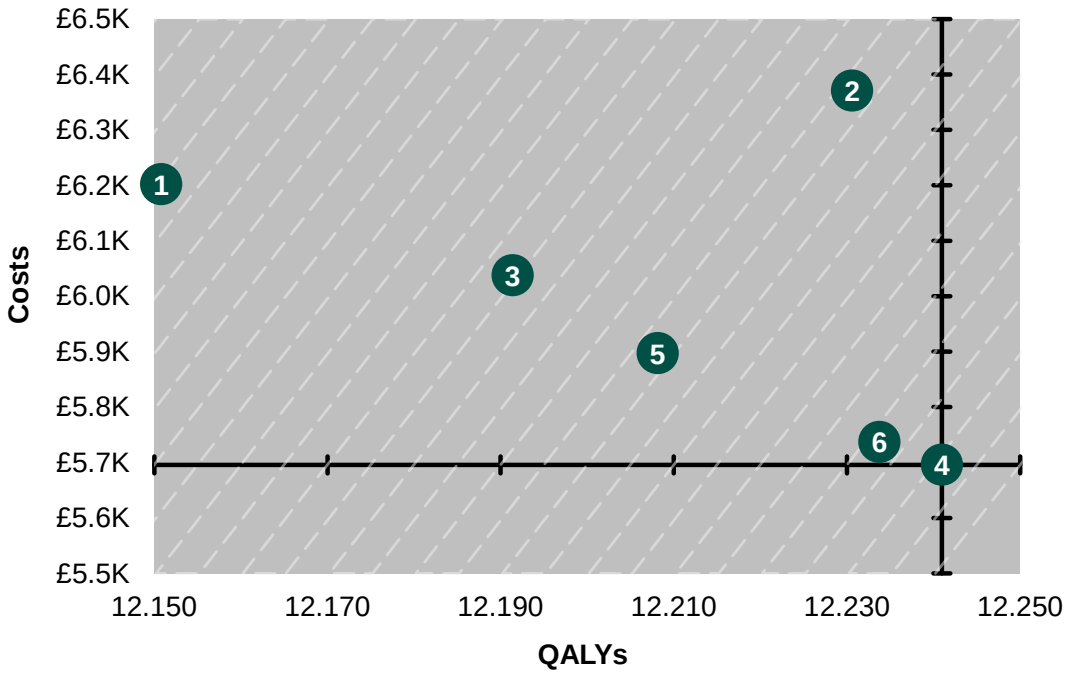


Figure 7: Maintenance: incremental c–u results - Base-case deterministic analysis (RE)

As there is more variation in the maintenance costs of the individual treatments due to a greater proportional contribution to overall treatment costs, the clinical effectiveness is no longer the overriding factor of influence over the estimates of cost- effectiveness.

Table 7: Maintenance: incremental c–u results - Based on means of probabilistic analysis (RE)

Name	Absolute		Incremental			Absolute Net Monetary Benefit
	Costs	QALYs	Costs		ICER	£20K/QALY
Rabe20(8wk)→Lanso30	£5580	12.159				£237,609
Rabe20(8wk)→Panto40	£5612	12.157	£32	-0.003	dominated	£237,522
Rabe20(8wk)→Panto20	£5718	12.139	£138	-0.020	dominated	£237,065
Rabe20(8wk)→Lanso15	£5836	12.128	£256	-0.032	dominated	£236,717
Rabe20(8wk)→Esome20	£6232	12.155	£652	-0.005	dominated	£236,865
Rabe20(8wk)→Placebo	£6241	12.066	£661	-0.093	dominated	£235,082

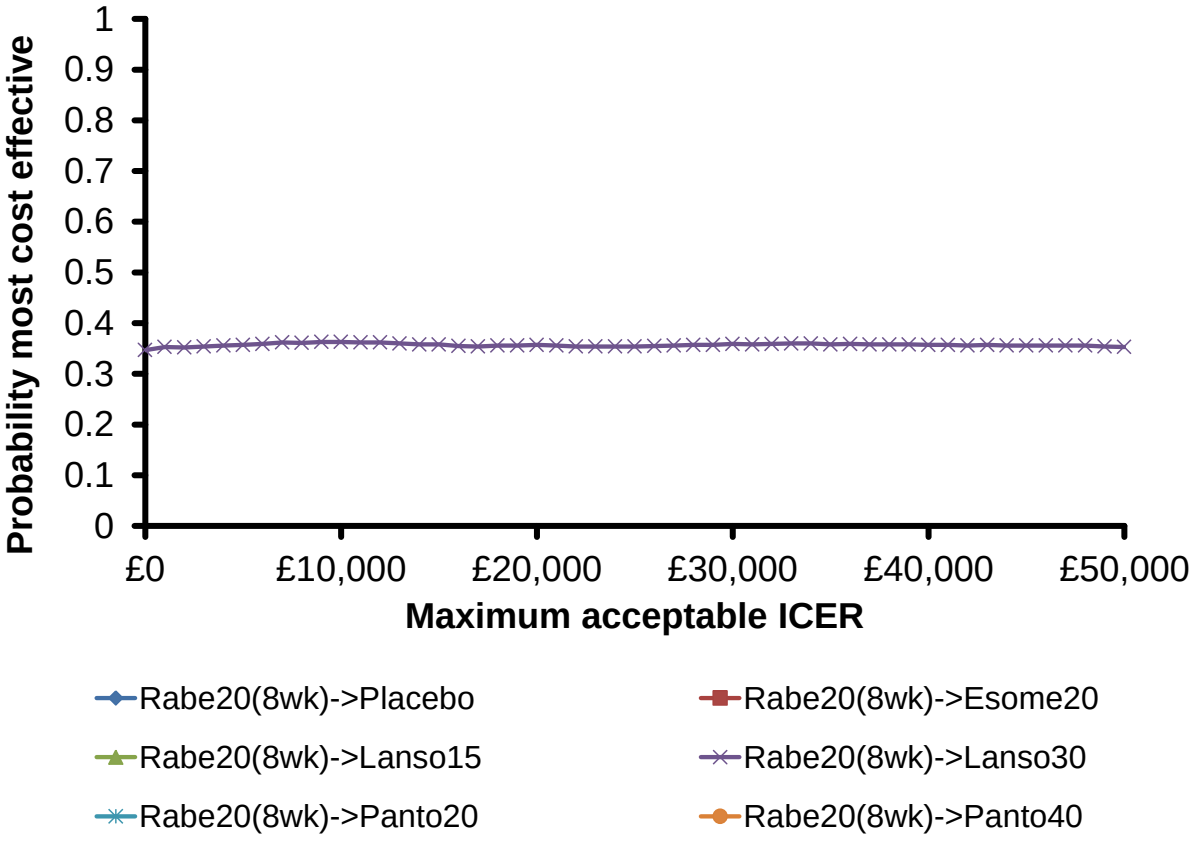


Figure 8: Maintenance: c–u results – PSA (RE)- Cost-effectiveness acceptability frontier (CEAF)

The maintenance treatment which has the highest probability of being cost-effective is Lansoprazole 30mg. This does not change when the uncertainty in the estimates is taken into consideration.

H.3.5 Discussion – Scenario analyses

- No relapse after 5 years

  This scenario has the largest impact upon the maintenance element of treatment however its impact on the results as a whole is minimal. The gaps between the estimates of cost-effectiveness for maintenance treatments very slightly increased however the conclusions are not changes as a result.

- % in initial cohort with BO

  This scenario does not make a material difference to the results but impacts a little on the healing element of the model. The costs for each treatment increase and the QALYs decrease but the incremental differences between treatment options remain similar. The conclusions of the treatments that are the most likely to be cost-effective does not change as a result.

- Symptoms correlated with healing of oesophagitis.

  When symptoms are directly correlated with the healing of oesophagitis there is a paradoxical incentive to fail treatment and be referred to management in secondary care. This occurs as healing occurs more quickly along this pathway. This may accurately represent clinical reality or the assumptions underpinning the effectiveness of oesophagitis healing once managed by a specialist may be too strong. Either way, with an incentive to fail treatment the least effective PPI treatments become the most cost-effective therefore this scenario is not very useful when the aim is to make decisions on which PPI to use as treatment for oesophagitis.

H.3.5.1 Principal findings

The treatments which are the most likely to heal the oesophagitis and maintain the healing are also likely to be the most cost-effective treatments. This remains to be the case when the uncertainty in parameter estimates is taken into consideration through probabilistic sensitivity analysis. The cost of treatments do not play a significant role in the healing phase but influence the cost-effectiveness of treatments for the maintenance of oesophagitis healing. One-way sensitivity analysis demonstrates that the effectiveness of treatments drives the estimates of cost-effectiveness. The conclusions were tested in a number of scenario analyses which, with the exception of the correlated symptom scenario, did not materially alter the results.

H.3.5.2 Strengths of the analysis

The model is based on a synthesis of all the available published effectiveness evidence for treatments options, in patients with severe erosive disease. The network-meta analytical approach enabled a series of effectiveness estimates to be modelled, along with the uncertainty in those estimates.

As the first cost-utility analysis in this population, the model demonstrates the quality of life and cost implications of treating this patient group.

The model has face-validity through the iterative involvement of the GDG in the conceptualisation, parameterisation and validation of the model.

The design of the model and how it represents the clinical pathway considered by the review question was presented to, and discussed with, the rest of the guideline development team

and the other health economists within the department, with amendments made based on their evaluation.

The functionality of the model was tested by a health economist within the team who had not been involved in its development. Validation checks involve both consideration of the model specification and its mechanics, including assessing formulae for accuracy and varying model inputs to check observed effects match expectations.

The model structure allowed thousands of sequencing scenarios of treatments to be tested. Such flexibility enabled the most plausible treatment options to be explored and tested for any anomalies, and a range of scenarios to be presented to the GDG.

H.3.5.3 Weaknesses of the analysis

The treatment options available are limited to those in which there was evidence of clinical effectiveness in the severe reflux oesophagitis population.

The effectiveness evidence is based on two network meta -analyses that are judged to be weak in quality, therefore although uncertainty is taken into consideration through the sensitivity analysis conducted as part of the modelling, it is still reliant on the evidence on interrelationships between PPI treatments generated by the network.

In order to represent clinical treatment, the structure of the model is based upon treatments being trialled in sequences according to successful healing. The evidence base for this review question does not contain estimates of effectiveness for sequences of treatments and therefore we reuse the same probability of effectiveness for each drug, regardless of whether it is being used as a first-line or second-line therapy.

Estimates of the health related quality of life for patients with severe erosive reflux disease specifically could not be obtained, leading to considerable uncertainty in our representation of utility in this patient group. The results of the one way sensitivity analysis however demonstrate that the model is not sensitive to variation in the utility estimates within the model therefore providing we are confident that the true utility value of this patient group plausibly lies within the ranges specified within the sensitivity analysis, then we can have some confidence in the cost-effectiveness estimates produced.

A lack of evidence resulted in a failure to appropriately represent the relationship between healing and symptoms and thus produced unhelpful results.

The utility decrement allocated to patients whose disease is being managed in the secondary care setting is also a source of uncertainty as it is an estimate. The GDG agreed with its inclusion both as a theoretical concept, and the value estimated however one-way sensitivity for the healing phase demonstrated that it had a significant influence on the cost-effectiveness estimates.

A number of parameter values were estimated based on the insight of the GDG. The uncertainty around the estimates is tested in probabilistic sensitivity analysis. The ability to estimate these parameters and to represent the clinical pathway adds to the face validity of the model. Although the values are limited as simply estimates, the results of the one-way sensitivity analysis show that they do not have a significant influence on the estimates of cost-effectiveness.

H.3.5.4 Conclusions

Uncertainty in the estimates of clinical effectiveness manifests itself into uncertainty in the estimates of cost-effectiveness. Increased accuracy in the effectiveness evidence would translate to more confidence in the estimates of cost-effectiveness.

H.4 References

Bhat et al (2011). Risk of Malignant Progression in Barrett's Esophagus Patients: Results from a Large Population-Based Study. Journal of the national cancer institute. 103 (13).

British Medical Association. (2013). Royal Pharmaceutical Society BNF. British Medical Assoc.;Royal Pharmaceutical Society: London,.

Bate & Richardson (1993). Clinical and economic factors in the selection of drugs for gastroesophageal reflux disease. Pharmacoeconomics 3(2):94-99.

Dept of Health(2013). NHS reference costs 2011-2012. at https://www.gov.uk/government/publications/nhs-reference-costs-financial-year-2011-to-2012

Fenwick et al (2001). Representing uncertainty: the role of cost-effectiveness acceptability curves. Health Economics. 10: 779-787.

Garside, R. et al. (2006) Surveillance of Barrett's oesophagus: exploring the uncertainty through systematic review, expert workshop and economic modelling. Health Technol Assess 10, 1–142, iii–iv.
Gerson et al (2000). A cost-effectiveness analysis of prescribing strategies in the management of gastroesophageal reflux disease. American Journal of Gastroenterology 95 (2) 395-407.

Gerson et al (2012). Variation of health-care resource utilization according to GERD-associated complications .Diseases of the Esophagus 25 (8) 694-701.

Gerson, et al (2007). Does cancer risk affect health-related quality of life in patients with Barrett's esophagus? Gastrointestinal Endoscopy 65, 16–25.

Grant et al (2008). The effectiveness and cost-effectiveness of minimal access surgery amongst people with gastro-oesophageal reflux disease – a UK collaborative study. The REFLUX trial. Health Technology Assessment 2008; Vol. 12: No. 31.

Inadomi et al (2003). Screening and surveillance for Barrett's esophagus in high-risk groups: a cost-utility analysis. Annals of internal medicine. 138: 178-188.

Kaltenthaler et al (2011) NICE DSU Technical Support Document 13: Identifying and reviewing evidence to inform the conceptualisation and population of cost-effectiveness models. Available from http://www.nicedsu.org.uk.

Lundell et al (2001). Continued (5-Year) Followup of a Randomized Clinical Study Comparing Antireflux Surgery and Omeprazole in Gastroesophageal Reflux Disease. Journal of American College of Surgery. 192: 172-179.

