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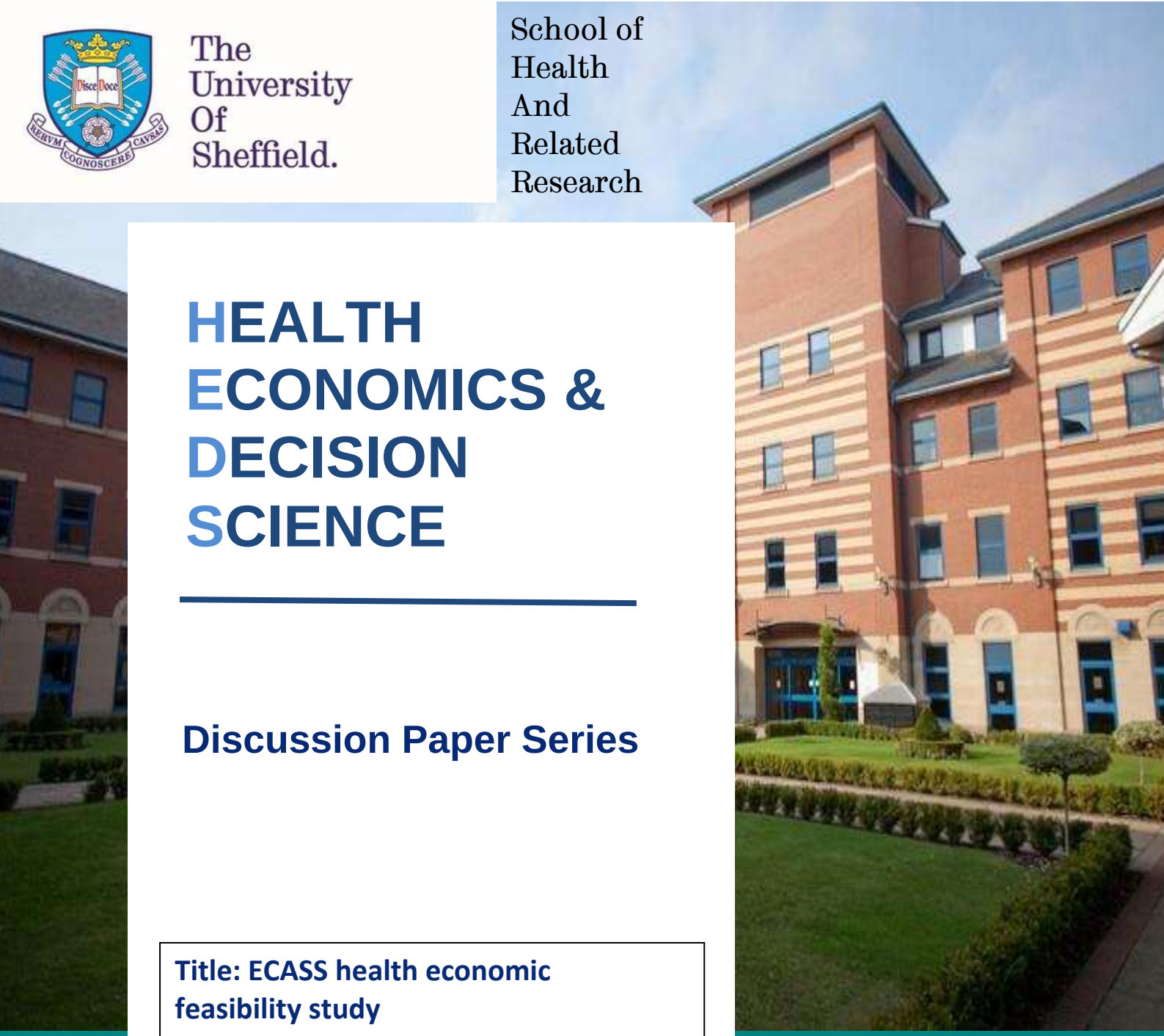

HEALTH ECONOMICS & DECISION SCIENCE

Discussion Paper Series

Title: ECASS health economic feasibility study

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This series is intended to promote discussion and to provide information about work in progress. The views expressed in this series are those of the authors. Comments are welcome, and should be sent to the corresponding author.

ECASS: Phase II exploratory randomised controlled trial comparing use of electronic clinical decision support (eCDS) for suspected oesophago-gastric cancer in primary care with usual care. The oesophago-gastric risk evaluation trial (ISRCTN: 12595588)

ECASS health economic feasibility study

Final Report

Review and Feasibility Study: July 2016

AUTHORS: Duncan Chambers, Chloe Thomas, Sophie Whyte

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Contents

1 Background

1.1 OG cancer symptoms

Oesophageal and gastric (oesophago-gastric or OG) cancers can cause a variety of symptoms, many of which are common and non-specific. The key 'alarm' symptoms which should trigger urgent referral for further investigation are dysphagia (difficulty swallowing) and unexplained weight loss.(1) These symptoms are present in only a minority of patients and their presence is associated with advanced disease that has spread beyond the original site and for which curative treatment is not possible.

The nature of OG cancer symptoms means that many patients visit their general practitioner (GP) several times before being referred to hospital and receiving a diagnosis. A study of patients in England reported that 36% of patients with stomach cancer and 25% of those with oesophageal cancer (274/1099) had consulted their GP three or more times about their cancer symptoms before being referred to hospital.(2)

1.2 OG cancer incidence and survival

According to cancer registry data collated by Cancer Research UK, there were approximately 8,800 new cases of oesophageal and 7,100 new cases of gastric cancer in the UK in 2013 (the most recent data available). (reference to be added) In recent decades, the incidence of oesophageal cancer has increased, particularly in men, while that of gastric cancer has decreased. Survival is poor, with data from 2010/11 showing only 42% of individuals surviving for one year, and less than 20% of individuals surviving for five years or more.

While rates of survival have improved over time, long-term survival remains relatively low. This supports the need for earlier diagnosis to improve the chance of being able to offer the patient a treatment aimed at curing their cancer.

1.3 Gastroscopy rates

Diagnosis of OG cancer requires an upper gastrointestinal (GI) endoscopy, often referred to as gastroscopy. This is normally performed as an outpatient or day case procedure under local anaesthetic or intravenous sedation and will often include a biopsy for histological confirmation of the diagnosis. Patients presenting with symptoms of possible OG cancer may be referred to hospital for a gastroscopy. This may require referral to a hospital specialist first, but more recently open access or direct access systems have been available (i.e. without seeing a hospital specialist). Given that gastroscopy is an invasive procedure with a small but significant risk of adverse effects, and that most patients seen in primary care do not have cancer (or another significant health problem), it is important to optimise referral decisions as far as possible and minimise inappropriate variation between individual GPs, GP practices and regions. Data from NHS sources suggest that there is considerable variation in rates of referral for gastroscopy between areas and GP practices (see section 4.5.4).

1.4 eRATs

Electronic risk assessment tools (eRATs) are computerised CDS tools for the assessment of cancer risk. Macmillan Cancer Support has been involved in developing and promoting use of eRATs for a number of cancers,(3) based on previous work from the CAPER (Cancer Prediction in Exeter studies.(4) The eRAT can be integrated with GP clinical computer systems and used to support decision-making during patient consultations. A pilot study of eRATs for five different cancer types (lung, colorectal, OG, pancreatic and ovarian) has been carried out.(5) This has suggested that using an eRAT does not influence the GPs decision to refer in 81% of cases, but in the other 19% of cases GPs would not have referred if they hadn't used the tool. There is also evidence from the pilot study that GPs used the tool to support decisions not to refer, suggesting that use of the eRAT could also cut down on unnecessary referrals. However, given the resource implications of increased referrals and investigations, it is important to assess the cost-effectiveness of eRATs for possible OG cancer in routine primary care practice.

1.5 ECASS trial

The ECASS trial is a phase II cluster randomised controlled trial comparing use of the OG eRAT with usual care for patients visiting the GP with symptoms of possible OG cancer.(6) The aims of the trial are to establish the acceptability of the eRAT system and to collect process data including practitioner, service and patient outcomes to inform a subsequent phase III trial. The phase III trial would be designed to examine the effect of the eRAT on cancer stage at diagnosis, surgical treatment and survival. This report describes a health economic modelling feasibility study undertaken as part of the trial.

1.6 ECASS trial health economic feasibility study

The aims of this health economic feasibility study are:

- to map the potential impact of the eRAT tool from a health economic viewpoint by determining where in the clinical pathway the eRAT may impact on costs to the NHS and benefits to the patient (measured as quality-adjusted life-years [QALYs])
- to develop a simple health economic model using the eRAT impacts and populated by cost estimates obtained from published literature and other sources.
- to generate estimates of health economic outcomes using the phase II trial data and explore data requirements and possible modelling approaches for a health economic evaluation of a subsequent definitive trial