MIMS Drug Guide (Oct 2013) at http://www.mims.co.uk/

NHS Drug tariff (Oct 2013) at http://www.ppa.org.uk/ppa/edt_intro.htm

PSSRU (2011). Unit costs of health and social care at http://www.pssru.ac.uk/project-pages/unit-costs/2011/index.php

Remak et al (2005) Cost-effectiveness comparison of current proton-pump inhibitors to treat gastro-oesophageal reflux disease in the UK. Current Medical Research and Opinion. 21: 1505-1517

Ronkainen et al (2011). Erosive Esophagitis Is a Risk Factor for Barrett's Esophagus: A Community-Based Endoscopic Follow-Up Study. The American Journal of Gastroenterology. 106, 1946-1952

Shenfine et al (2005). A pragmatic randomised controlled trial of the cost-effectiveness of palliative therapies for patients with inoperable oesophageal cancer. Health Technology Assessment 2005; Vol. 9: No. 5

Stal et al (1998). A cost-utility analysis comparing omeprazole with ranitidine in the maintenance therapy of peptic oesophageal stricture. Canadian Journal of Gastroenterology. 12:43-49.

Van Soest et al (2006). Persistence and adherence to proton pump inhibitors in daily clinical practice Alimentary Pharmacology & Therapeutics. 24: 377-385

H.5 RQ5 Economic Model

H.6 General

The approach to providing health economic evidence to support decision making around a clinical review question begins with a systematic search of the literature. The aim of this is to source any published economic evaluations of relevance to the topic of interest. At this stage it may become apparent that evidence exists in the literature which exactly meets the review question criteria and therefore there is no need for original economic analysis. If this proves not to be the case it may be decided that economic modelling can generate some useful analysis. The aim is to produce a cost–utility analysis in order to weigh up the benefits and harms of comparable interventions. The extent to which this is possible will be driven by the availability of evidence upon which to parameterise the clinical pathway and disease natural history.

H.7 Eradication of *H pylori* (RQ5)

H.7.1 Decision problem

Table 8: Research questions

RQ5 (i)	In patients with symptoms of dyspepsia who are positive for *H pylori*, which eradication regimens are the most clinically effective in the eradication of *H pylori*?
RQ5 (ii)	What *H pylori* eradication regimens should be offered as second-line (or third-line) treatments when first-line treatments fail?

Table 9: PICO

Population	Patients with confirmed *H pylori* infection.
Intervention	First and second-line *H pylori* eradication treatment regimens.
Comparator	Alternative *H pylori* eradication regimens.
Outcomes	A cost–utility analysis was constructed based on the quality of life (in quality adjusted life years[QALYs]) and costs of symptomatic and healed peptic ulcer disease.

H.7.2 Systematic review of published cost–utility analyses

H.7.2.1 Methods

Inclusion and exclusion criteria

The economic literature review aimed to identify economic evaluations in the form of cost–utility analyses exploring the costs and effects of different eradication regimens in people with confirmed *H pylori* infection.

Although studies comparing eradication and placebo were eligible to form part of the clinical evidence base, in order to inform the full network of eradication effectiveness evidence, we excluded such comparisons within an economic evaluation from this review. Guideline recommendations in support of *H pylori* eradication in patients testing positively for the infection are not in question; therefore, economic analysis concerning the effectiveness of a test and treat approach is outside of the scope of the decision problem we are considering here.

Search strategy

The search strategy was based on that used to identify clinical evidence for this question, with the RCT filter removed and a standard economic filter applied (see appendix C).

Quality appraisal

Studies that met the eligibility criteria were assessed using the quality appraisal criteria as outlined in the Guidelines Manual (2012).

H.7.2.2 Results

Study identification

The search returned 1076 studies; after title and abstract screening, we ordered the full texts of 24 studies. On perusal of the retrieved papers, no cost–utility analyses comparing eradication regimens for patients who have tested positive for *H pylori* could be included. Two studies, although outside the formal inclusion criteria, contained information of indirect relevance to the question and were therefore presented to the GDG.

Quality and results of indirectly relevant studies

Details of the design, quality and results of the studies are tabulated in Table 10.

The Mason et al. (2008) study only provided evidence on the cost effectiveness of *H pylori* eradication when compared with no eradication therapy, whereas the review question under consideration here is concerned with **which** eradication therapy should be offered as eradication treatment for *H pylori*. We excluded the study from formal consideration in the economic literature review on this basis. Nevertheless, we noted that the study provides support for the recommendation for routine eradication of *H pylori*, and gives an indication of the eradication rates that are likely to deliver good value for money (the regimen analysed was cost saving as long as probability of eradication was assumed to exceed 47%).

Duggan et al. (1998) present a UK-based cost-effectiveness study with eradication rate as the unit of effectiveness. The incremental results presented within the study refer to the cost per extra 1% eradication rate. Such a measure of effectiveness is difficult to put into practical decision making as the impact of an improved eradication rate is not taken into consideration. In addition, the costs parameters in the model are outdated and therefore not reflective of current UK practice (especially with regard to the unit costs of proprietary

omeprazole and clarithromycin, which are now inexpensively available as generic medications). For these reasons, we did not formally include this study in the economic literature review.

Table 10: Economic evidence tables

Study, Population, Comparators, Quality	Data Sources	Other Comments	Incremental			Conclusions	Uncertainty
			Cost	Effect	ICER		
Mason et al. (2008) Patients with long-term PPI use who tested positive for *H pylori*. *H pylori* eradication therapy vs placebo. Applicability: Partially applicable [(a)] Limitations Minor limitations [(b)]	Effects: Within trial reported effectiveness. Costs: Resource use within trial with costs allocated from the BNF and NHS Reference costs. Utilities: EQ-5D of patients.		Incremental cost saving of £93 (95% CI: £33–153) after two years in the eradication group. N.B. cost estimates include the costs of testing as well as the cost of eradication therapy.	0.089 (95%CI: −0.012 to 0.191) N.B. This effect-change was not found to be statistically significantly different from the quality of life differences reported in the placebo group.	*H pylori* eradication is an economically dominant strategy.	*H pylori* eradication for long-term PPI users results in a reduction in the costs of healthcare and the severity of dyspeptic symptoms.	*H pylori* prevalence would have to reach 12% before the cost savings associated with *H pylori* eradication in this patient group would be neutralised. Variation of each of the individual healthcare resource elements costs in turn did not impact the results. At an eradication rate of 47% there are no cost savings with *H pylori* eradication.
Duggan et al. (1998) Patients with duodenal ulcer	Effects: Published literature Costs: BNF	Prescribed drug therapies and breath	OAM: Base OCM:£9 OAM+UBT+OCM: £35.18	OAM: Base OCM:6% OAM+UBT+OCM: 9%	Incremental cost of obtaining a 1% improvement in eradication rate	OCM without secondary eradication was most cost-	Results sensitive to the costs related to *H pylori*

Study, Population, Comparators, Quality	Data Sources	Other Comments	Incremental			Conclusions	Uncertainty
			Cost	Effect	ICER		
disease, testing positively for *H pylori*. Omeprazole, amoxicillin & metronidazole (OAM) vs omeprazole, clarithromycin & metronidazole (OCM). Four strategies modelled. OAM, OCM, & eradication regimens in sequence with a breath test for *H pylori* following first-line eradication therapy. Applicability: Partially applicable [(c)] Limitations: Potentially serious limitations [(d)]	Utilities: N/A	tests were the only costs included within the model.	OCM+UBT+OAM: £42.43	OCM+UBT+OAM: 12%	reported. N.B strategy 4 used as base-case. OCM+UBT+OAM: Base OAM:£363.58 OCM:£589.59 OAM+UBT+OCM: £326.57	effective strategy.	relapse.

(a) Placebo as comparator rather than alternative eradication regimens
(b) Outcomes evaluated at one year and costs at two years. Sensitivity analysis not conducted on outcomes
(c) Cost per 1% increase in eradication rate as outcome measure.
(d) Unit costs of eradication regimens are outdated

H.7.2.3 Discussion

The evidence obtained from published economic evaluations was not sufficient to provide guidance to answer the review question.

H.7.3 Original cost–utility model – methods

The GDG did not consider the choice of *H pylori* eradication strategies a high priority for comprehensive original health economic analysis. However, the group agreed that a simplified cost–utility model could be useful to aid decision-making.

H.7.3.1 Overview of the model

Modelled population(s) and intervention(s)

Table 11: Economic Model PICO

Population	Patients with peptic ulcer disease with confirmed *H pylori* infection, subdivided into a) people with gastric ulcer and b) people with duodenal ulcer.
Intervention	First- and second-line *H pylori* eradication treatment regimens
Comparator	Alternative *H pylori* eradication regimens
Outcomes	Cost–utility analysis estimating the quality of life (in quality-adjusted life-years[QALYs]) and costs of symptomatic and healed peptic ulcer disease

Due to a lack of suitable parameters to inform the model, the non-ulcerative dyspeptic patient population is not addressed in the model. The clinical evidence to inform the comparisons of eradication regimens conforms to the population as defined in the decision problem, and incorporates information on effectiveness from a variety of populations comprising people with dyspepsia symptoms who have tested positive for *H pylori*. This results in the probability of eradication being independent of the underlying cause of the dyspepsia symptoms. All other parameters within the model are specific to the ulcerative population addressed.

The model uses a patient perspective for outcomes and an NHS perspective for costs, in line with the Guidelines Manual (2012).

Model structure

We built a Markov model with monthly cycles and a 1-year time horizon. The model was designed as a simplified representation of the pathway of treatment for people who test positive for *H pylori* infection as outlined in Chapter 4.5.

The Markov structure allows costs and utilities to be accrued for each month spent in a series of health states. There are 4 underlying health states in the model, representing all possible combinations of 2 binary characteristics: presence or absence of *H pylori* infection and presence or absence of peptic ulcer. These states are replicated twice in order to provide ‘memory’ of previous history. Figure 9 provides a schematic depiction of the model structure.

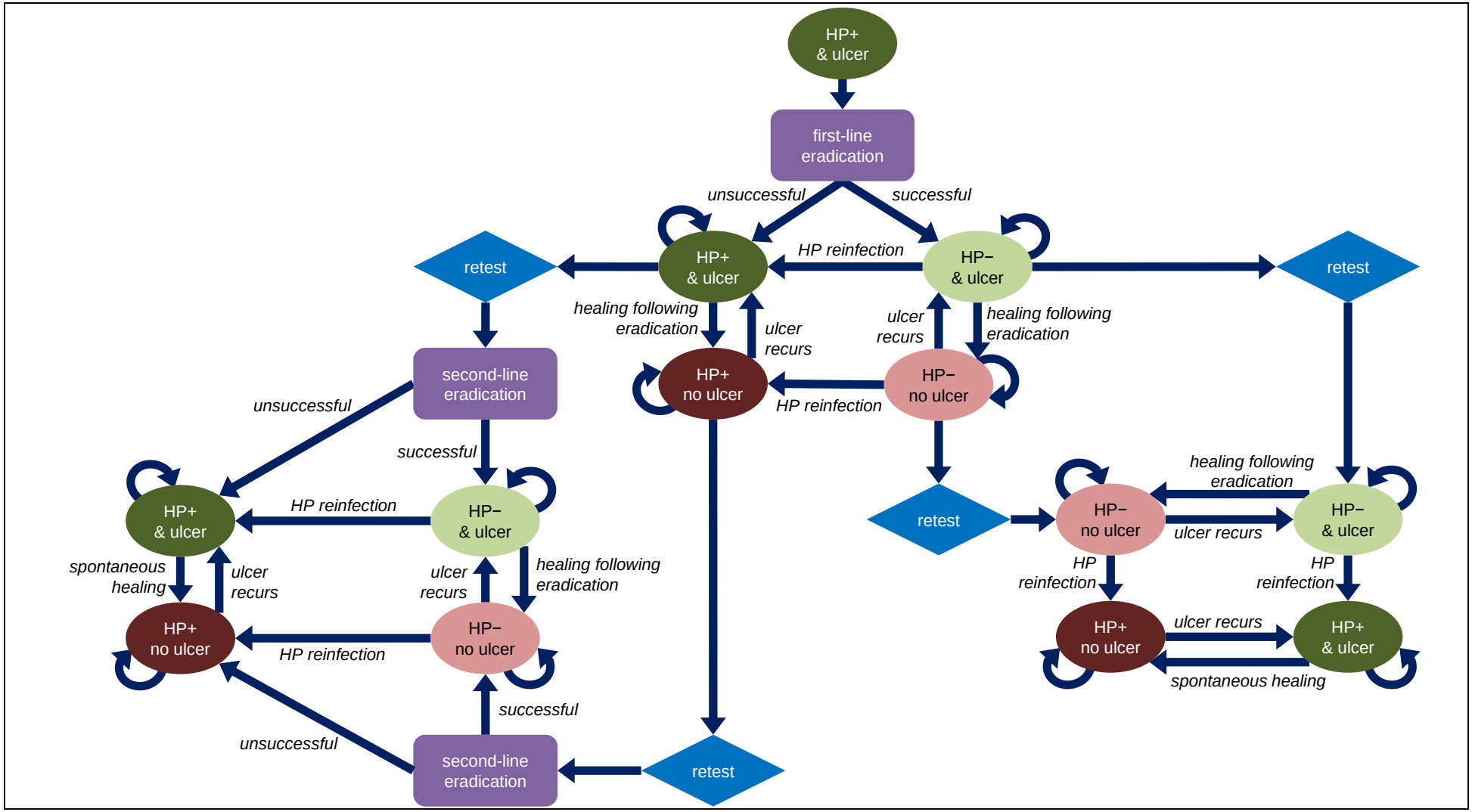


Figure 9: Structure of original cost–utility model

National Institute for Health and Care Excellence 2014.

The first line eradication element of the model is depicted in the top section of Figure 9. All patients are *H pylori* positive initially. Their chance of having their infection eradicated is determined by the first-line eradication effectiveness evidence. Patients then cycle around the first-line Markov model for two months before they are retested to identify their *H pylori* infection status. Both of the extended sections of the model are replicas of the first-line model in their transition probabilities. Patients who are *H pylori* positive on retest will be allocated second-line eradication therapy. The second-line eradication evidence is then used to determine the *H pylori* status of the patients who then continue to cycle around the Markov model. The patients who are not infected with *H pylori* on retest continue to cycle around the Markov model in the same way as in the first two months modelled. Any subsequent *H pylori* infection which occurs post-retest will not be picked up or treated within this model.

The model assumes that the accuracy of the diagnostic tests is 100%. This is a limitation of the model as in reality there may be some false positive and false negative test results which drive inappropriate treatment.