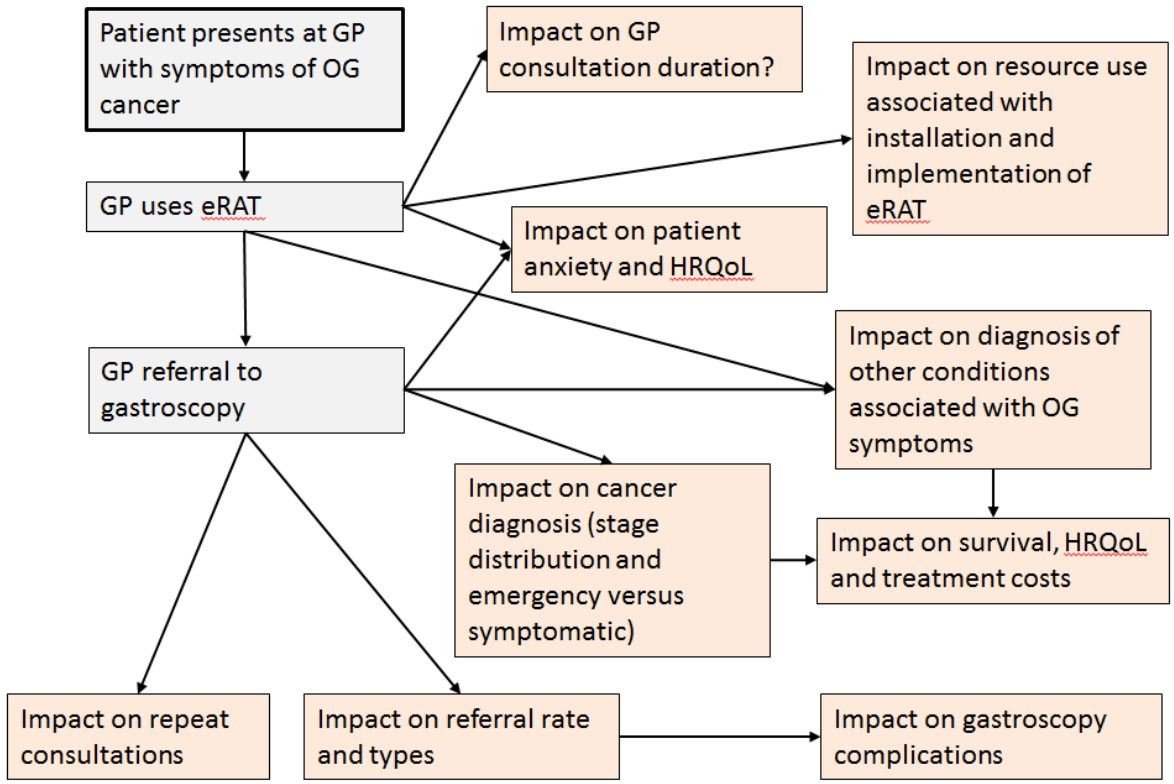
2 Conceptual Economic Model

The conceptual model was designed by mapping out the implications of using the tool from a health economics perspective with input from the trial team.

2.1 Implications of using the tool from a health economics perspective

An overview of the likely implications of using the tool on both costs from an NHS perspective and patient QALYs is shown in Figure 1. Each of these impacts is discussed further in turn below.

Figure 1: The implications of using the eRAT from a health economics perspective



2.1.1 Resource use associated with installation and implementation of eRAT

The eRAT is free to download and fully compatible with GP IT systems. However, there will be an administrative cost due to time spent downloading it and any software updates in future. More importantly, GPs need to be trained in its use, which will incur not only costs of providing training, but also GP time to undergo training.

2.1.2 Impact on GP consultations

Use of the eRAT may have an effect on the length of GP consultations. This could either be an increase if it takes time to use the eRAT, or a reduction if eRAT use accelerates referral decisions. Referral decision will also impact upon the number of repeat consultations that may be needed before a patient receives a diagnosis.

2.1.3 Impact on patient anxiety and health-related quality of life

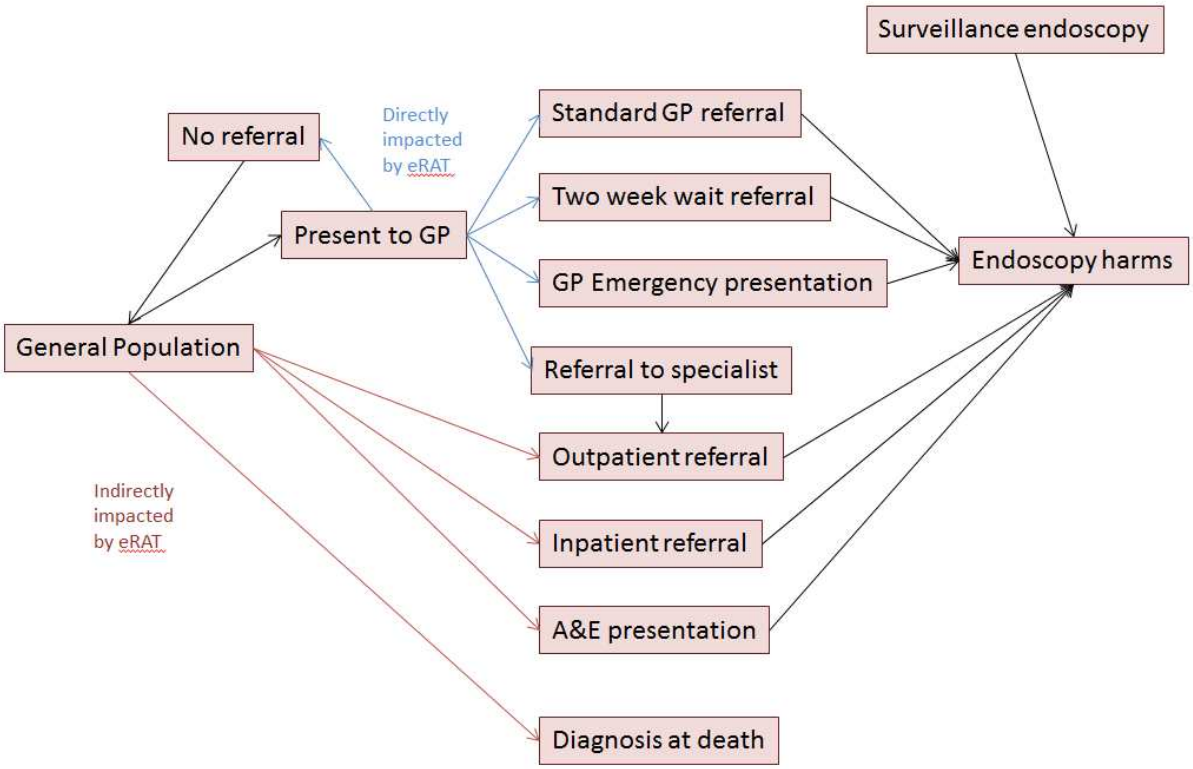
It is possible that use of the eRAT could increase patient anxiety if they see their cancer risk on the screen during the consultation. It may also impact upon the quality of GP/patient interactions as the GP must consult with the patient and use the tool simultaneously. Patients who undergo gastroscopy

and receive a negative result may be reassured and less anxious than patients whose symptoms have not been investigated further.

2.1.4 Impact on referral rate and types

There are several different types of GP referral to gastroscopy; which is used depends upon the urgency required (Figure 2). It is expected that use of the eRAT will impact upon both the rate of referral and the proportion of each type of referral. In the pilot evaluation of eRATs for all five cancer types, in 31% of cases the cancer risk was higher than the GP perceived and in 15% of cases it was lower (5). For OG cancer specifically, in 9% of cases GPs would not have referred or investigated if they hadn't used the tool.

Figure 2: Diagnostic pathways for OG cancer



2.1.5 Impact on gastroscopy rates and complications

An increase in referrals, whether via a specialist or not, will lead to an increase in gastroscopy rates and therefore complications of gastroscopy, including perforation, bleeding, aspiration pneumonia and cardiac and breathing problems. These can either be modelled as separate health states, or the cost and quality of life implications of adverse events can be taken into account as patients undergo diagnosis.

2.1.6 Impact on diagnosis of other conditions

Gastroscopy is a key method of diagnosis for a range of other OG conditions that have similar symptoms to OG cancer including gastro-oesophageal reflux disorder (GORD), peptic ulcer, Barrett's oesophagus and dyspepsia. Dyspepsia and GORD may also be diagnosed by the GP without referral to gastroscopy.

There are some interactions between these disorders that are important to take into account. GORD is a risk factor for development of Barrett's oesophagus. Barrett's oesophagus may present with no dysplasia, low grade dysplasia or high grade dysplasia and the latter increases the risk of OG cancer. Individuals with high grade dysplasia may therefore undergo regular surveillance gastroscopy with the aim of detecting OG cancer early. Gastric ulcer may progress to serious complications if not treated, so there is an advantage in early diagnosis.

2.1.7 Impact on cancer diagnosis – stage distribution and emergency presentation

It is likely that earlier diagnosis of OG cancer would lead to a shift in stage distribution at diagnosis, with an increase in earlier (stage 1-2) diagnoses. The Cancer Research UK website indicates that currently only 1% of gastric cancers are diagnosed at stage 1, 6% at stage 2, 14% at stage 3 and almost 80% are not diagnosed until stage 4.(7) Earlier diagnosis should also lead to a reduction in the numbers of diagnoses made through emergency presentation, a route that typically costs more and has poorer patient prognostics than other diagnostic pathways. A disease natural history model could be used to predict the impact of earlier presentation on stage at diagnosis and survival.

2.1.8 Impact on survival, HRQoL and treatment costs of differential diagnosis

Earlier diagnosis of OG cancer is likely to lead to improved survival. Statistics from the Cancer Research UK website indicate that 80% of people with stage 1 gastric cancer live for five years or more, compared with only 5% of people with stage 4 gastric cancer.(7) Earlier cancer diagnosis may also improve quality of life, particularly if less aggressive treatments are required for earlier stage cancers. Different health-related quality of life may apply for diagnosed versus undiagnosed cancer.

Other OG conditions are also likely to impact upon quality of life and earlier diagnosis of these conditions may result in earlier treatment and perhaps cure, which will result in higher lifetime QALY gain. Earlier diagnosis of peptic ulcer may prevent complications, which may impact upon quality of life and survival.

Resource use associated with the model is presented in Table 1. Costs are associated with use of the eRAT, changes to consultation practice, changes to referral and treatments for all conditions included in the model. Early diagnosis of OG cancer and other conditions may be associated with either increased or reduced costs depending upon the type and duration of treatment undergone. Some costs may be one-off costs (e.g. installation of the eRAT and training; endoscopy costs), whereas other costs may be ongoing (e.g. costs of GORD treatment).