The GDG agreed that a 1-year time horizon would be a sufficient period to produce results suitable for decision making, as it extends beyond the period of treatment, even when multiple attempts at eradication are required, and there are no mortality risks directly associated with treatment or other long-term direct consequences. Restricting analysis to 1 year may, however, underestimate the longer-term benefit of *H pylori* eradication, as persistence or recurrence of ulcers may extend beyond this timeframe. The analysis does not discount benefits and costs owing to the 1-year time horizon.

All patients in the model receive a retest for *H pylori* following first-line eradication. The model enables the proportion of patients who undergo endoscopy prior to second-line therapy to be varied in the duodenal ulcer cohort. As recommended in this guideline (see Chapter 5), all patients with a gastric ulcer receive endoscopy following initial eradication therapy to assess the healing status of the ulcer.

Key assumptions

There are a number of assumptions built into the economic model which need to be considered when analysing the results generated. These are summarised in Table 12.

Table 12: Key assumptions of original cost–utility model

• The probability of eradication is independent of cause of dyspepsia; therefore, it is assumed that eradication rates do not differ between subgroups of patients with dyspepsia.
• The utility values in the model are determined by the presence or absence of ulcers alone; therefore only peptic ulcer disease patients are included within the model.

- Because there was insufficient clinical evidence to demonstrate differential adverse event profiles for the regimens, the model assumes equivalent safety profiles.
- All patients with an ulcer are assumed to be symptomatic. Although, in the general population, people with *H pylori*-positive ulcer disease may not be symptomatic, all patients in the modelled group have dyspeptic symptoms and have been investigated to confirm the presence of *H pylori* infection.
- One-third of patients who have their ulcer healed remain symptomatic in the model (Ford et al., 2004). Apart from the cost of eradication therapy, asymptomatic patients in any period modelled do not incur any healthcare costs.
- Ulcer healing rates are directly related to *H pylori* status. This will not be an accurate assumption if any pharmacological therapies with identical eradication rates have different ulcer healing efficacy.
- Aside from ulcer healing, the model does not take into account any symptomatic relief brought about by the eradication regimens.
- Insufficient evidence was found in the clinical review to attribute adherence to the eradication regimens.
- In generating the estimates of effectiveness, the evidence from multiple studies using multiple combinations of drug therapies and variable doses and treatment durations were amalgamated at a class level. We used the class-level estimates within the model. The costs of each drug regimen were also calculated in a similar way. The costs of each drug in each treatment regimen to the NHS were calculated by allocating sufficient packs of drugs to the regimen. In the case of doses which are not available in the UK we estimated the use of multiple packs to equate to the study dosage. Class-level drug calculations in this way may generate variability in the costs of drug regimens which is driven by the dose and duration of the treatments in the studies used to generate the estimate, rather than reflect true prescribing cost differences. However, it is critical that the model reflects the costs that would be incurred to achieve the level of efficacy observed in the trials.
- Drug wastage was accounted for in cases where the pack size available to purchase in England exceeded the total prescribed dose of that drug.

H.7.3.2 Parameters – general approach

Identifying sources of parameters

With the exception of eradication rates, which were drawn from the systematic review conducted for this research question (see below), we identified parameters through informal searches that aimed to satisfy the principle of ‘saturation’ (that is, to ‘identify the breadth of information needs relevant to a model and sufficient information such that further efforts to identify more information would add nothing to the analysis’ [Kaltenthaler et al., 2011]). We conducted searches in a variety of general databases, including Medline (via PubMed), the Cochrane Database of Systematic Reviews and GoogleScholar.

We asked the GDG to identify papers of relevance. We reviewed the sources of parameters used in the published CUAs identified in our systematic review (see H.7.2, above); during the review, we also retrieved articles that did not meet the formal inclusion criteria, but appeared to be promising sources of evidence for our model. We studied the reference lists of articles retrieved through any of these approaches to identify any further publications of interest.

In cases where there was paucity of published literature for values essential to parameterise key aspects of the model, data were obtained from unpublished sources; further details are provided below.

Selecting parameters

Our overriding selection criteria were as follows:

- The selected studies should report outcomes that correspond as closely as possible to the health states and events simulated in the model.
- The selected studies should report a population that closely matches the UK population (ideally, they should be drawn from the UK population).
- All other things being equal, more powerful studies (based on sample size and/or number of events) were preferred.
- Where there was no reason to discriminate between multiple possible sources for a given parameter, we gave consideration to quantitative synthesis (meta-analysis), to provide a single summary estimate.

H.7.3.3 Parameters – cohort parameters and natural history

Natural history

Ulcer healing

We drew ulcer healing rates from a meta-analysis of trials looking at eradication treatment for patients with *H pylori*-associated peptic ulcers (Leodolter et al. 2001). The authors measure ulcer remission 12 months after eradication therapy. The results are presented in two groups – patients in whom *H pylori* eradication was successful and those with an unsuccessful eradication attempt

Ulcer recurrence

Ebell et al. (1997) produced an economic model considering the management of patients presenting to their GP with symptoms of dyspepsia. The authors sourced transition probabilities from a literature search, generating point estimates from weighted averages that took into account the study population and methodological quality. We used these data to provide our estimate of the annual probability of ulcer recurrence according to *H pylori* status.

HP reinfection

An HTA was conducted in 2003 (Roderick et al. 2003) to assess the cost effectiveness of a population screening programme for *H pylori*. A discrete-event simulation model was built which uses a base case reinfection value of 0% per year following successful *H pylori* eradication and 0.3% as part of the sensitivity analysis. This estimate was based, to some extent, on a study by Bell (1996) which looked at *H pylori* re-infection rates of patients treated with various eradication regimens.

Ulcer healed symptomatic

Ford et al. (2004) conducted a systematic review and economic analysis to assess the role of eradication therapy for patients with *H pylori* and peptic ulcer disease. They use an estimate for the proportion of patients who remain symptomatic after their ulcer has healed of 33%, which is generated from a review of 6 observational studies.

Table 13: Natural history parameters

Parameter	Description	Value (95%CI)		Source
		Gastric ulcer	Duodenal ulcer	
Reinfection	*H pylori* reinfection rate per year (independent of ulcer status)	0.3%		Roderick et al. (2003)
Recurrence (HP+)	Annual probability of an ulcer recurring in patients with *H pylori* infection.	25%	30%	Ebell et al. (1997)
Recurrence	Annual probability of an ulcer	5%	8%	Ebell et al.

Parameter	Description	Value (95%CI)		Source
		Gastric ulcer	Duodenal ulcer	
(HP−)	recurring in patients without *H pylori* infection.			(1997)
Healing (HP+)	Proportion of patients with a healed ulcer 12 months after unsuccessful eradication therapy.	60.9% (51.9%, 69.8%)	57.5% (50.1%, 64.8%)	Leodolter et al. (2001)
Healing (HP−)	Proportion of patients with a healed ulcer 12 months after successful eradication therapy.	97.1% (95.1%, 99.1%)	98.0% (96.9%, 99.0%)	Leodolter et al. (2001)
Ulcer healed symptomatic	Proportion of patients who remain symptomatic despite ulcer healing.	33% (25%, 43%)		Ford et al. (2004)

[(a)] *<Insert Note here>*

Mortality

Because the model was limited to a 1-year time horizon, and we did not assume any treatment-related mortality, it was not necessary to include mortality in the model: all simulated patients are assumed to survive for 1 year following treatment.

H.7.3.4 Parameters – treatment effects

We drew eradication rates for each of the treatment regimens from the clinical evidence review (Section 4.4.3). The network meta analysis produces estimates of each eradication regimen relative to the other regimens through combining both direct and indirect evidence of comparative effectiveness. In order to incorporate effectiveness evidence into the economic model we need an absolute estimate of effectiveness for each of the treatment options available.

An eradication regimen is chosen for which the estimates of effectiveness are meta-analysed to produce a baseline effectiveness value, with the uncertainty represented in confidence intervals. The relative effectiveness estimates from the network meta analysis can then be applied to this baseline to produce an absolute eradication effectiveness estimate, for use within the economic model.

The treatment regimens at the centre of each of the networks are chosen to produce the baseline effectiveness values, as these are the regimens with the most direct evidence for which we have more certainty, than estimates generated from indirect evidence. The treatment used as the baseline in the first-line eradication evidence is AMO-MAC-PPI and BIS-NIT-PPI-TET is used to generate absolute estimates for the second-line eradication regimens.

The probability of first-line eradication for each regimen is shown in Table 14:

Table 14: 1st-line eradication parameters

Regimen	Probability of eradication (95% CrI)
Bismuth-Nitroimidazoles-PPIs-Tetracyclines	0.808 (0.601, 0.931)
Macrolides-Penicillins-PPIs	0.796 (0.725, 0.852)
Penicillins-PPIs-Quinolones	0.792 (0.391, 0.980)
Bismuth-Macrolides-Nitroimidazoles	0.780 (0.364, 0.972)
Nitroimidazoles-Penicillins-PPIs	0.762 (0.521, 0.913)
Macrolides-Nitroimidazoles-PPIs	0.725 (0.467, 0.894)

Regimen	Probability of eradication (95% CrI)
Bismuth-H2RAs-Nitroimidazoles-Tetracyclines	0.717 (0.337, 0.932)
H2RAs-Nitroimidazoles-Penicillins	0.709 (0.239, 0.958)
Bismuth-H2RAs-Macrolides	0.667 (0.277, 0.937)
Bismuth-Nitroimidazoles-Tetracyclines	0.657 (0.316, 0.889)
Macrolides-PPIs	0.524 (0.232, 0.813)
Penicillins-PPIs	0.521 (0.247, 0.793)
PPIs	0.007 (0.000, 0.032)

As discussed in Section 4.4.3, it is immediately obvious that PPI monotherapy has by far the lowest rate of effectiveness. The effectiveness of the dual therapies in eradicating *H pylori* is lower than that of the triple or quadruple therapies. As the effectiveness rates are pooled from the network meta-analysis of clinical evidence which includes regimens of different drugs within the same class, variable doses, and treatment durations, there is some uncertainty surrounding the effectiveness of each of the regimens as displayed in the credible intervals.

The evidence review of the effectiveness of second-line therapy was based on the premise that the patients remained infected following first-line treatment with MAC-PEN-PPI .

Table 15: 2nd-line eradication parameters

Regimen	Probability of eradication (95% CrI)
Nitroimidazoles-Penicillins-PPIs	0.939 (0.741, 0.996)
Macrolides-Nitroimidazoles-Penicillins-PPIs	0.935 (0.609, 0.999)
Nitroimidazoles-PPIs-Quinolones	0.853 (0.483, 0.986)
Penicillins-PPIs-Quinolones	0.810 (0.546, 0.952)
Bismuth-H2RAs-Nitroimidazoles-Tetracyclines	0.809 (0.445, 0.962)
Bismuth-Nitroimidazoles-PPIs-Tetracyclines	0.766 (0.593, 0.888)
Penicillins-PPIs-Tetracyclines	0.760 (0.245, 0.981)
Bismuth-PPIs-Quinolones-Tetracyclines	0.727 (0.255, 0.969)
Macrolides-Nitroimidazoles-PPIs-Tetracyclines	0.708 (0.234, 0.966)
Bismuth-Penicillins-PPIs-Tetracyclines	0.559 (0.127, 0.927)
Bismuth-H2RAs-Macrolides-Penicillins	0.538 (0.052, 0.949)
Bismuth-Macrolides-Nitroimidazoles-PPIs	0.483 (0.088, 0.903)
Bismuth-Nitroimidazoles-Penicillins-PPIs	0.376 (0.025, 0.917)
Bismuth-Penicillins+Clav-PPIs-Tetracyclines	0.279 (0.024, 0.771)

The second-line sequencing model contains some new parameters which are detailed in Table 16 below:

Table 16: 2nd-line sequencing model additional parameters

		Value (95%CI)		
Parameter	**Description**	**Gastric ulcer**	**Duodenal ulcer**	**Source**
Repeat HP test	Probability (per cycle) of undergoing repeat HP test	Ulcer & Non-ulcer: 100%	Ulcer: 90% Non-ulcer: 33%	Estimate
Endoscopy	Proportion receiving	100%	0	Estimate based on CG17 and

		Value (95%CI)		
Parameter	**Description**	**Gastric ulcer**	**Duodenal ulcer**	**Source**
	endoscopy at retest			explored in sensitivity analysis
Breath test	Proportion receiving HP breath-test at retest	100%	100%	Assumption tested in sensitivity analysis

H.7.3.5 Parameters – costs

We explored 2 different scenarios to estimate the resource use and costs of patients who have had their infection successfully eradicated and those who remain *H pylori* positive. Both scenarios maintain an NHS and PSS perspective and exclude any privately borne costs such as over-the-counter symptomatic relief. The costs of the eradication regimens themselves are common to both approaches.

Drug costs

The eradication regimens described in the studies from which we drew effectiveness estimates were analysed in detail in order to be able to allocate a cost, relevant to the NHS, to each of the regimens. We took the unit costs of each drug from the April 2013 PPA tariff and MIMs prices where the PPA tariff indicated a category 'M' drug, as pharmacies are reimbursed for the provision of drugs in this category. In the majority of the drugs considered in this analysis, the MIMs price was lower than the price reported in the tariff; however, there were some exceptions (ranitidine and tetracycline) for which we used the higher MIMs price in the calculations for consistency.

The cost of the dosage prescribed in each study was constructed from formulations currently available in the UK, using combinations of doses where the exact dose in the study is not available.

The duration of each regimen was followed within the costing exercise; however, in each case the cost of a full pack (usually 28 tablets) was attributed to the cost of treatment, although eradication regimens often required fewer tablets to reach the prescribed dose. This enables a more accurate reflection of the cost to the NHS where it is not possible to prescribe a smaller dose in practice. In the case where the total number of tablets required to complete the dose exceeded the standard pack size, we calculated the cost of multiple packs until the dose was reached.

Having estimated the cost of each study-specific regimen in the evidence-base, we calculated a weighted average within each class-specific regimen to provide our final estimate of the cost (that is, the total cost of each of the individual drug regimens contained within the broader class-specific regimen was summed and divided by the total number of patients who received that regimen in the clinical evidence base).

We excluded unlicensed drugs (furazolidone and nitazoxanide) from the cost-effectiveness estimates as a cost reflective of an NHS purchase price could not be obtained and they cannot be recommended as part of the guideline.

Table 17 and Table 18 contain the estimated average cost for each regimen. We consider some regimens as both first- and second-line therapies. As the costs are averages based on the drug, dosage and treatment duration of the studies included to generate the estimates of effectiveness, the average cost may differ between first-line and second-line use.

Table 17: Drug regimen costs – 1st-line eradication

Regimen	Average cost
Macrolides-Penicillins-PPIs	£10.27
Bismuth-H2RAs-Macrolides	£12.43
Bismuth-H2RAs-Nitroimidazoles-Tetracyclines	£15.19
Bismuth-Macrolides-Nitroimidazoles	£13.79
Bismuth-Nitroimidazoles-PPIs-Tetracyclines	£18.95
Bismuth-Nitroimidazoles-Tetracyclines	£17.94
H2RAs-Nitroimidazoles-Penicillins	£53.68
Macrolides-Nitroimidazoles-PPIs	£7.47
Macrolides-PPIs	£14.85
Nitroimidazoles-Penicillins-PPIs	£8.40
Penicillins-PPIs	£4.78
Penicillins-PPIs-Quinolones	£51.23
PPIs	£5.10

Table 18: Drug regimen costs - 2nd-line eradication

Regimen	Average cost
Bismuth-H2RAs-Macrolides-Penicillins	£17.82
Bismuth-H2RAs-Nitroimidazoles-Tetracyclines	£20.87
Bismuth-Macrolides-Nitroimidazoles-PPIs	£12.04
Bismuth-Nitroimidazoles-Penicillins-PPIs	£11.51
Bismuth-Nitroimidazoles-PPIs-Tetracyclines	£22.55
Bismuth-Penicillins+Clav-PPIs-Tetracyclines	£16.57
Bismuth-Penicillins-PPIs-Tetracyclines	£20.73
Bismuth-PPIs-Quinolones-Tetracyclines	£48.26
Macrolides-Nitroimidazoles-Penicillins-PPIs	£10.45
Macrolides-Nitroimidazoles-PPIs-Tetracyclines	£21.79
Nitroimidazoles-Penicillins-PPIs	£9.29
Nitroimidazoles-PPIs-Quinolones	£37.31
Penicillins-PPIs-Quinolones	£39.82
Penicillins-PPIs-Tetracyclines	£25.01

Other costs

We estimated resource use and costs following eradication therapy using 2 different approaches:

- Microcosting of ulcer treatment pathways from CG17.
  - Provides: an estimate of cost per patient with an ulcer or symptoms post-ulcer healing.
  - Assumes: costs are dictated by patients' underlying ulcer status.
  - Includes: proton pump inhibitors for symptom control, GP consultations and referrals to secondary care.

  The first costing scenario was based upon the recommendations for treatment of patients with gastric and duodenal ulcers generated in the previous dyspepsia clinical guideline (CG17). The elements of resource use as detailed in the pathways presented in CG17 were used to estimate the annual treatment costs of a patient with peptic ulcer disease. All

patients with an ulcer and those who remained symptomatic despite ulcer healing were assumed to have an additional GP consultation over the year as well as be prescribed a low dose of PPIs every month for a year (pantoprazole in this case as currently the cheapest) and be referred to a gastroenterology specialist in secondary care. This method provided an estimate of cost per patient with an ulcer or symptoms post ulcer healing.

Table 19: Costs used in CG17 scenario

Parameter	Unit cost	Notes	Source
Low dose PPIs (prn)	£0.46	Pantoprazole, daily dose 20mg, 28 tablets	NHS drug tariff. CG17 assumes prn drug use of 0.4 tablets per day on average.
GP visit	£43	One consultation per year	Unit costs of health and social care
Gastroenterology consultation	£162.04	One consultation per year	NHS Reference Costs
Monthly cost – patient with an ulcer	£17.54	Costs consists of resource use elements above and the probability of their use within each patient group.	
Monthly cost – patient with a healed ulcer	£1.33	Costs consists of resource use elements above and the probability of their use within each patient group.	

The incremental difference in cost is small as the variation in resource use is only demonstrated in three facets. The resource use upon secondary care referral is for some patients likely to be much more than that of the initial consultation; however this is the only aspect of secondary care resource use estimated within this scenario.

- Extrapolation from HELP-UP trial (Mason et al. 2008).
  - Provides: an estimate of cost per patient following successful eradication of *H pylori* or with persistent infection.
  - Assumes: costs are dictated by patients' underlying *H pylori* status.
  - Includes primary care consultations and prescriptions, secondary care admission and investigations.

The average costs of each of the resource use contained within the paper were calculated. Resource use is based on being allocated to the eradication therapy or placebo arm and assumes all the difference in resource use is due to different eradication rates in the two arms of the trial. A cost per increase in eradication is then estimated.

Table 20: Unit costs used in Mason et al. scenario

Parameter	Unit cost	Notes	Source
PPI standard dose	£1.60	Pantoprazole, 40mg daily dose, 28 tablets	NHS drug tariff
PPI low dose	£1.14	Pantoprazole, 20mg daily dose, 28 tablets	NHS drug tariff
Eradication therapy	-	Drug costs calculated per regimen	NHS drug tariff
C-UBT breath test	£19.20		BNF
GP visit	£43		Unit costs of health and social care
GP home visit	£110		Unit costs of health and social care
A/E attendance	£146		Unit costs of health and social care
GI-related admission	£1,055.73	Average estimated	NHS Reference Costs
Endoscopy	£448.01	Average estimated	NHS Reference Costs
Ultrasound	£55.03	Average estimated	NHS Reference Costs
CT/MRI	£133.13	Average estimated	NHS Reference Costs
Colonoscopy	£548.83	Average estimated	NHS Reference Costs
ERCP	£830.41	Average estimated	NHS Reference Costs
Monthly cost – patient with h.pylori infection	£17.58	Costs consists of resource use elements above and the probability of their use within each patient group.	
Monthly cost – patient without h.pylori infection	£14.04	Costs consists of resource use elements above and the probability of their use within each patient group.	

The costs for ERCP, which were unavailable in 2006, are now contained within the NHS Reference Costs; therefore, we included them in the model. When calculating the average cost of an endoscopy, the costs of capsule endoscopies were included as their use seemed to include indications for patients needing investigations for upper GI symptoms.

There was a significant reduction in PPI usage within this patient population; however, as these patients are long-term PPI users, the benefit in terms of PPI prescriptions is likely to be overestimated for the *H pylori* positive dyspeptic patients as a whole.

The costs of a C-UBT breath test and an endoscopy to retest for *H pylori* are included within the second-line sequencing model.

H.7.3.6 Parameters – quality of life

We conducted a literature search to locate utility values to apply to the health states within the economic model.

The health-related quality of life of patients with symptoms of dyspepsia and confirmed *H pylori* infection is defined in the economic model by the presence or absence of a peptic ulcer. The model assumes that all patients with an ulcer are symptomatic and 33% of the patients whose ulcer has healed still have dyspepsia symptoms.

The source of the utility estimates used in the model is a study which pooled elements of data collected within the annual Health Survey for England (2003–2006). The investigators classified the health status of respondents using a question on long-standing illness which recorded and classified information on up to 6 types of illness per person. This method resulted in 39 distinct conditions. The investigators compared the health-related quality of life of participants with and without each of these conditions, using their responses to the EQ-5D questionnaire (Ara and Brazier, 2010).

619 patients, with an average age of 59.3, in the sample had 'stomach ulcer/abdominal hernia/rupture'. There were 650 patients of a similar age who did not have a stomach ulcer or abdominal hernia or rupture. A statistically significant difference in utility values between the people with a stomach ulcer, hernia or rupture was found when compared with people without this condition ($p < 0.05$).

Table 21 shows the utility values that the economic model uses. As one-third of patients with a healed ulcer are assumed to continue to experience symptoms, the average utility value for the group of patients without an ulcer takes into account the proportions of both symptomatic and asymptomatic individuals in the group of patients.

Table 21: Utility values used within the model

	State	Value (95%CI)	Source
a	Ulcer	0.688 (0.654, 0.720)	Ara & Brazier (2010)
b	No ulcer	0.806 (0.781, 0.830)	
c	Proportion symptomatic despite healing	33% (25%, 43%)	Ford et al. (2004)
	Healed ulcer	0.767	a × c + b × (1−c)

There was insufficient evidence in the clinical review to be able to incorporate a quality of life decrement for adverse events of the eradication therapies. It is therefore assumed, for the purpose of the economic modelling, that all the eradication regimens carry the same side-effect profile.

H.7.3.7 Parameters – summary

The transition probabilities and utility parameters used in the model are summarised in Table 22, including details of the distributions and parameters used in probabilistic analysis.

Table 22: Parameters in original cost–utility model

Parameter	Point estimate	Probabilistic analysis		Source
		Distribution	Parameters	
Transition probabilities:				
Gastric ulcer:				
Spontaneous healing in HP+	0.61	Beta	α=68.94; β=44.65	Leodolter et al. (2001)
Healing of ulcer in HP-	0.97	Beta	α=261.62; β=7.84	
Ulcer relapse in HP+	0.25	Triangular	min=0.10; max=0.50[a]	Ebell et al. (1997)
Ulcer relapse in HP-	0.05	Triangular	min=0.02; max=0.15[a]	

Parameter	Point estimate	Probabilistic analysis		Source
		Distribution	Parameters	
Duodenal ulcer:				
Spontaneous healing in HP+	0.58	Beta	α=99.34; β=73.84	Leodolter et al. (2001)
Healing of ulcer in HP-	0.98	Beta	α=668.29; β=13.66	
Ulcer relapse in HP+	0.30	Triangular	min=0.10; max=0.60[a]	Ebell et al. (1997)
Ulcer relapse in HP-	0.08	Triangular	min=0.04; max=0.20[a]	
Probability of reinfection	0.003	Triangular	min=0; max=0.006[b]	Roderick et al. (2006)
Utilities:				
Ulcer	0.69	Beta	α=520.27; β=236.25	Ara & Brazier (2010)
No Ulcer	0.81	Beta	α=805.75; β=194.13	
Proportion symptomatic despite healing	0.33	Beta	α=34.27; β=70.25	Ford et al. (2004)
Utility decrement for endoscopy	-0.003	Triangular	min=-0.005 max=0	Assumption of one day with a utility value of zero.
Resource Use:				
% retested for h.pylori (GU)	1	N/A		All patients are retested in line with recommendations made in CG17.
% retested for h.pylori (DU)	0,9	Triangular	min=0.33 max=1	Assumption
% retested for h.pylori (healed ulcer)	0.33	Triangular	min=0 max=0.66	Assumption
% endoscopy on retest (DU)	1	Triangular	min=0 max=0.2	Assumption
% endoscopy on retest (GU)	0	Triangular	min=0.8 max=1	Assumption
% endoscopy on retest (healed ulcer)	0	Triangular	min=0 max=0.2	Assumption

(a) ranges assumed by investigators; source unclear
(b) varied +/- 0.003 in absence of evidence on variability

H.7.3.8 Sensitivity analyses

We presented two versions of the model to represent second-line treatment of *H pylori* to the GDG. The first model replicated the model structure we used to provide analysis in comparing first-line treatments for *H pylori*. In this scenario we assume that all of the patients within the model failed to have their *H pylori* infection eradicated with first-line therapy and therefore need to be treated with a second course of eradication therapy. All parameters, with the exception of the eradication regimens considered and their associated effectiveness, remained the same as in the original, first-line model.

In the second version of the model to compare second-line eradiation therapy strategies, the model simulates both the first-line and second-line treatments. We assume all patients have tested positively for *H pylori* when they entering into the modelling framework but can then either have their infection eradicated or continue to be infected. After two model cycles all patients have a further *H pylori* test. We assume the repeat *H pylori* testing is perfectly accurate. Those testing positively are treated with second line eradication therapy.

As the results generated from each of these two models did not differ enough from each other to influence the recommendations made, the GDG agreed to take forward analysis with the second version of the model, which more closely represented clinical reality.

H.7.3.9 Probabilistic sensitivity analyses

We configured the models to perform probabilistic sensitivity analysis to quantify uncertainty in the true values of input parameters.

Probability distributions were estimated for all input variables with the exception of the direct (drug) costs of the eradication regimens. Distribution parameters were sourced from the study in which the value was obtained, where possible, or were estimated based on the usual properties of data of that type.

The distribution for each of the parameters used within the probabilistic sensitivity analysis is driven by the variable type and the availability of reported information. Beta distributions are used for variables denoting a probability, as bounded between 0 and 1, where data are reported to estimate the standard error; otherwise, a triangular distribution is used. A beta distribution is also estimated for the utility values, which are also traditionally confined to values between 0 and 1.

The proportion of patients using each element of resource use is also estimated to follow a beta distribution. The variables which denote a number of events are estimated to follow a normal distribution. Triangular distributions are estimated for the probability of resource use in the pathway costing scenario.

H.7.3.10 Scenario analyses

The model results presented are for a cohort of patients with gastric ulcers at the start of the model.