Table 1: Resource use associated with the model

eRAT consultation
Cost of installation Cost of training Cost of consultation (related to the duration of consultation) Cost of repeat consultations Cost of GORD or dyspepsia treatments given without referral
Referral
Cost of specialist consultation Cost of GP referral emergency endoscopy Cost of GP referral 2 week wait endoscopy Cost of standard GP referral endoscopy

Cost of A&E presentation for endoscopy
Cost of non GP outpatient referral endoscopy
Cost of inpatient referral endoscopy
Cost of endoscopy harms
Treatment
Cost of OG cancer treatment by stage (lifetime costs)
Cost of peptic ulcer treatment
Cost of complications of peptic ulcers
Cost of treatment for Barrett's Oesophagus
Cost of surveillance for Barrett's Oesophagus
Cost of GORD treatment
Cost of dyspepsia treatment

3 Literature reviews

3.1 Methods

Literature was identified by targeted database searches performed by an Information Specialist; by following up references cited in the ECASS study protocol and relevant NICE guidelines; and by broad Internet searches using Google/Google Scholar. Data were extracted by one reviewer to address issues relevant to the development of the economic model. Literature was not assessed for quality (risk of bias) and there were no restrictions on the types of literature included.

3.2 Impact of eRATs on consultation length

An initial scoping search of MEDLINE using terms for primary care/general practice, decision support and time savings resulted in 848 references being retrieved. As sifting this number of references with a low probability of finding anything relevant was not thought to be feasible, we examined whether consultation length was reported in any relevant systematic reviews.

A 2005 systematic review by Kawamoto et al.(8) sought to identify features of clinical decision support systems (CDSS; a broader category than eRAT) that were critical to the systems' ability to improve clinical practice. 'Saves clinicians time or requires minimal time to use' was identified as a potential explanatory feature from the literature. The review authors were unable to include the feature in their analysis because 'most studies did not conduct formal or informal evaluations of the time costs and savings associated with system use'.

A later (2009) systematic review by Mollon et al.(9) looked at factors predicting the success of CDSS specifically for prescribing. These authors included 41 randomised trials in their review and reported that 17 saved time or required minimal time to use. However, no quantitative data on time savings were reported in the paper and the fact that this review dealt only with systems to support prescribing means that the results may not be generalizable to the setting of the ECASS trial.

Two systematic reviews have examined the effectiveness of CDSS or RATs in primary care. Bryan et al. in 2008 reviewed interventions using a CDSS in outpatient clinics or primary care settings.(10) The authors concluded that CDSS had the potential to significantly improve outcomes but variation in the included studies and limitations in the review itself limited the conclusions that could be drawn. A 2015 systematic review by Walker et al.(11) evaluated the impact of RATs for cancer in primary care with respect to their clinical utility, screening uptake and psychosocial outcomes for patients. Eleven randomised trials were included but clinician time saving was not reported as an outcome.

Another source of literature examined was known publications cited in the ECASS study protocol reporting evaluations of eRATs and similar tools in primary care. An examination of several published evaluation s(12-15) did not identify any information specifically on consultation length, although related issues such as the number of systems and prompts that GPs already have to deal with were raised.

Thus, systematic reviews of CDSS and RATs did not reveal any data on effects of decision aids for clinicians on consultation length. However, some data were reported in a broader Cochrane systematic review of decision aids for people facing treatment or screening decisions.(16) This review covered all types of health condition and included randomised trials comparing decision aids with usual care and/or alternative interventions. Of 115 studies in the review, 10 evaluated consultation length with a decision aid compared with usual care (9 studies) or a simple decision aid (1 study). Six of these studies involved use of a decision aid during the consultation and all of them reported longer consultations in the decision aid group. The difference in length of consultations ranged from 2.5 to 23 minutes and was statistically significant in two studies (5.9 minutes and 23 minutes). The other studies reported statistically non-significant differences of 2.5 to 3.8 minutes. None of these trials involved people with upper GI symptoms or other symptoms of possible cancer (one involved women considering prevention of breast cancer and one women considering breast cancer chemotherapy). Furthermore, this review related to aids for shared decision-making between clinicians and patients and the data may not be relevant to clinician decisions about whether to refer patients for further investigation.

In summary the limited available data suggest a possible small increase in consultation length but the findings may not be generalizable to the ECASS intervention and population and will need to be supplemented by data from the trial.

3.3 Impact of eRATs on patient anxiety or HRQoL

Three of the RCTs included in the systematic review of cancer RATs in primary care(11) reported patient anxiety/worry as an outcome. However, two of these recruited patients with a risk of familial cancer who may be different from the population in the ECASS trial (because the RAT is assessing potential future cancer risk rather than risk of current undiagnosed cancer based on symptoms). The remaining trial evaluated a paper-based RAT for women undergoing cervical cancer screening (again a different population from ECASS).(17) It appears that the intervention was delivered by a practice nurse. Compared with those receiving usual care, women from intervention practices were less likely to be 'fearful of cervical cancer', 'concerned about chances of serious problems…in the future' or 'anxious about a recent smear test'. There was no statistical difference for 'concern about their smear test result'. The review authors noted that none of the three trials that measured patient anxiety reported an increase after risk assessment.

While the review of cancer RATs by Walker et al. was the most specific review located, there is an extensive literature on decision support systems and decision aids and on risk assessment and communication. These studies focus on decision aids for patients rather than systems used by health professionals where the results may or may not be explicitly shared with the patient. A 2014 systematic review of decision aids for cancer screening and treatment found no difference in anxiety scores between patients who used a decision aid and those who did not.(18) The outcome measure was State-Trait Anxiety Inventory scores (weighted mean difference = 0.1; 95% Credible Interval, -1.0 to 0.7 on a 20-80 scale; 16 comparison strata; 2,958 participants).

A broader Cochrane review of decision aids for people facing any type of treatment or screening decisions, also published in 2014, found no difference between patients receiving decision aids compared with control groups for anxiety based on 30 randomised trials.(16)

A related Cochrane review looked at personalised risk communication to promote informed decision making about taking screening tests (again a slightly different situation to the use of an E-RAT).(19) Anxiety was a secondary outcome in this review. A meta-analysis of six studies reported a small and statistically non-significant decrease in anxiety in the group receiving personalised risk information compared with controls receiving general information. This evidence was considered to be very low quality because, among other reasons, not all studies showed the same direction of effect.

3.4 Diagnostic Pathways

There are a number of routes to diagnosis for patients with cancer; key diagnostic recommendations from relevant NICE guidelines are summarised below (see section 4.5.5). A study by Elliss-Brookes et al. used data from multiple sources to categorise cases of cancer diagnosed in England in 2006–2008 into one of eight 'routes to diagnosis'.(20) The routes were: screen-detected (certain cancers only); two-week wait (TWW) referral; GP referral (other than TWW or emergency referral); other outpatient; inpatient elective; emergency presentation; death certificate only (DCO); and unknown.

Table 2 reproduces more detailed descriptions of each route (except screen-detected which is not relevant to OG cancer).(20)

Table 2: routes to cancer diagnosis (20)

Diagnosis route	Description
TWW	Urgent GP referral with a suspicion of cancer
Emergency presentation	An emergency route via A&E, emergency GP referral, emergency transfer, emergency consultant outpatient referral, emergency admission or attendance
GP referral	Routine and emergency referrals other than TWW referrals
Inpatient elective	No earlier admission can be found before admission from a waiting list, booked or planned
Other outpatient	An elective route starting with an outpatient appointment: self-referral, consultant to consultant, other or unknown
DCO	No data available but diagnosis flagged on death certificate
Unknown	No data available

The proportion of patients presenting by each route is summarised in the table below (Table 3).

Table 3: routes to diagnosis for oesophageal and gastric cancer (20)

	TWW	GP referral	Other outpatient	Inpatient elective	Emergency	DCO	Unknown
Oesophagus n=19,449	34%	16%	8%	14%	22%	1%	5%
Stomach n=18,613	23%	17%	8%	13%	33%	1%	5%
Weighted average	28.6%	16.5%	8%	13.5%	27.4%	1%	5%

There were some differences (not analysed statistically) between gastric and oesophageal cancer, with a higher proportion of TWW referrals for oesophageal (34 vs. 23%) and more emergency presentations for gastric cancer (33 vs. 22%). The route of presentation was associated with survival: patients diagnosed after emergency presentation had lower 1-year survival than those who presented by other routes (see Table 4).

Table 4: 1-year survival by route of presentation (20)

	All routes	TWW	GP referral	Other outpatient	Inpatient elective	Emergency	Unknown
	1-year relative survival (95% CI)						
Oesophagus n=19,449	40% (39-40)	42% (41-43)	47% (45-48)	50% (48-53)	49% (47-51)	18% (17-20)	44% (41-48)
Stomach n=18,613	41% (40-41)	43% (42-45)	52% (50-54)	55% (52-58)	53% (51-55)	23% (21-24)	44% (41-47)

The National Oesophago–Gastric Cancer Audit (NOGCA) for 2015(21) reported that 13.6% of patients with OG cancer were diagnosed following an emergency presentation, down from 15.3% in 2009. Data from the NOGCA may be more accurate than those estimated by Elliss-Brookes et al. because this is a specific national audit (covering England and Wales) rather than an analysis of national data using an algorithm to allocate patients to diagnostic routes (the method developed by Elliss-Brookes et al.). In addition, the data from the NOGCA appear to be more recent than those used by Elliss-Brookes et al.

Table 5 summarises the figures reported by the NOGCA for percentage of OG cancers diagnosed following emergency presentation covering patients diagnosed between 2007 and 2014.

Table 5: Percentage of OG cancers diagnosed following emergency presentation (21)

NOGCA report date	Time period	Oesophageal	Gastric	Overall
2009	1/10/07 to 31/3/09	12%	23%	15.3%
2012	1/10/07 to 30/6/09	13%	24.1%	16.4%
2013	1/4/11 to 31/3/12	11%	25%	15%
2015	1/4/12 to 31/3/14	NR	NR	13.6%

If a patient is not referred when they first present with symptoms of possible cancer, they may return for a further consultation at a later date, possibly resulting in increased costs and delayed diagnosis. Alternatively, if they do not consult again they may go down the route of diagnosis following emergency presentation, which is associated with markedly reduced survival (see Table 4).