H.7.4 Original cost–utility model – results

H.7.4.1 Clinical outcomes from the model

Table 23: Clinical outcomes 1 year after treatment (no 2nd-line eradication)

	Clinical outcomes 1 year after treatment			
	Gastric ulcer		Duodenal ulcer	
Name	HP+	Ulcer	HP+	Ulcer
BIS-MAC-NIT	18.04%	12.92%	18.04%	13.37%
MAC-PEN-PPI	20.47%	13.96%	20.47%	14.53%
NIT-PEN-PPI	22.94%	15.02%	22.94%	15.71%
BIS-NIT-PPI-TET	18.23%	13.00%	18.23%	13.46%
MAC-NIT-PPI	25.83%	16.27%	25.83%	17.08%
BIS-H2RA-NIT-TET	26.87%	16.71%	26.87%	17.57%
BIS-H2RA-MAC	31.76%	18.81%	31.76%	19.90%
BIS-NIT-TET	32.71%	19.22%	32.71%	20.35%

	Clinical outcomes 1 year after treatment			
	Gastric ulcer		Duodenal ulcer	
Name	HP+	Ulcer	HP+	Ulcer
PEN-PPI-QUI	17.15%	12.54%	17.15%	12.95%
PEN-PPI	48.23%	25.88%	48.23%	27.74%
MAC-PPI	47.70%	25.66%	47.70%	27.49%
H2RA-NIT-PEN	27.12%	16.82%	27.12%	17.70%
PPI	99.68%	47.98%	99.68%	52.23%

Table 24: Clinical outcomes 1 year after treatment 1st- and 2nd-line eradication

	Clinical outcomes 1 year after treatment			
	Gastric ulcer		Duodenal ulcer	
Name	HP+	Ulcer	HP+	Ulcer
1st: MAC-PEN-PPI; 2nd: NIT-PEN-PPI	1.07%	5.81%	6.30%	8.03%
1st: MAC-PEN-PPI; 2nd: MAC-NIT-PEN-PPI	0.84%	5.71%	6.13%	7.96%
1st: MAC-PEN-PPI; 2nd: BIS-H2RA-NIT-TET	3.42%	6.79%	8.01%	8.82%
1st: MAC-PEN-PPI; 2nd: BIS-NIT-PPI-TET	4.80%	7.37%	9.02%	9.28%
1st: MAC-PEN-PPI; 2nd: PEN-PPI-TET	4.10%	7.08%	8.51%	9.05%
1st: MAC-PEN-PPI; 2nd: MAC-NIT-PPI-TET	5.44%	7.64%	9.49%	9.49%
1st: MAC-PEN-PPI; 2nd: NIT-PPI-QUI	2.48%	6.40%	7.33%	8.50%
1st: MAC-PEN-PPI; 2nd: BIS-MAC-NIT-PPI	10.75%	9.87%	13.36%	11.27%
1st: MAC-PEN-PPI; 2nd: BIS-H2RA-MAC-PEN	9.28%	9.26%	12.29%	10.78%
1st: MAC-PEN-PPI; 2nd: BIS-PEN-PPI-TET	9.01%	9.14%	12.09%	10.69%
1st: MAC-PEN-PPI; 2nd: PEN-PPI-QUI	3.58%	6.86%	8.13%	8.87%
1st: MAC-PEN-PPI; 2nd: BIS-NIT-PEN-PPI	13.73%	11.13%	15.54%	12.27%
1st: MAC-PEN-PPI; 2nd: BIS-PPI-QUI-TET	4.95%	7.44%	9.13%	9.33%
1st: MAC-PEN-PPI; 2nd: BIS-PEN+CLAV-PPI-TET	15.78%	11.99%	17.03%	12.95%

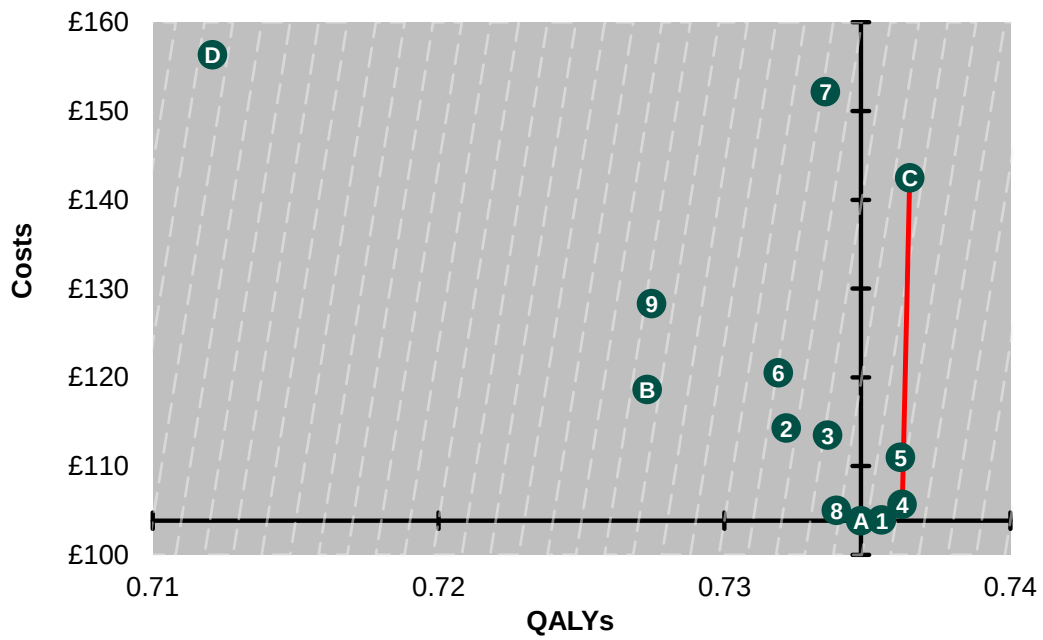
H.7.4.2 Base-case cost–utility results – First-line

The results of the analysis of first-line eradication therapies is shown below. The results presented apply to a population of patients with gastric ulcer. The results of the two costing scenarios are presented for completeness.

Table 25: Base-case deterministic cost–utility results – 1st- line eradication (gastric ulcer; pathway microcosting)

	Absolute		Incremental			Absolute Net Monetary Benefit	
Name	Costs	QALYs	Costs	QALYs	ICER	£20K/QALY	£30K/QALY
NIT-PEN-PPI	£103.84	0.735				£14,592	£21,939
MAC-PEN-PPI	£103.91	0.736	£0.07	0.001	£97	£14,606	£21,961
MAC-NIT-PPI	£105.01	0.734	£1.10	-0.002	dominated	£14,573	£21,912
BIS-MAC-NIT	£105.66	0.736	£1.75	0.001	£2,440	£14,619	£21,981
BIS-NIT-PPI-TET	£110.97	0.736	£5.30	0.000	dominated	£14,612	£21,974
BIS-H_2RA-NIT-TET	£113.48	0.734	£7.82	-0.003	dominated	£14,559	£21,895

Name	Absolute		Incremental			Absolute Net Monetary Benefit	
	Costs	QALYs	Costs	QALYs	ICER	£20K/QALY	£30K/QALY
BIS-H_2RA-MAC	£114.28	0.732	£8.62	-0.004	dominated	£14,529	£21,851
PEN-PPI	£118.60	0.727	£12.94	-0.009	dominated	£14,427	£21,700
BIS-NIT-TET	£120.48	0.732	£14.82	-0.004	dominated	£14,517	£21,836
MAC-PPI	£128.30	0.727	£22.63	-0.009	dominated	£14,421	£21,695
PEN-PPI-QUI	£142.46	0.736	£36.79	0.000	£139,933	£14,587	£21,952
H_2RA-NIT-PEN	£152.16	0.734	£9.70	-0.003	dominated	£14,519	£21,854
PPI	£156.34	0.712	£13.88	-0.024	dominated	£14,085	£21,206



1=Macrolides-Penicillins-PPIs; 2=Bismuth-H2RAs-Macrolides; 3=Bismuth-H2RAs-Nitroimidazoles-Tetracyclines
4=Bismuth-Macrolides-Nitroimidazoles; 5=Bismuth-Nitroimidazoles-PPIs-Tetracyclines; 6=Bismuth-Nitroimidazoles-Tetracyclines
7=H2RAs-Nitroimidazoles-Penicillins; 8=Macrolides-Nitroimidazoles-PPIs; 9=Macrolides-PPIs
A=Nitroimidazoles-Penicillins-PPIs; B=Penicillins-PPIs; C=Penicillins-PPIs-Quinolones
D=PPIs

Figure 10: Cost-effectiveness plane – 1st- line eradication (gastric ulcer; pathway microcosting)

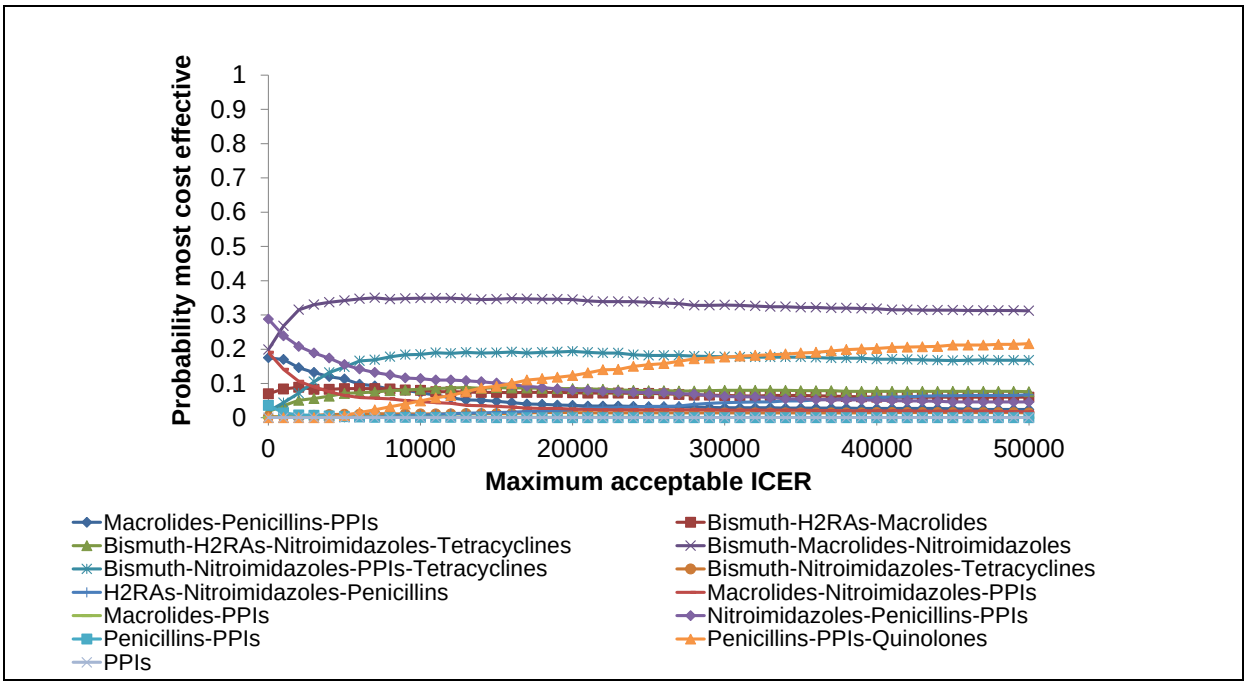
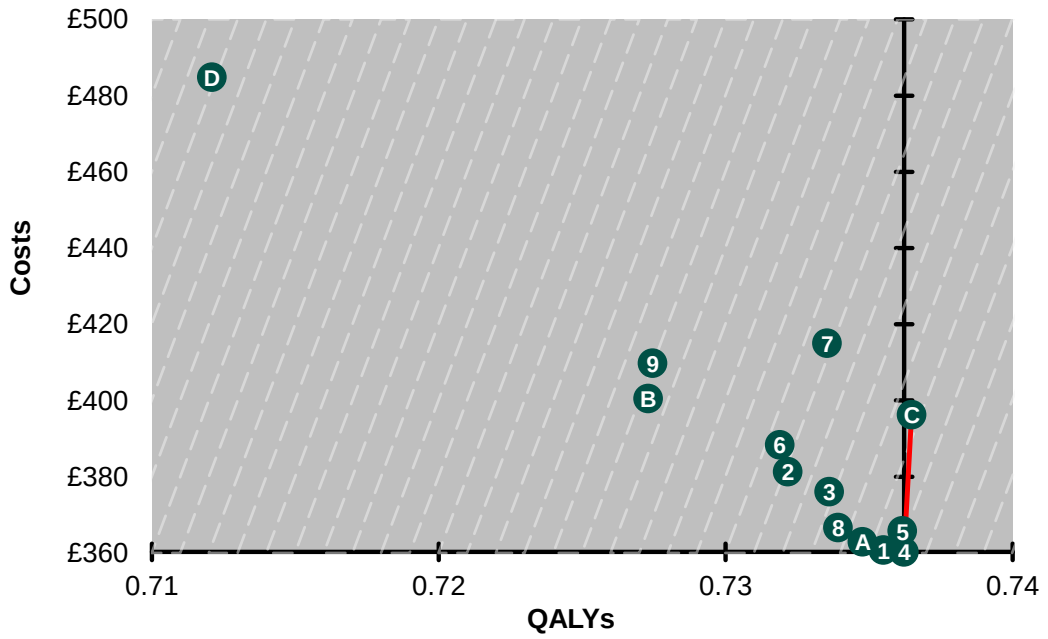


Figure 11: Cost-effectiveness acceptability curve – 1st- line eradication (gastric ulcer; pathway microcosting)

Table 26: Base-case deterministic cost–utility results – 1st- line eradication (gastric ulcer; Mason costs)

	Absolute		Incremental			Absolute Net Monetary Benefit	
Name	**Costs**	**QALYs**	**Costs**	**QALYs**	**ICER**	**£20K/QALY**	**£30K/QALY**
BIS-MAC-NIT	£360.26	0.736				£14,364	£21,726
MAC-PEN-PPI	£360.71	0.736	£0.45	-0.001	dominated	£14,349	£21,704
NIT-PEN-PPI	£362.88	0.735	£2.62	-0.001	dominated	£14,333	£21,680
BIS-NIT-PPI-TET	£365.74	0.736	£5.48	0.000	dominated	£14,358	£21,719
MAC-NIT-PPI	£366.66	0.734	£6.40	-0.002	dominated	£14,312	£21,651
BIS-H_2RA-NIT-TET	£376.07	0.734	£15.81	-0.003	dominated	£14,296	£21,632
BIS-H_2RA-MAC	£381.29	0.732	£21.03	-0.004	dominated	£14,262	£21,584
BIS-NIT-TET	£388.36	0.732	£28.10	-0.004	dominated	£14,249	£21,568
PEN-PPI-QUI	£396.25	0.736	£35.99	0.000	£136,870	£14,333	£21,698
PEN-PPI	£400.53	0.727	£4.28	-0.009	dominated	£14,145	£21,418
MAC-PPI	£409.74	0.727	£13.49	-0.009	dominated	£14,139	£21,414
H_2RA-NIT-PEN	£414.98	0.734	£18.73	-0.003	dominated	£14,364	£21,726
PPI	£484.82	0.712	£88.58	-0.024	dominated	£14,349	£21,704



1=Macrolides-Penicillins-PPIs; 2=Bismuth-H2RAs-Macrolides; 3=Bismuth-H2RAs-Nitroimidazoles-Tetracyclines
4=Bismuth-Macrolides-Nitroimidazoles; 5=Bismuth-Nitroimidazoles-PPIs-Tetracyclines; 6=Bismuth-Nitroimidazoles-Tetracyclines
7=H2RAs-Nitroimidazoles-Penicillins; 8=Macrolides-Nitroimidazoles-PPIs; 9=Macrolides-PPIs
A=Nitroimidazoles-Penicillins-PPIs; B=Penicillins-PPIs; C=Penicillins-PPIs-Quinolones
D=PPIs

Figure 12: Cost-effectiveness plane – 1st- line eradication (gastric ulcer; Mason costs)

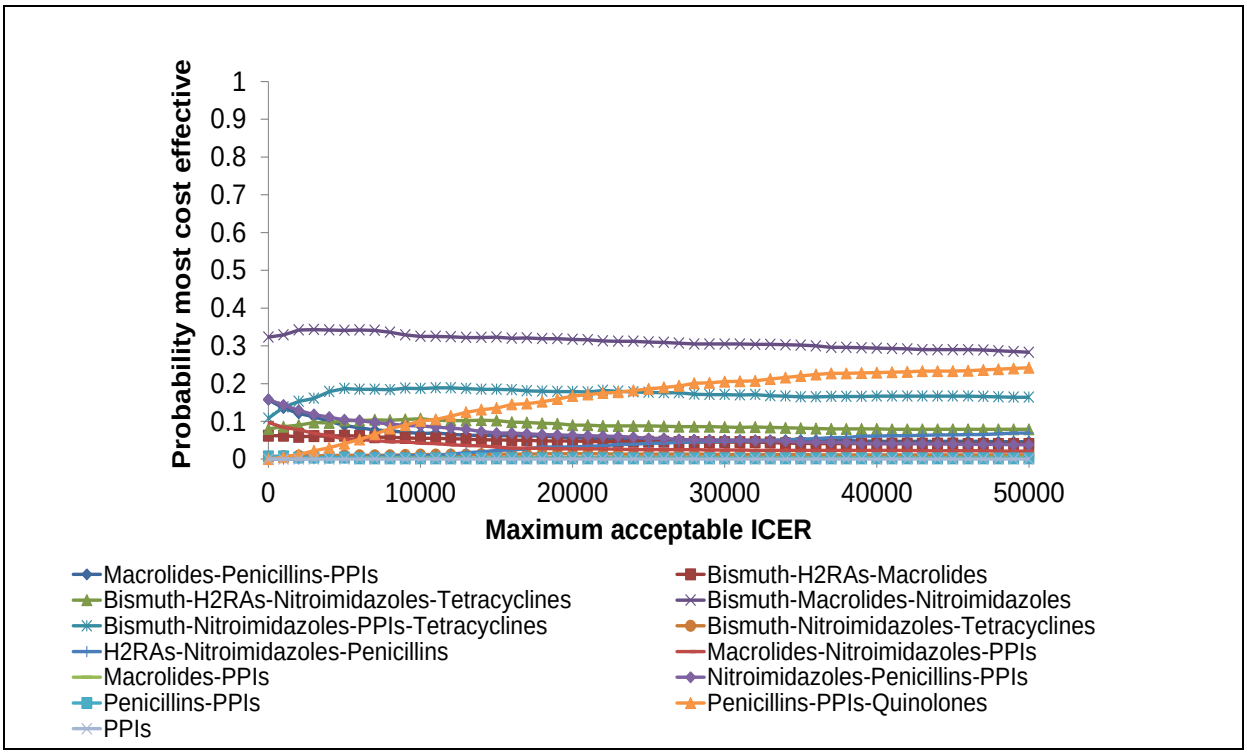


Figure 13: Cost-effectiveness acceptability curve – 1st- line eradication (gastric ulcer; Mason costs)

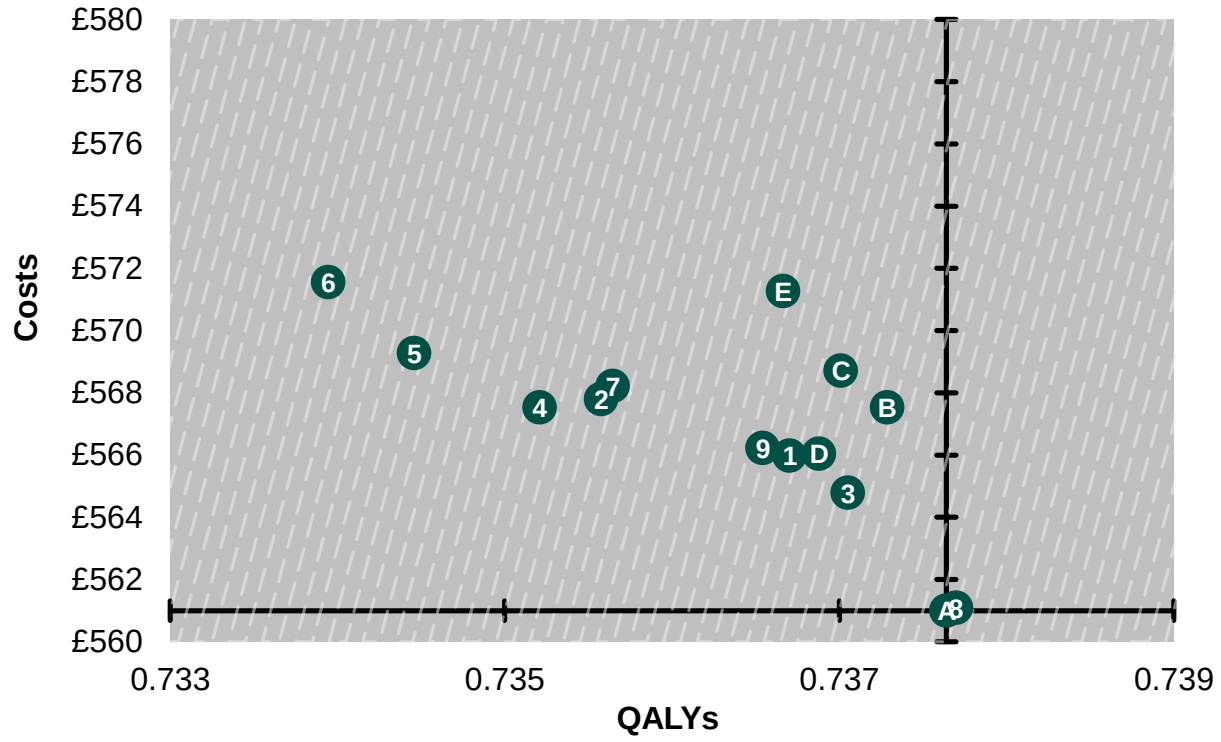
As additional elements of resource use are added the downstream costs of each of the regimens increases. Three regimens (NIT-PEN-PPI/ MAC-PEN-PPI/ BIS-MAC-NIT) are presented with positive ICERs in the CG17 costing scenario and one regimen (BIS-MAC-NIT) in the Mason costing scenario. The deterministic results suggest these regimens may provide additional benefits to quality of life at an increased cost. The probabilistic sensitivity analysis demonstrates that the even the regimen which is the most likely to be cost-effective only has a probability of being so around 30% of the time. The rest of the time another regimen is the most cost-effective option.

H.7.4.3 Base-case cost–utility results – Second-line eradication

In reflection of the recommendations for first-line eradication therapy, the analysis of second-line eradication therapy is based on patients who were treated with MAC-PEN-PPI as their first-line regimen. There was no evidence of second-line eradication effectiveness when NIT_PEN_PPI was the first line therapy.

Table 27: Base-case deterministic cost–utility results – 1st- and 2nd-line eradication (gastric ulcer; pathway microcosting)

	Absolute		Incremental			Absolute Net Monetary Benefit	
Name	**Costs**	**QALYs**	**Costs**	**QALYs**	**ICER**	**£20K/QALY**	**£30K/QALY**
1st: MAC-PEN-PPI; 2nd: NIT-PEN-PPI	£561.00	0.738				£14,191.82	£21,568.23
1st: MAC-PEN-PPI; 2nd: MAC-NIT-PEN-PPI	£561.09	0.738	£0.09	0.000	£1,634	£14,192.87	£21,569.85
1st: MAC-PEN-PPI; 2nd: BIS-H2RA-NIT-TET	£564.79	0.737	£3.70	-0.001	dominated	£14,176.25	£21,546.76
1st: MAC-PEN-PPI; 2nd: BIS-NIT-PPI-TET	£565.98	0.737	£4.89	-0.001	dominated	£14,168.09	£21,535.13
1st: MAC-PEN-PPI; 2nd: PEN-PPI-TET	£566.05	0.737	£4.96	-0.001	dominated	£14,171.54	£21,540.33
1st: MAC-PEN-PPI; 2nd: MAC-NIT-PPI-TET	£566.22	0.737	£5.13	-0.001	dominated	£14,164.63	£21,530.05
1st: MAC-PEN-PPI; 2nd: NIT-PPI-QUI	£567.53	0.737	£6.44	0.000	dominated	£14,178.20	£21,551.06
1st: MAC-PEN-PPI; 2nd: BIS-MAC-NIT-PPI	£567.53	0.735	£6.44	-0.002	dominated	£14,136.65	£21,488.74
1st: MAC-PEN-PPI; 2nd: BIS-H2RA-MAC-PEN	£567.80	0.736	£6.71	-0.002	dominated	£14,143.75	£21,499.52
1st: MAC-PEN-PPI; 2nd: BIS-PEN-PPI-TET	£568.22	0.736	£7.13	-0.002	dominated	£14,144.71	£21,501.17
1st: MAC-PEN-PPI; 2nd: PEN-PPI-QUI	£568.72	0.737	£7.63	-0.001	dominated	£14,171.49	£21,541.59
1st: MAC-PEN-PPI; 2nd: BIS-NIT-PEN-PPI	£569.27	0.734	£8.18	-0.003	dominated	£14,119.89	£21,464.48
1st: MAC-PEN-PPI; 2nd: BIS-PPI-QUI-TET	£571.27	0.737	£10.18	-0.001	dominated	£14,162.03	£21,528.68
1st: MAC-PEN-PPI; 2nd: BIS-PEN+CLAV-PPI-TET	£571.56	0.734	£10.47	-0.004	dominated	£14,107.33	£21,446.78



1 = 1st: MAC-PEN-PPI; 2nd: BIS-NIT-PPI-TET
2 = 1st: MAC-PEN-PPI; 2nd: BIS-H2RA-MAC-PEN
3 = 1st: MAC-PEN-PPI; 2nd: BIS-H2RA-NIT-TET
4 = 1st: MAC-PEN-PPI; 2nd: BIS-MAC-NIT-PPI
5 = 1st: MAC-PEN-PPI; 2nd: BIS-NIT-PEN-PPI
6 = 1st: MAC-PEN-PPI; 2nd: BIS-PEN+CLAV-PPI-TET
7 = 1st: MAC-PEN-PPI; 2nd: BIS-PEN-PPI-TET
8 = 1st: MAC-PEN-PPI; 2nd: MAC-NIT-PEN-PPI
9 = 1st: MAC-PEN-PPI; 2nd: MAC-NIT-PPI-TET
A = 1st: MAC-PEN-PPI; 2nd: NIT-PEN-PPI
B = 1st: MAC-PEN-PPI; 2nd: NIT-PPI-QUI
C = 1st: MAC-PEN-PPI; 2nd: PEN-PPI-QUI
D = 1st: MAC-PEN-PPI; 2nd: PEN-PPI-TET
E = 1st: MAC-PEN-PPI; 2nd: BIS-PPI-QUI-TET

Figure 14: Cost-effectiveness plane – 1st- and 2nd-line eradication (gastric ulcer; pathway microcosting)

National Institute for Health and Care Excellence 2014.

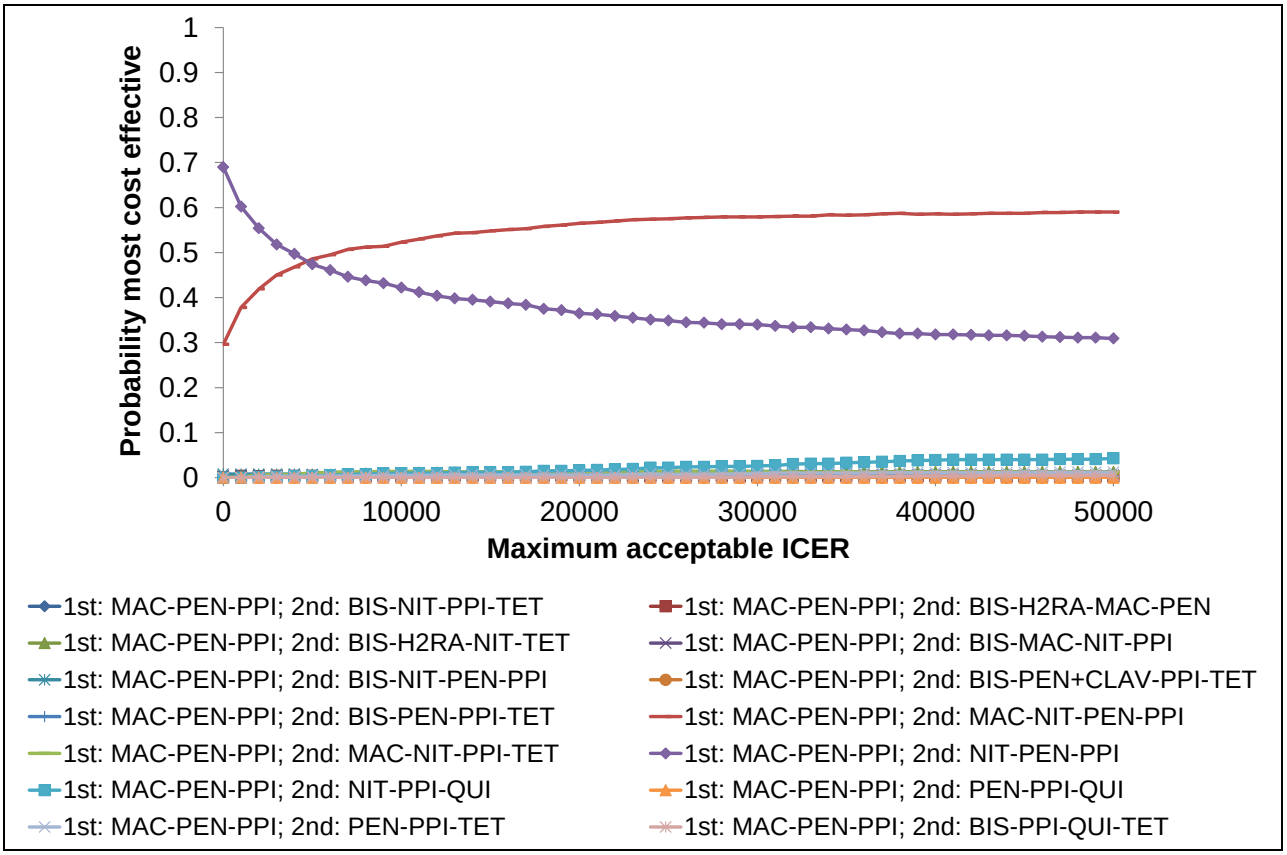
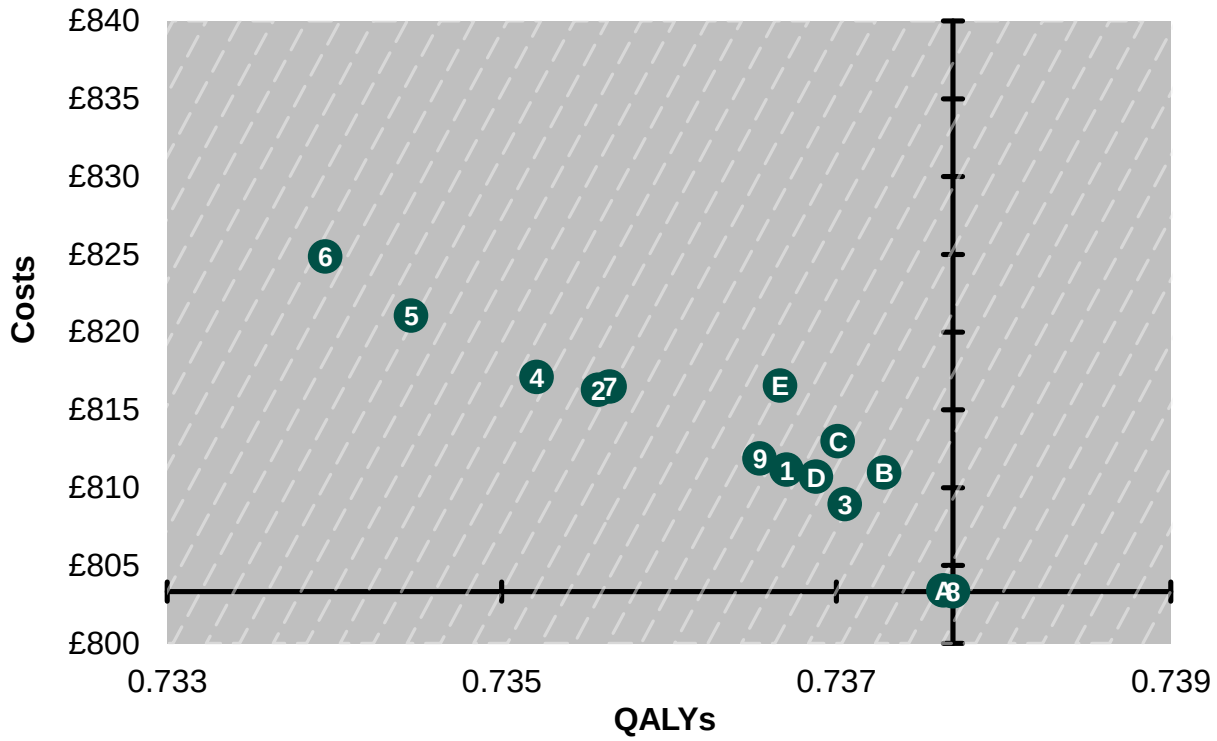