Data from the National Cancer Patient Experience Survey for England in 2010(2) indicated that 36% of patients with stomach cancer (269/748) and 24.9% of those with oesophageal cancer (274/1099) had consulted their GP three or more times about their cancer symptoms before being referred to hospital. This represents a weighted average for OG cancer of 29.4% (543/1847). However, it should be noted that there may be a difference between gastric and oesophageal cancer as the respective rates suggest. In the study authors' statistical analysis using rectal cancer as a reference, the odds of having

three or more consultations were significantly higher for stomach cancer (adjusted OR 1.96, 95% CI 1.65 to 2.34) but not for oesophageal cancer (adjusted OR 1.15, 95% CI 0.98 to 1.36). In conclusion, stomach cancer appears to be associated with a higher risk of multiple GP appointments and a higher risk of diagnosis after emergency presentation compared with oesophageal cancer.

3.5 Gastroscopy

3.5.1 Overview

Gastroscopy (upper GI endoscopy) is normally performed as an outpatient procedure under local anaesthetic or intravenous sedation. The procedure may include a biopsy for histological analysis to confirm a diagnosis of, for example, OG cancer or Barrett's oesophagus.

3.5.2 Costs

NHS reference costs (2014–15) are quoted as £416 (IQR £295–£468) for 'diagnostic endoscopic upper GI tract procedures' and £467 (IQR £351–£555) for 'diagnostic endoscopic upper GI tract procedures with biopsy' (https://www.gov.uk/government/publications/nhs-reference-costs-2014-to-2015). For comparison, the economic modelling study by Benaglia et al. used a cost of £517 (standard error £150.57) for endoscopy + biopsy (screening/surveillance).(22) This figure was taken from NHS reference costs for 2007–8.

3.5.3 Adverse Events

Gastroscopy is regarded as a relatively safe procedure and serious adverse events are rare. Adverse events include events related to sedation (where used), including nausea, aspiration pneumonia, cardiac and breathing problems; bleeding caused by damage to blood vessels; and perforation of the lining of the oesophagus or stomach. A 2012 review cites overall complication rates and mortality rates of 0.13% and 0.004%, respectively.(23) Rates of perforation are reported to be <0.03%, with a mortality rate of 0.001%.

3.5.4 Referral to gastroscopy

Data on referral rates to gastroscopy in practice are reviewed in this section. NICE guidance on indications for referral is summarised in section 4.5.5.

Rates of referral for diagnostic gastroscopy from primary care vary widely. *The NHS Atlas of Variation 2011* mapped rates of activity at the level of Primary Care Trusts (PCTs) in England. Data are presented as indirectly standardised rates adjusted for age, sex and deprivation. In 2009/10, the rate ranged from 77.4 to 225.7 per 10,000 population, representing a 2.9-fold variation (Table 6). When the five PCTs with the highest rates and those with the lowest rates were excluded, the range was 91.4 to 185.9 per 10,000.(24) These data refer to all endoscopy procedures undertaken, not just those resulting from referral by GPs, so investigations requested by hospital clinicians would also be covered.

Data from 2011/12 were reported in the *NHS Atlas of Variation in Diagnostic Services*.(25) Data were reported for both PCTs and their replacement CCGs. Comparing the PCT data from 2009/10 with those from 2011/12, the authors noted that the degree of variation appeared to have decreased slightly.

Table 6: Rates of referral per 10,000 population by PCT and CCG (24, 25)

	Range	Fold difference	Range after exclusion of outliers	Fold difference
PCT (2009/10)	77.4–225.7	2.9	91.4–185.9	2.0

PCT (2011/12)	78.2–208.3	2.7	97.1–178.6	1.8
CCG (2011/12)	76.3–208.3	2.7	93.9–178.6	1.9

The *Atlas of Variation in Diagnostic Services* also reported on the proportion of gastroscopies performed on people aged under 55 (Table 7). This is regarded as an indicator of the appropriateness of referrals because, based on current guidelines for dyspepsia and reflux, the rate of gastroscopy in younger patients should be 'relatively low'.(25) Overall, 33% or more of gastroscopies were performed on patients under 55 in two-thirds of PCTs and over 60% of CCGs.

Table 7: Percentage of patients undergoing gastroscopy aged under 55 by PCT and CCG 2011/12 (19)

	Range	Fold difference	Range after exclusion of outliers	Fold difference
PCT	25.2–56.2	2.2	28.2–49.4	1.8
CCG	25.1–57.9	2.3	27.8–48.4	1.7

Shawihdi et al HES data study

Data on variation in gastroscopy rates at the level of individual practices were reported by Shawihdi et al.(26) This study used data from the Hospital Episode Statistics for England for 2006–8 linked to death registration to assess whether gastroscopy referral rates were associated with subsequent OG cancer outcomes. General practices with new cases of OG cancer were included and divided into three groups (tertiles; 2171 practices in each) based on their per capita elective gastroscopy rates. Mean annual rates of gastroscopy were 4.4 (SD 1.8)/1,000 for practices in the lowest tertile; 8.1 (0.8) for the middle tertile; and 12.9 (3.1) for the high tertile.

Of 587,256 patients undergoing diagnostic gastroscopy, 12,569 (2.1%) were diagnosed (based on codes in their medical records) with upper GI cancer; 68,229 (11.6%) had 'major acid-peptic lesions'; 229,706 (51%) were diagnosed as 'normal or minor pathologies only'; 14,920 (2.5%) had other GI neoplasms; 142,955 (24.3%) had upper GI symptom codes only; and 48,877 (8.3%) had miscellaneous other codes.

The study investigated 22,488 cases of OG cancer, of which 6196 came from the low gastroscopy group of practices; 7913 from the medium group; and 8379 from the practices with the highest baseline gastroscopy rates. Patients from the low tertile practices had the lowest rate of major surgery (i.e. potentially curative); highest rate of diagnosis following emergency admission; and highest rate of death at 12 months. The difference was greatest for the most socioeconomically deprived group of patients. In logistic regression analysis, the gastroscopy rate of the patient's general practice was an independent predictor of emergency admission, major surgery and mortality.

The authors concluded that initiatives aimed at limiting the use of gastroscopy may worsen cancer outcomes. They suggested a more targeted strategy to increase gastroscopy rates in low-referring practices, especially those serving more deprived populations, while aiming to reduce gastroscopy in younger patients with dyspepsia as recommended in the 2004 NICE guidance current at the time of the study.(27)

Recent NICE guidance on recognition and referral for suspected cancer(1) and on management of gastro-oesophageal reflux disorder/disease (GORD) and dyspepsia(28) is expected to increase referrals from primary care because specific new recommendations have been introduced and the threshold risk for referral has been reduced from 5% to 3% for most types of cancer. Referral recommendations are largely based on age and the presence of 'alarm symptoms' or 'red flags'. However, alarm symptoms are associated with advanced cancer not suitable for curative treatment. An observational study cited in the ECASS study protocol(29) looked at patients referred for open access gastroscopy in 1990–98 in Newcastle-on-Tyne. Criteria for referral were dyspepsia or dysphagia in patients aged 35 or older. Of 4,018 patients referred for gastroscopy, 123 (3%) had OG cancer. Of these, 104 (85%) had 'alarm' symptoms but the remaining 15% had symptoms of uncomplicated dyspepsia. Patients with 'alarm' symptoms were more likely to have metastatic disease than those without (47% vs. 11%); less likely to undergo surgical resection (50% vs. 95%); and had poorer survival (median 11 vs. 39 months).

3.5.5 Gastroscopy indicators

Table 8 summarises the current NICE guidance for referral for gastroscopy for people with suspected oesophageal or gastric cancer. Gastroscopy is covered by a NICE Quality Standard (see https://www.nice.org.uk/guidance/qs96), although this relates to the guidance on management of GORD or dyspepsia.(28) A quality standard for referral for suspected cancer is expected to be published in May 2016.

Table 8: NICE gastroscopy referral guidance for suspected OG cancer (1)

Offer urgent (TWW) direct access gastroscopy for people • with dysphagia • aged 55 and over with weight loss and upper abdominal pain, reflux or dyspepsia
Consider non-urgent direct access gastroscopy for people with haematemesis
Consider non-urgent direct access gastroscopy for people aged 55 or over with • treatment-resistant dyspepsia • upper abdominal pain with low haemoglobin levels • raised platelet count and nausea, vomiting, weight loss, reflux, dyspepsia or upper abdominal pain • nausea or vomiting and weight loss, reflux, dyspepsia or upper abdominal pain

Table 9 briefly summarises some key recommendations of the NICE guidance for people with dyspepsia, peptic ulcer or GORD (including pharmacological treatment as well as referral for gastroscopy.(28) This guidance also covers surveillance for people with Barrett's oesophagus.

Table 9: NICE guidance for people with dyspepsia, GORD or peptic ulcer (23)

For people presenting with dyspepsia together with significant acute gastrointestinal bleeding, refer them immediately to a specialist
If people have had a previous endoscopy and do not have any new alarm signs, consider continuing management according to previous endoscopic findings
For uninvestigated dyspepsia: • offer empirical full-dose PPI therapy for 4 weeks • offer *H. pylori* 'test and treat'

Manage uninvestigated 'reflux-like' symptoms as uninvestigated dyspepsia
Offer people with GORD a full-dose PPI for 4 or 8 weeks
Do not routinely offer endoscopy to diagnose Barrett's oesophagus but consider it if the person has GORD
Offer *H. pylori* eradication therapy to people who have tested positive for *H. pylori* and who have peptic ulcer disease
Manage endoscopically determined functional dyspepsia using initial treatment for *H. pylori* if present, followed by symptomatic management and periodic monitoring
Consider referral to a specialist service for people: • of any age with gastro-oesophageal symptoms that are non-responsive to treatment or unexplained • with suspected GORD who are thinking about surgery • with *H. pylori* that has not responded to second-line eradication therapy
Consider surveillance to check progression to cancer for people who have a diagnosis of Barrett's oesophagus (confirmed by endoscopy and histopathology), taking into account • the presence of dysplasia • the person's preference • the person's risk factors. Emphasise that the harms of endoscopic surveillance may outweigh the benefits in people who are at low risk of progression to cancer

3.6 Cost of treatment of OG cancer by stage and route to diagnosis

3.6.1 Types of treatment

The type of treatment offered for OG cancer and the associated costs will depend on the route to diagnosis and the stage at which the cancer is diagnosed. Both oesophageal and gastric cancers are generally staged using either the TNM (Tumour, Node, Metastasis) or the numerical system (stage 0 to 4). Treatment will involve some combination of surgery (curative or palliative), chemotherapy and/or radiotherapy. Advanced cancer that has spread beyond the OG region is classified as stage 4 or M1 (any T, any N, M1) and treatment aims to relieve symptoms and/or slow progression.

The T part of the TNM system is briefly summarised here (Figure 1) in view of its use in the Gordon et al. modelling study summarised below.

Figure 3: Classification of oesophageal tumour spread

TX: The primary tumour cannot be evaluated.

T0: There is no cancer in the oesophagus.

Tis: This is called carcinoma (cancer) in situ. Carcinoma in situ is very early cancer. Cancer cells are in only one small area of the top lining of the oesophagus without any spread into the lining.

T1: There is a tumour in the lamina propria and the 2 inside layers of the oesophagus called the submucosa. Cancer cells have spread into the lining of the oesophagus.

T2: The tumour is in the third layer of the oesophagus called the muscularis propria. Cancer cells have spread into but not through the muscle wall of the oesophagus.

T3: The tumour is in the outer layer of the oesophagus called the adventitia. Cancer cells have spread through the entire muscle wall of the oesophagus into surrounding tissue.

T4: The tumour has spread outside the oesophagus into areas around it. Cancer cells have spread to structures surrounding the oesophagus, including the large blood vessel coming from the heart called the aorta, the windpipe, diaphragm, and the pleural lining of the lung.

There are no centrally collected UK statistics available on different stages of cancer or the treatments people have received (http://www.cancerresearchuk.org/about-cancer/type/oesophageal-cancer/treatment/statistics-and-outlook-for-oesophageal-cancer). For OG cancer, some data are available from the National Oesophago–Gastric Cancer Audit (NOGCA). Its latest report (2015) describes the care received by patients diagnosed between 1st April 2012 and 31st March 2014 and their outcomes.(21) Data were collected on therapies received by patients (such as surgery) until December 2014. The report also covers patients with high-grade dysplasia.

Table 10 summarises the data on the number of patients included and types of treatment received. Overall, 38.1% of patients included in the NOGCA had a curative treatment plan. The proportion was 42.1% for tumours located in the lower oesophagus and 33.3% for stomach tumours. Surgery (with or without chemotherapy or radiotherapy) was planned for over 80% of patients managed with curative intent, with 15.6% receiving oncological treatment only and 4.3% treated endoscopically. Of those who underwent curative surgery (oesophagectomy or gastrectomy), 78% of oesophageal cancer patients and 54% of gastric cancer patients received chemotherapy and/or radiotherapy. Minimally invasive surgery was used in 41% of oesophageal and 14% of gastric cancer procedures. Ninety-day post-operative mortality was 4.3% (95% CI 3.6 to 5.1) for oesophagectomy and 4.2% (95% CI 3.3 to 5.3) for gastrectomy; complication rates were 36.9% and 23.7% respectively.

Table 10: Summary of OG cancer treatment data, NOGCA 2015 (21)

Patient numbers		
Patients with OG cancer	21,301	
Patients treated with palliative intent	16,726	
Patients treated with curative intent	5,038	

Patients with coding errors in tumour site and/or main procedures (i.e. not known)	87	
Patients with main procedures appropriate to the site of the cancer	4,951	
Curative treatment		
	Oesophagectomy (n=3,036)	Gastrectomy (n=1,701)
Surgery only	656 (21.6%)	760 (44.7%)
Surgery and chemotherapy	2,211 (72.8%)	902 (53.0%)
Surgery and chemoradiotherapy	102 (3.4%)	16 (0.9%)
Other	67 (2.2%)	23 (1.4%)
Palliative treatment		
	Oesophageal (all types)	Stomach
No active treatment	30.8%	48.2%
Palliative surgery	3.1%	4.3%
Palliative oncology (radio/chemotherapy)	50.4%	41.7%
Endoscopic palliative treatment	15.6%	5.9%

The majority of patients with OG cancer in the NOGCA received palliative treatment. The most common type of treatment was palliative chemotherapy and/or radiotherapy. A substantial proportion of patients received no active treatment (Table 10).

A 2009 study by Lyratzopoulos et al. examined treatments received by patients covered by the Eastern England Cancer Registration and Information Centre (EECRIC) for the period 1995–2006.(30) The EECRIC covers a population of about 5.5 million people and 14,077 patients with OG cancer (excluding SCC) were included. Treatments (summarised in Table 11) were categorised differently from the NOGCA data. It should be noted that these data are less current than those from the NOGCA.

Table 11: Treatments for OG cancer, EECRIC 1995–2006 (30)

Treatment	n (total n=14,077)
Curative surgery	3,541 (25.2%)
Curative surgery plus chemotherapy	778 (5.5%)
Palliative surgery	1,176 (8.4%)
Chemotherapy	2,792 (19.8%)
Radiotherapy	1,496 (10.6%)

3.6.2 Treatment costs

Our literature searches and checking of references identified three papers reporting data on costs of treatment of oesophageal cancer (and associated utilities).

Benaglia et al

Data from a UK NHS perspective are available from a paper by Benaglia et al.(22) This study compared endoscopic and non-endoscopic screening for Barrett's oesophagus in patients with a history of gastro-oesophageal reflux disease (GORD) so it does not represent a model of the full treatment pathway.

Costs reported in this paper are based on NHS reference costs for 2007–8 (Table 12) and utilities were derived from NICE guidance on ablative therapy for Barrett's oesophagus.(31)

In the model developed by Benaglia et al., it was assumed that 25% of patients with symptomatic oesophageal adenocarcinoma would be treatable by surgery. Post-operative mortality was assumed to be 4.5% based on 2010 data from the NOGCA. Survivors entered a post-surgery state until they died from either cancer recurrence or other causes. For patients untreatable by surgery, the annual probability of death was assumed to be 0.78. Patients with high-grade dysplasia or intramucosal cancer were treated by radical endotherapy (therapeutic endoscopy), which was assumed to be 93% effective in eradicating dysplasia; 4% of patients treated with endotherapy went on to have surgery. Details of endoscopic surveillance regimens and various supplementary analyses were reported in the paper.(22)

Table 12: Costs and other parameters used by Benaglia et al. (22)

Parameter	Benaglia et al.(22)
Barrett's prevalence	8% (in 50-year-old men with history of GORD symptoms)
Barrett's subtype distribution	No dysplasia 86%; LGD 10%; HGD 2%; IC 2%
Annual transition rates	Normal to BE 0.005; BE to normal 0.0175; BE to LGD 0.0289; LGD to BE 0.1291; LGD to HGD 0.0345; HGD to LGD 0.0476; HGD to IC 0.1187; IC to symptomatic cancer 0.143
Proportion of symptomatic cancer patients suitable for surgery	0.25
Annual mortality in untreatable cancer	0.78
Mortality from other causes	Age-dependent
Mortality from oesophagectomy	0.045 (0.027 for HGD/IC detected by surveillance)
Efficacy of endotherapy	HGD to normal 0.89; HGD to Barrett's without dysplasia 0.04; HGD to LGD 0.0299
Patients needing oesophagectomy after endotherapy	0.04
Mortality from endotherapy	0.0001
Rate of reoperation after oesophagectomy for symptomatic cancer	10.2%
Cost of surgery for cancer	£7514.80
Average length of stay for surgery	12 days
Average length of stay considered by cost code	8.69 days
Excess inpatient stay day cost	£176.45
Post-surgery follow-up (2 outpatient visits/year)	£258.53
Endotherapy (RFA with or without EMR)	£1,135
Endoscopy + biopsy	£517
Cytosponge screening	£100
Utilities No Barrett's	 1.00

Barrett's without dysplasia	0.91
LGD	0.85
HGD/IC	0.77
Symptomatic cancer	0.675
Untreatable cancer	0.4
Surgery for HGD/IC	0.49
Surgery for perforation	0.49
Surgery for cancer	0.414
Post-surgery state	0.863
Endotherapy	0.77

Abbreviations: BE, Barrett's oesophagus; EAC, oesophageal adenocarcinoma; EMR, endoscopic mucosal resection; GORD, gastro-oesophageal reflux disorder; HGD, high-grade dysplasia; IC, intramucosal (subclinical) cancer; LGD, low-grade dysplasia; RFA, radiofrequency ablation

Gordon et al

Gordon et al. have published two papers as part of the Australian Cancer Study Clinical Follow-Up Study. The first paper reports on healthcare resource use and costs associated with management of oesophageal cancer,(32) while the second(33) presents a decision-analytic model of strategies for treating oesophageal adenocarcinoma and Barrett's oesophagus with high-grade dysplasia.

Table 13 summarises key data from these studies (parameters included, utilities and transition probabilities). A disease modelling study of transition from Barrett's oesophagus to dysplasia and cancer is summarised below (section 4.11.3).