Figure 15: Cost-effectiveness acceptability curve – 1st- and 2nd-line eradication (gastric ulcer; pathway microcosting)

National Institute for Health and Care Excellence 2014.

Table 28: Base-case deterministic cost–utility results – 1st- and 2nd-line eradication (gastric ulcer; Mason costs)

	Absolute		Incremental			Absolute Net Monetary Benefit	
Name	**Costs**	**QALYs**	**Costs**	**QALYs**	**ICER**	**£20K/QALY**	**£30K/QALY**
1st: MAC-PEN-PPI; 2nd: MAC-NIT-PEN-PPI	£803.33	0.738				£13,950.63	£21,327.61
1st: MAC-PEN-PPI; 2nd: NIT-PEN-PPI	£803.40	0.738	£0.08	0.000	dominated	£13,949.42	£21,325.82
1st: MAC-PEN-PPI; 2nd: BIS-H2RA-NIT-TET	£808.93	0.737	£5.60	-0.001	dominated	£13,932.10	£21,302.62
1st: MAC-PEN-PPI; 2nd: PEN-PPI-TET	£810.70	0.737	£7.37	-0.001	dominated	£13,926.89	£21,295.68
1st: MAC-PEN-PPI; 2nd: NIT-PPI-QUI	£810.98	0.737	£7.65	0.000	dominated	£13,934.74	£21,307.61
1st: MAC-PEN-PPI; 2nd: BIS-NIT-PPI-TET	£811.15	0.737	£7.82	-0.001	dominated	£13,922.93	£21,289.96
1st: MAC-PEN-PPI; 2nd: MAC-NIT-PPI-TET	£811.87	0.737	£8.54	-0.001	dominated	£13,918.98	£21,284.41
1st: MAC-PEN-PPI; 2nd: PEN-PPI-QUI	£812.98	0.737	£9.65	-0.001	dominated	£13,927.22	£21,297.32
1st: MAC-PEN-PPI; 2nd: BIS-H2RA-MAC-PEN	£816.29	0.736	£12.96	-0.002	dominated	£13,895.26	£21,251.03
1st: MAC-PEN-PPI; 2nd: BIS-PEN-PPI-TET	£816.50	0.736	£13.18	-0.002	dominated	£13,896.42	£21,252.88
1st: MAC-PEN-PPI; 2nd: BIS-PPI-QUI-TET	£816.56	0.737	£13.23	-0.001	dominated	£13,916.74	£21,283.39
1st: MAC-PEN-PPI; 2nd: BIS-MAC-NIT-PPI	£817.11	0.735	£13.78	-0.002	dominated	£13,887.07	£21,239.16
1st: MAC-PEN-PPI; 2nd: BIS-NIT-PEN-PPI	£821.07	0.734	£17.74	-0.003	dominated	£13,868.10	£21,212.69
1st: MAC-PEN-PPI; 2nd: BIS-PEN+CLAV-PPI-TET	£824.87	0.734	£21.54	-0.004	dominated	£13,854.03	£21,193.47



(1) 1st: MAC-PEN-PPI; 2nd: BIS-NIT-PPI-TET
(2) 1st: MAC-PEN-PPI; 2nd: BIS-H2RA-MAC-PEN
(3) 1st: MAC-PEN-PPI; 2nd: BIS-H2RA-NIT-TET
(4) 1st: MAC-PEN-PPI; 2nd: BIS-MAC-NIT-PPI
(5) 1st: MAC-PEN-PPI; 2nd: BIS-NIT-PEN-PPI
(6) 1st: MAC-PEN-PPI; 2nd: BIS-PEN+CLAV-PPI-TET
(7) 1st: MAC-PEN-PPI; 2nd: BIS-PEN-PPI-TET
(8) 1st: MAC-PEN-PPI; 2nd: MAC-NIT-PEN-PPI
(9) 1st: MAC-PEN-PPI; 2nd: MAC-NIT-PPI-TET
(A) 1st: MAC-PEN-PPI; 2nd: NIT-PEN-PPI
(B) 1st: MAC-PEN-PPI; 2nd: NIT-PPI-QUI
(C) 1st: MAC-PEN-PPI; 2nd: PEN-PPI-QUI
(D) 1st: MAC-PEN-PPI; 2nd: PEN-PPI-TET
(E) 1st: MAC-PEN-PPI; 2nd: BIS-PPI-QUI-TET

Figure 16: Cost-effectiveness plane – 1st- and 2nd-line eradication (gastric ulcer; Mason costs)

National Institute for Health and Care Excellence 2014.

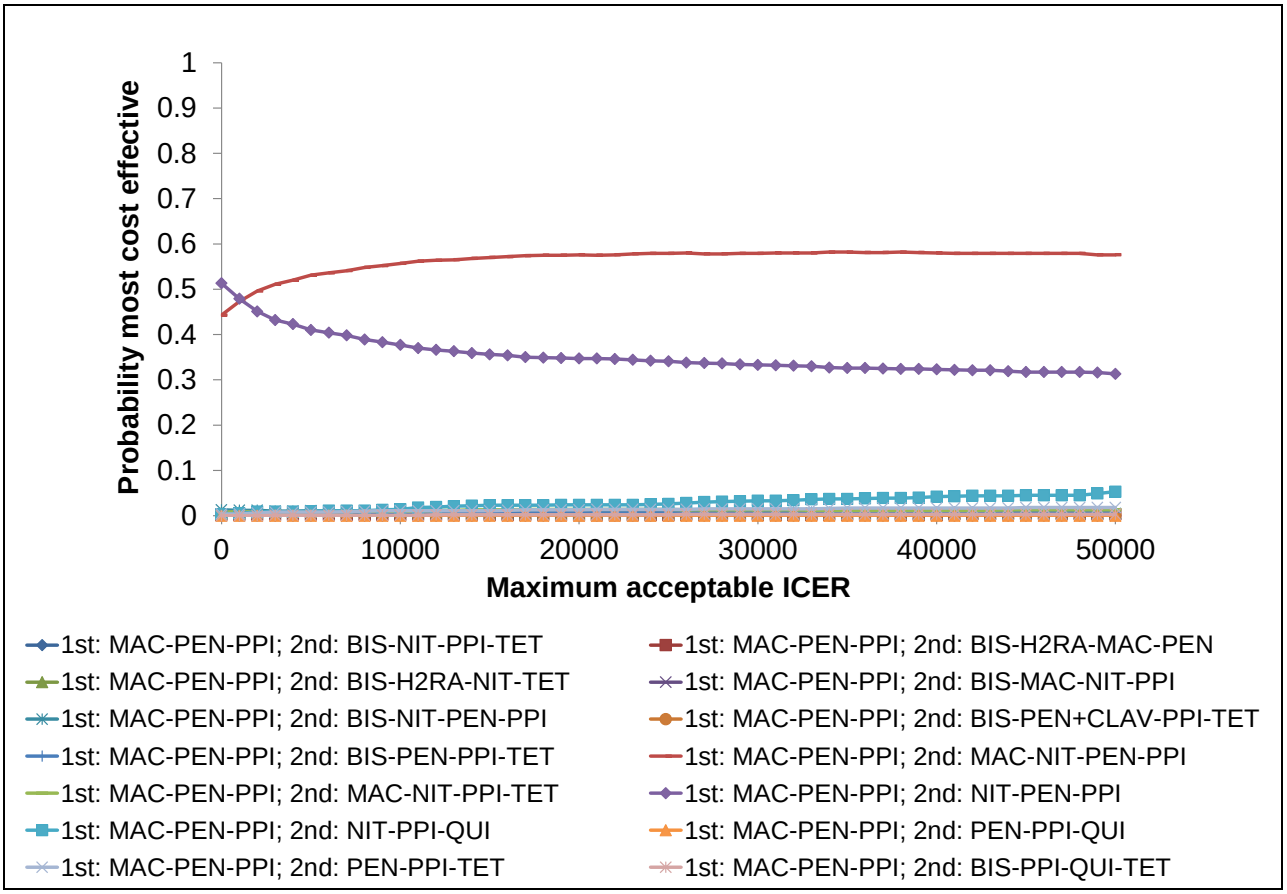


Figure 17: Cost-effectiveness acceptability curve – 1st- and 2nd-line eradication (gastric ulcer; Mason costs)

The regimens which are the most likely to be cost-effective are the same in both of the costing scenarios in second-line eradication (NIT-PEN-PPI/ MAC-NIT-PEN-PPI).

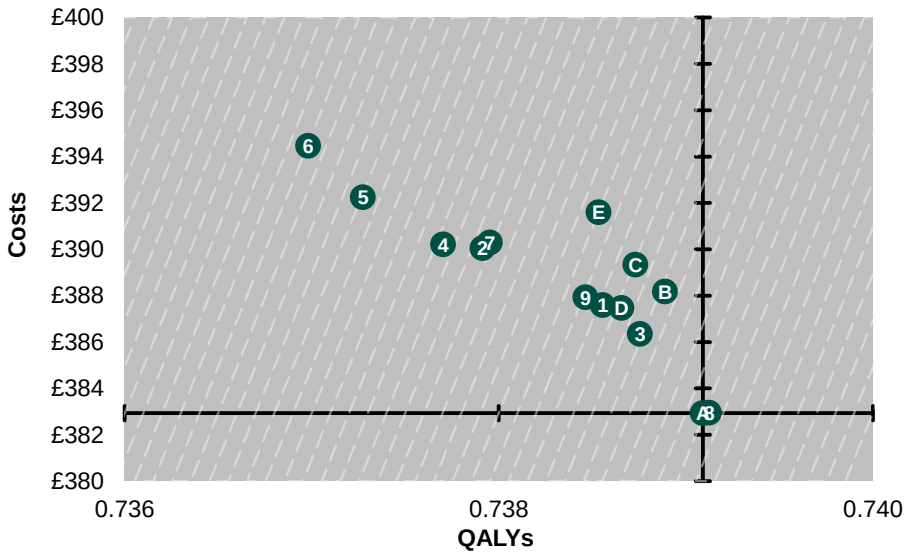
National Institute for Health and Care Excellence 2014.

H.7.4.4 Scenario analysis – Duodenal ulcer

We ran the model with alternative healing and *H pylori* recurrence parameter estimates in order to assess the implications for the population with duodenal ulcer on the cost-effectiveness estimates.

Table 29: Base-case deterministic cost–utility results – Mason costs - 1st- and 2nd-line eradication - Duodenal ulcer

	Absolute		Incremental			Absolute Net Monetary Benefit	
Name	Costs	QALYs	Costs	QALYs	ICER	£20K/QALY	£30K/QALY
1st: MAC-PEN-PPI; 2nd: NIT-PEN-PPI	£382.93	0.739				£14,398.89	£21,789.79
1st: MAC-PEN-PPI; 2nd: MAC-NIT-PEN-PPI	£382.95	0.739	£0.01	0.000	£442	£14,399.52	£21,790.76
1st: MAC-PEN-PPI; 2nd: BIS-H2RA-NIT-TET	£386.35	0.739	£3.41	0.000	dominated	£14,388.74	£21,776.28
1st: MAC-PEN-PPI; 2nd: PEN-PPI-TET	£387.46	0.739	£4.52	0.000	dominated	£14,385.66	£21,772.22
1st: MAC-PEN-PPI; 2nd: BIS-NIT-PPI-TET	£387.59	0.739	£4.64	-0.001	dominated	£14,383.53	£21,769.09
1st: MAC-PEN-PPI; 2nd: MAC-NIT-PPI-TET	£387.93	0.738	£4.98	-0.001	dominated	£14,381.35	£21,765.99
1st: MAC-PEN-PPI; 2nd: NIT-PPI-QUI	£388.18	0.739	£5.24	0.000	dominated	£14,389.59	£21,778.47
1st: MAC-PEN-PPI; 2nd: PEN-PPI-QUI	£389.34	0.739	£6.40	0.000	dominated	£14,385.27	£21,772.58
1st: MAC-PEN-PPI; 2nd: BIS-H2RA-MAC-PEN	£390.05	0.738	£7.10	-0.001	dominated	£14,368.21	£21,747.34
1st: MAC-PEN-PPI; 2nd: BIS-MAC-NIT-PPI	£390.21	0.738	£7.26	-0.001	dominated	£14,363.84	£21,740.87
1st: MAC-PEN-PPI; 2nd: BIS-PEN-PPI-TET	£390.29	0.738	£7.35	-0.001	dominated	£14,368.75	£21,748.27
1st: MAC-PEN-PPI; 2nd: BIS-PPI-QUI-TET	£391.60	0.739	£8.65	-0.001	dominated	£14,379.08	£21,764.42
1st: MAC-PEN-PPI; 2nd: BIS-NIT-PEN-PPI	£392.25	0.737	£9.30	-0.002	dominated	£14,353.23	£21,725.98
1st: MAC-PEN-PPI; 2nd: BIS-PEN+CLAV-PPI-TET	£394.47	0.737	£11.52	-0.002	dominated	£14,345.15	£21,714.96



1 = 1st: MAC-PEN-PPI; 2nd: BIS-NIT-PPI-TET
2 = 1st: MAC-PEN-PPI; 2nd: BIS-H2RA-MAC-PEN
3 = 1st: MAC-PEN-PPI; 2nd: BIS-H2RA-NIT-TET
4 = 1st: MAC-PEN-PPI; 2nd: BIS-MAC-NIT-PPI
5 = 1st: MAC-PEN-PPI; 2nd: BIS-NIT-PEN-PPI
6 = 1st: MAC-PEN-PPI; 2nd: BIS-PEN+CLAV-PPI-TET
7 = 1st: MAC-PEN-PPI; 2nd: BIS-PEN-PPI-TET
8 = 1st: MAC-PEN-PPI; 2nd: MAC-NIT-PEN-PPI
9 = 1st: MAC-PEN-PPI; 2nd: MAC-NIT-PPI-TET
A = 1st: MAC-PEN-PPI; 2nd: NIT-PEN-PPI
B = 1st: MAC-PEN-PPI; 2nd: NIT-PPI-QUI
C = 1st: MAC-PEN-PPI; 2nd: PEN-PPI-QUI
D = 1st: MAC-PEN-PPI; 2nd: PEN-PPI-TET
E = 1st: MAC-PEN-PPI; 2nd: BIS-PPI-QUI-TET

Figure 18: Cost-effectiveness plane - First & Second-line eradication - Mason costs - duodenal ulcer

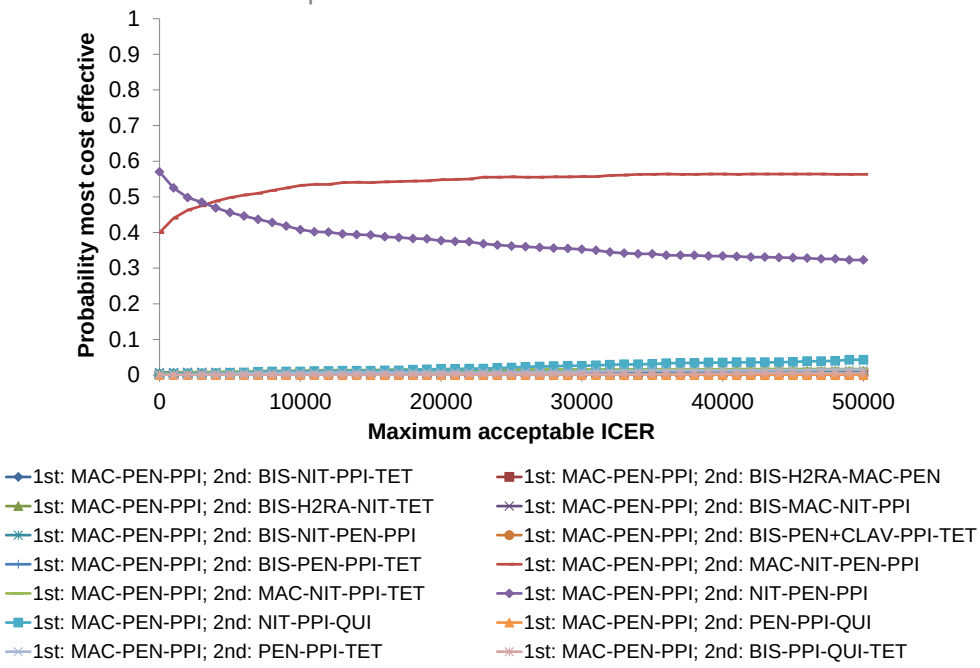


Figure 19: CEAC - First & Second-line eradication - Mason costs - duodenal ulcer

The two regimens which are the most likely to be cost-effective do not change for the population of patients with a duodenal ulcer.

H.7.5 Discussion

H.7.5.1 Principal findings

The clinical effectiveness of the eradication regimen is the key driver of cost-effectiveness. As the variation in drug costs between each of the regimens is a small proportion of the total treatment costs modelled, it is unlikely to generate sufficient discrimination to alter cost-effectiveness rankings which are consistent with rankings based on eradication effectiveness alone.

H.7.5.2 Strengths of the analysis

The analysis enables a comparison to be made between each of the eradication regimens identified within the clinical evidence review.

The model has face-validity through the iterative involvement of the GDG in the conceptualisation, parameterisation and validation of the model.

The design of the model and how it represents the clinical pathway considered by the review question was presented to, and discussed with, the rest of the guideline development team and the other health economists within the department, with amendments made based on their evaluation.

The functionality of the model was tested by a health economist within the team who had not been involved in its development. Validation checks involve both consideration of the model specification and its mechanics, including assessing formulae for accuracy and varying model inputs to check observed effects match expectations.

The model enables first-line and second-line eradication to be analysed in sequence to generate estimates of the effectiveness of pathways of care. However as the second-line evidence is based upon clinical trials in which the patients receive MAC-PEN-PPI as first-line treatment, the accuracy in predicting the effectiveness of any sequence of therapies that does not include a MAC-PEN-PPI first-line treatment is severely limited.

H.7.5.3 Weaknesses of the analysis

The model only addresses the patient population with ulcerative dyspepsia whilst the recommendations are made for the population as a whole, regardless of dyspeptic pathology.

It was only possible to generate economic analysis on the treatment regimens in which there was both effectiveness evidence and the ability to generate an estimate of the cost of the treatment. This means that regimens containing a drug that is not available (or an equivalent that we could use to generate a cost estimate) in the UK are not included within the economic modelling.

The effectiveness evidence is based on a network meta-analysis that is judged to be weak in quality, therefore although uncertainty is taken into consideration through the sensitivity analysis conducted as part of the modelling, it is still reliant on the evidence on interrelationships between eradication regimens generated by the network.

The exclusion of second-line eradication in the modelling of first-line treatment options was necessary but may have had an important impact.

H.7.5.4 Comparison with other CUAs

Without previously published CUAs addressing this question there is a lack of a clear reference point for this analysis.

H.7.5.5 Conclusions

The cost-effectiveness of each of the regimens and our uncertainty in these estimates, in both first-line and second-line therapies is entirely driven by the probability of eradication, and the uncertainty in the underlying effectiveness evidence.

If we knew, with confidence which regimen is the most effective, it would almost certainly be the cost effective option.

The two second-line regimens that are the most likely to be cost-effective are those with the highest probability of eradicating the hpylori infection.

This result seems robust when accounting for the uncertainty surrounding first-line eradication with MAC-PEN-PPI.

No evidence on effectiveness – hence, no evidence on cost-effectiveness – for second-line therapy following failed eradication with NIT-PEN-PPI

The costs of the eradication regimens have fallen while the costs of downstream healthcare have risen. As a result, it may be that incremental gains are perhaps more achievable, however very difficult to demonstrate on the basis of current evidence.

H.8 References

Ara, R. & Brazier, J. (2010). Using health state utility values from the general population to approximate baselines in decision analytic models when condition specific data are not available. HEDS Discussion Paper 10/11. Available from: http://eprints.whiterose.ac.uk/11177/

Bell GD, & Powell KO. Helicobacter pylori infection after opportunistic eradication (1996). The Ipswich experience. Scand J Gastroenterol 31:96–104.

Ebell,M., Warbasse,L., & Brenner,C. (1997). Evaluation of the dyspeptic patient: A cost–utility study. J. Fam. Pract. 44(6):545-55.
Ford, A., Delaney, B., Forman, D. et al. (2004). Eradication therapy in *H pylori* positive peptic ulcer disease: systematic review and economic analysis. American Journal of Gastroenterology. 99:1833-1855.

Ford,A.C.; Delaney,B.C.; Forman,D.; Moayyedi,P. (2004). Eradication therapy in Helicobacter pylori positive peptic ulcer disease: Systematic review and economic analysis. Am.J.Gastroenterol. 99(9):1833-55.

Kaltenthaler, E., Tappenden, P., Paisley, S., Squires, H. (2011) NICE DSU Technical Support Document 13: Identifying and reviewing evidence to inform the conceptualisation and population of cost-effectiveness models. Available from http://www.nicedsu.org.uk.

Leodolter, A., Kulig, M., Brasch, M. et al. (2001). A meta-analysis comparing eradication, healing and relapse rates in patients with *H pylori*-associated gastric or duodenal ulcer. Aliment Pharmacol Ther. 1:1949-1958.

MIMS Drug Guide (Apr 2013) at http://www.mims.co.uk/

NICE (2004). Dyspepsia (CG17). Available from: http://guidance.nice.org.uk/CG17

NHS Drug tariff (Apr 2013) at http://www.ppa.org.uk/ppa/edt_intro.htm

PSSRU (2011). Unit costs of health and social care at http://www.pssru.ac.uk/project-pages/unit-costs/2011/index.php

Roderick, P., Davies, R., Raftery, J., et al. (2003). The cost-effectiveness of screening for *H pylori* to reduce mortality and morbidity from gastric cancer and peptic ulcer disease: a discrete-event simulation model. *Health Technology Assessment* 2003; Vol. 7: No. 6

H.9 Specialist management - effectiveness of fundoplication compared with medical management - Excluded Economic Evaluations

Table 30: Economic Evaluations considered not applicable to decision problem, but presented for completeness.

Study	Incremental cost surgery vs. medical management (per patient)	Incremental QALYs of surgery vs. medical management (per patient)	ICER of surgery vs. medical management	Uncertainty
Goeree et al. 2011	CAN$3,205	0.109 QALYs (HUI-3)	CAN$29,404 per QALY (HUI-3) CAN$79,310 per QALY (EQ-5D)	Results sensitive to instrument used to measure utility and price of PPIs.
Comay etc al. 2008	CAN$5,001	0.013 QALYs	CAN$392,432 per QALY	Results sensitive to price of omeprazole and effectiveness measure used.
Arguedas et al. 2004	US$1,677	-0.04 QALYs	Medical management dominates (surgery more expensive and less effective)	Three one-way sensitivity analyses performed. Results sensitive to utility estimates.
Romagunolo et al. 2002	-CAN$1, 945	-0.015 QALYs	Surgery less effective but costs less than medical management	Results sensitive to cost of medical management, cost of surgery, and projected time horizon
Heudebert 1997	US$3,383	0.002	>US$1,000,000 per QALY	Results sensitive to changes in quality

Study	Incremental cost surgery vs. medical management (per patient)	Incremental QALYs of surgery vs. medical management (per patient)	ICER of surgery vs. medical management	Uncertainty
				of life associated with postoperative symptoms and long-term medication use.

H.10 Surveillance for Barrett's Oesophagus - Excluded Economic Evaluations

Table 35: Economic Evaluations considered by the GDG but excluded due to health setting

Study, Population, Comparators, Quality	Data Sources	Other Comments	Incremental			Conclusions
			Cost (per patient)[1]	QALYs (per patient)	ICER	
Provenzale et al. 1999 No surveillance 1-year interval 2-year interval 3-year interval 4-year interval 5-year interval **Applicability:** Not applicable **Limitations:** Minor limitations	**Effects:** Published estimates **Costs:** Direct costs (New England Medical Centre) **Utilities:** Assumption	Treatment of HGD with esophagectomy	$7,025 $39,067 $32,127 $26,558 $24,845 $23,817	11.81 12.04 12.06 12.10 12.10 12.09	- $801,041 $358,602 $217,038 $187,579 $167,918	Surveillance is unlikely to be cost-effective at an acceptable threshold value.
Inadomi et al. 2003 No surveil. or screen. 2-year interval 3-year interval 4-year interval 5-year interval **Applicability:** Not applicable **Limitations:** Minor limitations	**Effects:** Published estimates **Costs:** Published estimates & Health Care Financing Administration data **Utilities:** Expert opinion valued with time-trade off & responses from patients who had	Treatment of HGD with surveillance	$140 $3,490 $3,115 $2,904 $2,769	16.466 16.626 16.625 16.624 16.624	- $21,015 $18,742 $17,463 $16,640	Surveillance of Barrett's in patients without dysplasia is not cost-effective, even at 5-year intervals.

[1] Evidence adapted from Hirst et al 2011. Costs adjusted to 2009 US$ equivalent

Study, Population, Comparators, Quality	Data Sources	Other Comments	Incremental			Conclusions
			Cost (per patient)[1]	QALYs (per patient)	ICER	
	undergone oesophagectomy					
Inadomi et al. 2009 No surveillance 5-year interval **Applicability:** Not applicable **Limitations:** Minor limitations	**Effects:** Published estimates **Costs:** CMS data (2007) **Utilities:** Published estimates	Treatment of HGD with ablation	$494 $11,532	12.03 15.43	- $22,865	Surveillance is likely to be cost-effective. Surveillance following successful ablative therapy however is expensive.
Das et al. 2009 No surveillance 3-year interval **Applicability:** Not applicable **Limitations:** Minor limitations	**Effects:** Published estimates **Costs:** Published estimates **Utilities:** Published estimates	Treatment of HGD with surveillance or Esophagectomy	$3,305 $14,863	17.959 18.076	- $98,696	Surveillance is unlikely to be cost-effective at 3-year intervals.