Table 13: Costs and other parameters used by Gordon et al. (33)

Parameter	Gordon et al.(33)
Costs ($ AUS, mean (SD))	Oesophagectomy 51,565 (36,749); Neoadjuvant chemoradiotherapy 25,732 (34,693); Radiotherapy for pts treated surgically 5,782 (3,339); EMR (5 years) 12,134; Ablation (5 years) 17,419; Diagnostic tests 2,338 (749); Follow-up in surgically treated patients 11,524 (5,762); Palliative chemoradiotherapy and stenting 10,500; Definitive chemoradiotherapy for patients not treated surgically 17,900; Definitive chemoradiotherapy for patients treated surgically 3,500
Probabilities	Patients in each stage (T1–T4, DM) 0.022, 0.152, 0.228, 0.431, 0.052, 0.115 Treatment for HGD (EMR, ablation, no treatment) 0.85, 0.08, 0.07 EMR of T1 will detect a T1a 0.784 T1a receives ablation 0.9 T1b pt eligible and receives surgery 0.7 T1b pt not receiving surgery will get radiation 0.722 Local recurrence after ablation receiving EMR 0.33 Alive (at 5 years) for recurrent local T1 receiving EMR 0.8 Alive for T1 receiving radiation only Alive after oesophagectomy for T1 tumour 0.636 Alive if HGD receives no treatment 0.6 T1 death from surgery 0.017
Survival (mean, years)	With DM 0.971 For those dying perioperatively 0.5 T1–T2 cases receiving surgery with neoadjuvant therapy 1.805

	T1–T2 not receiving surgery 1.243 T3–T4 receiving neoadjuvant therapy 1.622 T3–T4 not receiving surgery 1.112 Any T stage receiving surgery 1.753
Utilities	Diagnosis of HGD 0.84; T1 or T2 0.838; T3 or T4 0.66; DM 0.345 Successful ablation 0.93 Residual metastases/dysplasia after ablation 0.9 Immediately after oesophagectomy 0.86 Long-term utility following oesophagectomy 0.92

Abbreviations: DM, distant metastases; EMR, endoscopic mucosal resection; HGD, high-grade dysplasia

3.7 Other conditions: Barrett's oesophagus, Dyspepsia, GORD, Peptic ulcer

Other conditions of possible relevance to the economic model because they may be present in people with symptoms of possible OG cancer include Barrett's oesophagus (with or without dysplasia), gastro-oesophageal reflux disease/disorder (GORD/GERD) and peptic ulcer. The term 'dyspepsia' is also frequently used but according to the NICE guidance on GORD and dyspepsia, it has no generally accepted definition.(28) Symptoms associated with dyspepsia include upper abdominal pain, heartburn, acid reflux and nausea or vomiting.

Literature searches have identified two economic evaluations of treatment strategies for dyspepsia.(34, 35) Both studies were conducted in Canada so may be of limited relevance to the UK setting. In addition, Horowitz et al. developed and evaluated a clinical decision support model for upper abdominal complaints in primary care.(36) It appears that this was a paper-based system (not an eRAT) and was focused on management of upper GI tract symptoms rather than referral for possible cancer, which limits its relevance to the ECASS study. This cluster randomised trial, covering eight primary care clinics in Israel, found that patients managed using the decision support system showed more improvement in symptoms and quality of life compared with controls. The intervention group also had fewer GP and gastroenterologist visits, lower medication costs and underwent fewer imaging tests and endoscopies.

3.8 GORD

The NICE definition of GORD covers endoscopically-determined oesophagitis or endoscopy-negative reflux disease (i.e. with no evidence of oesophageal damage or inflammation).

Among people who undergo gastroscopy for upper GI symptoms, about 40% have functional or non-ulcer dyspepsia; 40% have GORD; 13% have peptic ulcer; 2% have gastric cancer; and 1% have oesophageal cancer (http://patient.info/doctor/peptic-ulcer-disease, citing NICE 2004 guidance(27)). This may not reflect the true situation in primary care as not all patients with symptoms are referred for gastroscopy. For example, GORD is often diagnosed by asking the patient about their symptoms. Further testing may only be requested if patients have other symptoms such as difficulty swallowing (dysphagia) or if symptoms do not improve after taking medication to control GORD (see http://www.nhs.uk/Conditions/Gastroesophageal-reflux-disease/Pages/Diagnosis.aspx). The value of

endoscopy for patients with GORD is a topic of debate in the literature.(37, 38) Gastroscopy may confirm the diagnosis of GORD or identify an alternative cause of the symptoms.

3.8.1 Treatment

GORD can be treated using medication such as proton pump inhibitors (PPIs) or surgically. Patients with treated GORD may continue taking a PPI on a long-term basis, generally at a lower dose, to prevent relapse.

3.8.2 HRQoL and outcomes

Assessment of HRQoL in GORD was reviewed by Irvine in 2004.(39) This review reported that several descriptive studies have reported significant HRQoL impairment in GORD patients compared with the general population, similar to other chronic conditions, such as myocardial infarction. Most studies show an improvement in HRQoL following medical or surgical therapy but the author emphasised the importance of evaluating long-term outcomes.

Although GORD was not the main focus of the review, we located three economic modelling studies, one from the UK(40) and two from the USA.(41, 42) A limitation of these studies is that two of them were conducted as long ago as 2002 and are therefore unlikely to reflect current practice and costs. A more targeted literature search would be expected to locate additional relevant studies.

3.9 Peptic Ulcer

3.9.1 Overview

A peptic ulcer occurs when the lining of the oesophagus, stomach or duodenum is corroded by stomach acid and digestive juices. Peptic ulcers can often be distinguished from GORD based on symptoms or presence of *Helicobacter pylori* infection but endoscopy is required for an accurate diagnosis.

3.9.2 Treatment

Treatment normally involves eradication of *H. pylori* and PPIs to reduce acid secretion and allow healing of the ulcer. Surgery may be required if the ulcer fails to respond to drug treatment.

3.9.3 HRQoL and outcomes

Drug therapy promotes healing within 6 to 8 weeks in more than two-thirds of cases (http://www.nmihi.com/u/ucler.htm). In the remaining cases, long-term drug therapy is generally required. In the absence of treatment, complications such as bleeding, perforation or obstruction occur in 20–25% of patients according to a recent review.(43)

The literature on costs and treatments for ulcers overlaps with that on GORD and dyspepsia since eradication of H.pylori and treatment with PPIs is relevant to all three conditions.

3.10 Barrett's oesophagus

3.10.1 Overview

Barrett's oesophagus arises when cells in the lining (epithelium) of the oesophagus are replaced by a type of cell (columnar epithelium) normally found in the small and large intestines (ileum and colon). Over time, Barrett's oesophagus may develop into a pre-cancerous state (dysplasia) and eventually

into oesophageal cancer. Dysplasia is classified as low or high-grade, where high-grade dysplasia represents a higher level of abnormality (i.e., closer to a cancerous state).

Barrett's oesophagus is associated with long-term acid reflux and GORD but not everyone who has acid reflux will go on to develop Barrett's oesophagus. Some people with Barrett's oesophagus have no symptoms and the condition will only be discovered if the person undergoes endoscopy for another reason. The most common symptom is long-term heartburn and indigestion. Other symptoms include nausea, vomiting and difficulty in swallowing. Vomiting blood (haematemesis) is a rare but serious symptom.

Endoscopy (gastroscopy) is needed to diagnose Barrett's oesophagus. Once diagnosed, people often undergo regular surveillance using endoscopy with biopsy to detect any changes in the condition. Changes can occur in both directions, i.e. dysplastic Barrett's oesophagus can revert to a non-dysplastic state as well as vice versa.

3.10.2 Treatment and surveillance

Treatment for Barrett's oesophagus involves lifestyle changes and medication (PPIs) to control symptoms. Surgical procedures (fundoplication or repair of hiatus hernia) may be used to reduce acid reflux. When dysplasia is detected, treatment may be offered to remove the affected area. Treatment may be delivered by endoscopy (for example, endoscopic mucosal resection or radiofrequency ablation (which uses heat to destroy abnormal cells)) or conventional surgery (surgical resection). For high-grade dysplasia, endoscopic treatment is recommended over surgical resection or continued surveillance. Data from the NOGCA indicated that the majority of patients with high-grade dysplasia received endoscopic treatment (67.5%). Only 6.2% of patients underwent curative surgical treatment but 26.2% were managed by continued surveillance contrary to guideline recommendations.(21)

The optimum strategy for surveillance of Barrett's oesophagus is unclear and is a topic of ongoing research. The BOSS study is a randomised trial in the UK comparing surveillance with no surveillance but full publication of this long-term trial is not expected until 2024 (see http://www.nets.nihr.ac.uk/projects/hta/051201). Current evidence from observational studies suggests that surveillance is associated with earlier detection of cancer and improved survival.(44)

Guidelines on surveillance from the British Society of Gastroenterology (published in 2013) are summarised in Table 14.(44)

Table 14: UK guideline recommendations for surveillance of Barrett's oesophagus (44)

Dysplasia	Features of Barrett's oesophagus	Recommended strategy for surveillance
No	Maximum length <3 cm Intestinal metaplasia	Endoscopy every 3 to 5 years
No	Maximum length ≥3 cm	Endoscopy every 2 to 3 years
Yes	Low grade dysplasia	Endoscopy every 6 months; if two consecutive findings of non-dysplastic Barrett's, treat as non-dysplastic
Yes	High grade dysplasia	Therapeutic intervention (e.g. endoscopic resection or ablation)

Other organisations have different recommendations for surveillance of Barrett's oesophagus, highlighting the complexity of decision-making in this area and the need for continuing research.(45)

3.10.3 HRQoL and outcomes

Benaglia et al. (22) estimated the quality of life (utility) associated with Barrett's oesophagus as follows (based on data from NICE guidance)(31):

- No Barrett's 1.00
- Non-dysplastic Barrett's 0.91
- Low-grade dysplasia 0.85
- High-grade dysplasia/Intramucosal cancer 0.77

These authors also estimated annual probabilities of transition between these various states (see section 4.6.2). The utility estimate associated with endoscopic treatment (radiofrequency ablation and/or mucosal resection) was 0.77 (standard error 0.14).(22)

In terms of long-term outcomes, patients with non-dysplastic Barrett's oesophagus may remain under surveillance indefinitely but it is unclear whether such a strategy is cost-effective.(45) The BSG guidelines recommend that discharging patients from surveillance should be considered under certain circumstances (maximum length <3 cm confirmed by a repeat endoscopy and presence of gastric rather than intestinal metaplasia).(44)

3.11 Natural history of OG cancer

3.11.1 Incidence

The main subtypes of oesophageal cancer are squamous cell carcinoma (SCC) and oesophageal adenocarcinoma. Adenocarcinomas are most common in the developed world and SCC in developing countries. SCC arises from epithelial cells lining the oesophagus, while adenocarcinoma arises from glandular cells in the lower part of the oesophagus. Barrett's oesophagus may develop, via dysplasia, into oesophageal adenocarcinoma.(46) The incidence of adenocarcinoma has increased rapidly in recent years. Cancer research UK estimate that over half of oesophageal cancers are adenocarcinomas and this figure is increasing (see http://www.cancerresearchuk.org/about-cancer/type/oesophageal-cancer/about/types-of-oesophageal-cancer). Castro et al. reported data from the Cancer Incidence in Five Continents study that allowed a more precise estimate.(47) Overall 46.2% of oesophageal cancers reported from England, Northern Ireland and Scotland were adenocarcinomas, the frequency being higher in men (57.3%) than women (28.5%). However, although published in 2014, these data appear to refer to the period 1998–2002.

Gajperia et al. reported on 16,319 cases of OG cancer diagnosed in the East of England between 1995 and 2006.(48) During this period, the age-standardised incidence of oesophageal adenocarcinoma and junctional/cardia adenocarcinoma increased, while that of oesophageal squamous cell carcinoma and non-cardia gastric adenocarcinoma decreased. Oesophageal adenocarcinoma and junctional/cardia adenocarcinoma were more than 4 times more frequent in men than women, while the sex ratio was lower for the other cancer types. Just over half (50.7%) of oesophageal cancers and 69.5% of gastric

cancers were classified as adenocarcinomas. Prevalence of each type of OG cancer in the overall sample is summarised in Table 15.

Table 15: Prevalence of different types of OG cancer in patients from Eastern England (48)

Tumour type	n	%
OSCC	2,242	13.7%
OAC	3,726	22.8%
O 'Other defined'	143	0.9%
O 'Poorly defined'	1,243	7.6%
JCA	2,108	12.9%
NCGA	4,765	29.2%
G 'Other defined'	425	2.6%
G 'Poorly defined'	1,667	10.2%
Total	16,319	100%

OSCC, oesophageal squamous cell carcinoma; OAC, oesophageal adenocarcinoma; O, oesophageal; G, gastric; JCA, junctional/cardia adenocarcinoma; NCGA, non-cardia gastric adenocarcinoma

Detailed data on incidence of oesophageal and gastric cancer by age and sex are available from Cancer Research UK (see http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/oesophageal-cancer/incidence and http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/stomach-cancer/incidence). Incidence data by stage appear to be limited, especially for the UK. Lyratzopoulos et al. analysed data for 14,077 patients with OG cancer for the period 1995–2006.(30) Of these, only 440 patients (out of 1,009 diagnosed during 2004–6) had stage information available and few further details were reported in the paper. Data from the US Survival Epidemiology and End Results (SEER) programme for 1998–2009 indicated that 35% of patients with oesophageal cancer had distant metastatic disease at diagnosis, although the number of patients studied was not reported (Table 16).(49)

Table 16: Stage at diagnosis of oesophageal cancer (US data) (49)

Stage at diagnosis	% of patients	5-year survival
Localised	22%	37.8%
Regional (spread to regional lymph nodes)	30%	19.8%
Distant metastasis	35%	3.4%
Unknown	13%	10.5%

3.11.2 Natural history

Data on the natural history of early stomach cancer are available from a study of elderly patients in Japan.(50, 51) Participants were 71 patients diagnosed before 1988 but who were not immediately operated on because of age, infirmity or refusal of treatment. Thirty-six patients (51%) progressed to advanced cancer. After exclusion for partial follow-up, the rate of progression over 5 years was estimated to be 63%. Thirty-eight patients never underwent surgery and 23 of these (61%) died from gastric cancer. Estimated 5-year survival in this group ranged from 63 to 68% depending on how patients with unknown outcomes were allocated. The commentary on the paper noted that this kind of study would be difficult to repeat in the future because of the availability of endoscopic mucosal resection to treat early gastric cancer without the need for major surgery.(50)

3.11.3 Transition from Barrett's oesophagus to cancer

In 2015 Kroep et al. published a model of the long-term natural history of progression of Barrett's oesophagus to oesophageal adenocarcinoma.(46) The study aimed to reconcile different published estimates of the progression rate from Barrett's oesophagus to oesophageal adenocarcinoma derived from population studies and prospective cohort studies. The disparity was suggested to reflect the increased rate of endoscopic surveillance in prospective cohort studies, resulting in preclinical cancers being detected at an earlier stage. This would explain the higher transition rates generally reported in prospective cohort studies.

Kroep et al. calibrated their model to match the annual progression rate reported in population studies (0.18%), then simulated the design of prospective studies by introducing more endoscopic surveillance. The model's predicted progression rates for both types of study and different lengths of follow-up were compared with published data.

For the first 5 years of follow-up, the model predicted an annual progression rate of 0.36% in studies with a prospective design, compared with a rate of about 0.41% reported in published studies. The progression rate for population-based studies was 0.19%. After 20 years, progression rates in both types of study were 0.63 to 0.65%, representing a cumulative cancer incidence of 9.1 to 9.5%. The authors concluded that the 'true' rate of progression during the first 5 years after diagnosis is likely to be closer to the figure from population-based studies than the higher estimates derived from prospective cohort studies.

Key data used in this model are summarised in Table 17. Data sources are referenced in the paper. Preclinical or 'detected' cancer refers to cancer detected endoscopically at a stage before it causes any symptoms. In this model regression from dysplasia to Barrett's oesophagus without dysplasia is possible. Values used in the model were mainly derived from published sources (cited in the paper). The mean times to transition and transition probabilities were defined as 'optimised parameters', i.e. the value quoted is a result of the model.(46)

Table 17: Key parameters in a model of transition from Barrett's oesophagus to cancer (46)

Model parameter	Value used in model
Symptomatic GORD prevalence	20% of total population
BE from symptomatic GORD population	60% of people with BE have symptomatic GORD
BE prevalence in people aged 60–64 years	1.4%
Percentage of LGD in total BE at age 60–65 years	8.2%
Percentage of HGD in total BE at age 60–65 years	1.2%
Annual progression rate from diagnosed BE to clinical EAC	0.07%
Annual progression rate from diagnosed BE to clinical and detected EAC	0.18%
Mean time from preclinical cancer to clinical (symptomatic) cancer	5.0 years
Mean time in BE to next transition	6.7 years
Mean time in LGD to next transition	1.0 years
Mean time in HGD to next transition	1.1 years
Regression transition probabilities	

LGD to BE without dysplasia	88%
HGD to LGD	15%

Abbreviations: BE, Barrett's oesophagus; EAC, oesophageal adenocarcinoma; GORD, gastro-oesophageal reflux disorder; HGD, high-grade dysplasia; LGD, low-grade dysplasia

4 Modelling Methods

4.1 Model Structure:

The model structure was designed with the following principles in mind:

- to reflect key impacts from the conceptual model
- to be parameterisable using available published evidence and data observed in the clinical trial
- to provide an accurate representation of diagnostic referral pathways
- to be a simplification of the real world to allow a model structure that is feasible and not overly complex

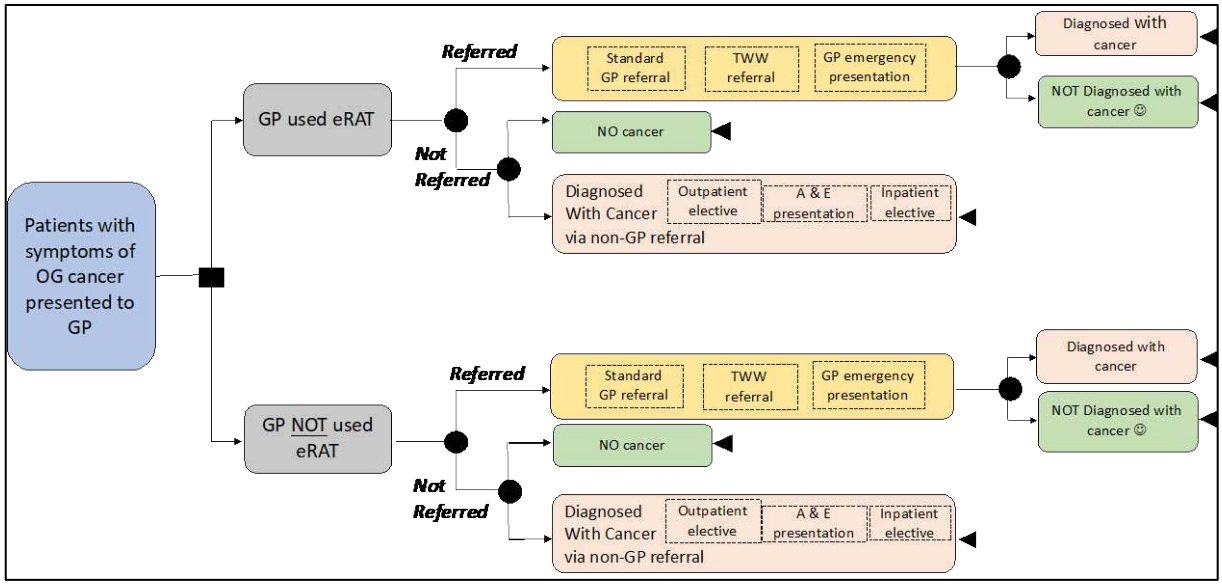
Based on the data observed in the ECASS trial and in the published literature, a simple model structure based on the referral pathway was considered instead of a more complicated structure based on natural history modelling.

A hybrid decision tree and Markov model were developed to simulate the short term and long effects of using the eRAT in patients with symptoms of OG cancer presenting to the GP compared with no eRAT on clinical and cost-effectiveness outcomes. The model population consisted of a cohort of patients aged 68.2 (the mean age of participants in the ECASS trial) with symptoms of OG cancer presenting to the GP.

Short-term model (Decision tree):

A decision tree was constructed to evaluate the short-term (1-year) impact of the eRAT on referral pathways in patients consulting the GP with symptoms of OG cancer (Figure 1).

Figure 4: Decision tree



Black squares represent decision node whether GP used the eRAT or not, black circles represent chance (probabilities) with the branches representing the possible outcome of each option and black triangles represent the terminal node or the final outcome of that decision branch

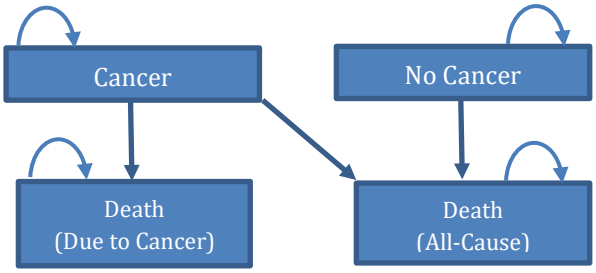
In the model, the initial decision node was whether the GP used the eRAT or not. In both of the scenarios, the GP either would refer the patients for gastroscopy for further diagnosis or would

not refer. The GP could refer the patients with either of three routes: standard referral, two-week wait (TWW) referral and emergency referral, based on the severity level of the symptoms. From each referral pathway, the patient would either diagnosed with cancer or not diagnosed with cancer. Patients who had not been referred for a gastroscopy could still have a chance of being diagnosed with cancer. Diagnosis of cancer in this branch could be through one of the following paths: outpatient elective (in which patients are self-referred), A&E presentation (in the case of severe complications and admitted to emergency wards), and inpatient elective (patients hospitalised for other reasons). The model terminates at the outcome of the patient's cancer diagnosis result. The probabilities associated with each branch of the decision tree were sourced from the ECASS clinical trial. The time horizon of the short-term model was 1-year and no discounting on cost and outcomes was applied.

Long-term model:

To evaluate the long-term impact of the GP using the eRAT, a survival-based Markov model was developed. The model includes four health states: OG cancer, no OG cancer, death (due to OG cancer), and death (all cause) (Figure 2). These health states include patients who have been diagnosed with cancer, or not diagnosed with cancer, coming from different referral pathways in the short-term model. The patients in the "cancer" health state would remain in the same health state over time or die because of cancer or other causes and move to "death (due to cancer or all-cause)" health states. In the "no cancer" health state, the patients would either remain in the same health state over time or die and move to the "death (all-cause)" health state. The long-term model assumed that the patients from the "cancer" health state would not move to the "no cancer" health state or vice versa.

Figure 5: Long-Term Model



The model estimated the probability of being in each of the four health states at the end of each cycle. The model assumed that the health benefits accrued at yearly-spaced discrete time points over the lifetime time horizon.

4.1.1 Perspective

The economic analyses were conducted from NHS health care payer's perspective.

4.1.2 Time Horizon and Cycle Length

Recommendations from several HTA agencies require a lifetime time horizon. The NICE Guide to Methods of Technology Appraisal state that the time horizon should be long enough to reflect the differences in costs and outcomes between the technologies being considered [1]. To enable this, the model approximated a lifetime horizon by calculating over up to 32 years of follow-up of patient aged 68.2 who had symptoms of oesophageal cancer and presented to GP and considered

a lifetime as a base case. The impact of alternative time horizons was explored via sensitivity analyses.

The cycle length in the model was considered to be 1-year. The model also included a half-cycle correction to improve the accuracy of the results.

4.1.3 Discount Rate

As per the NICE guidelines, the health outcomes were discounted at a rate of 3.5% per year [1]. In the model, the cost was considered only for the first year and so was not discounted. To capture uncertainty around the discount rate, sensitivity analyses were performed between 0% and 5%.

4.1.4 Model Output

Model outputs include: total cost per person in each arm, total life-year (LY) and total quality adjusted life-year (QALY) per person in each arm, change in cost, change in LY, change in QALY, incremental cost-effectiveness ratio (ICER), proportion of emergency cases in each arm and proportion of emergency cases avoided per 10,000. The results were presented for long-term model.

4.2 Model Parameters and Assumptions

4.2.1 Clinical Study

The clinical inputs for the model were sourced from the ECASS trial. It is a two-arm, multi-centre, cluster randomised controlled trial with a follow-up of over an 18-month period, across 60 general practices in Cambridge, Teesside and County Durham. Each practice was randomised either to receive the intervention (eRAT) or control (usual care). The summary of patients and baseline characteristic of the study are listed in Table 1 and Table 2

Table 18: Summary of Patients

Summary	Total	Intervention Arm	Control Arm
Eligible patients	5144	1303	3841
Patients invited	1623	434	1189
Patients recruited	530	138	392
Patients recruited as % of those eligible	10.3%	10.6%	10.2%
Patients recruited as % of those invited	32.7%	31.8%	33.0%

Table 19: Baseline Characteristics of Patients by Trial Arm Status

Characteristic	Intervention Arm	Control Arm
Sample Size	N = 138	N = 392
Female, n (%)	84 (60.9%)	225 (57.4%)
Age, mean (SD)	68.4 (8.7)	68.0 (8.6)
Region		

North East, n (%)	27 (19.6%)	227 (57.9%)
Eastern, n (%)	111 (80.4%)	165 (42.1%)

4.2.2 Clinical Inputs

The model used the results from the ECASS trial for the proportion of patients in different referral pathways. As per the trial findings there were around 51% of patients in the intervention arm referred to the GP for diagnosis compared to 49% in the control arm. Most of the patients referred were through a standard pathway or TWW (49% vs 45%; intervention and control arm). In the model, the proportion of patients in different referral pathway based on intervention and control arm were standardised to account for patients referred through "other" routes and missing data. We assumed that people with missing data and referred through "other" routes were distributed amongst referral routes in the same proportions as those referred through standard, 2WW and emergency referral.

To ensure an identical population in both of the arms for comparative analysis, it was important that the proportion of patients diagnosed with cancer in both of the arms was equal. To account for this, a weighted average of those found to have cancer in the two trial arms was taken (1.5 % vs 2.10 %; intervention *vs* control) (i.e. 1.8%) and applied to both the arms in the model.

For the patients who were diagnosed with cancer but not referred through either standard, TWW or emergency referral were assumed to be diagnosed through outpatient elective, A&E presentation or through inpatient elective. The proportions assumed to be referred through each of these routes was sourced from a study conducted by Brookes L et al (2012) [2].

In the model, we have also considered the complications related to gastroscopy such as bleeding. Based on the study by Blero et al (2012), it was considered that around 13 out of 10,000 patients would have bleeding during gastroscopy [3].

Table 3 describes the clinical inputs considered in the model.

Table 20: Inputs on the Proportion of Patients in Each Treatment Pathway

Input Parameter	Mean Value	Distribution used in PSA	Source
Proportion – Intervention (eRAT) Arm			
Proportion of patients referred	51.09%	Beta (70, 67)	ECASS Study
Proportion of patients NOT referred	48.91%	Beta (67, 70)	ECASS Study
Proportion of patients referred via "standard route"	26.28%	Beta (36, 101)	ECASS Study
Proportion of patients referred via "two week wait (TWW)"	22.63%	Beta (31, 106)	ECASS Study
Proportion of patients referred via "emergency route"	0.73%	Beta (1,136)	ECASS Study
Proportion of patients referred via "other route"	1.46%	Beta (2, 135)	ECASS Study
Patient was diagnosed with cancer	1.50%	Beta (2, 134)	ECASS Study
Patient diagnosed with cancer had been referred via standard	100.00%	Beta (2,2)	ECASS Study
Patient diagnosed with cancer had been referred via 2WW	0.00%	Beta (0,2)	ECASS Study
Patient diagnosed with cancer had been referred via Emergency	0.00%	Beta (0,2)	ECASS Study
Patient diagnosed with cancer had been not referred	0.00%	Beta (0,2)	ECASS Study
Proportion - Control Arm			
Proportion of patients referred	48.59%	Beta (189, 200)	ECASS Study
Proportion of patients NOT referred	51.41%	Beta (200, 189)	ECASS Study
Proportion of patients referred via "standard route"	19.11%	Beta (73,309)	ECASS Study
Proportion of patients referred via "two week wait (TWW)"	25.92%	Beta (99,283)	ECASS Study
Proportion of patients referred via "emergency route"	0.79%	Beta (3, 279)	ECASS Study
Proportion of patients referred via "other route"	1.83%	Beta (7, 375)	ECASS Study
Patient was diagnosed with cancer	2.10%	Beta (8, 381)	ECASS Study
Patient diagnosed with cancer had been referred via standard	16.67%	Beta (1,5)	ECASS Study
Patient diagnosed with cancer had been referred via 2WW	83.33%	Beta (5,1)	ECASS Study
Patient diagnosed with cancer had been referred via Emergency	0.00%	Beta (0, 6)	ECASS Study
Patient diagnosed with cancer had been not referred	25.00%	Beta (2, 6)	ECASS Study

Proportion - Other			
Proportion general population outpatient referral	8.00%	Beta (92, 1131)	[1]
Proportion general population inpatient referral	13.50%	Beta (86, 554)	[1]
Proportion general population A&E presentation	27.40%	Beta (72, 192)	[1]
Gastroscopy complication rate	0.13%	Beta (1.3, 998.7)	[2]

4.2.3 Survival Input

The data for one-year survival of the oesophageal cancer patients stratified by the treatment referral route were sourced from Brookes L et al (2012) (Table 4) [2]. The survival rates of the patients who were referred through the standard pathway or TWW pathway were 47% and 42%, respectively. The emergency referral patients had the least survival rate with 18%. For the patients who diagnosed with cancer through outpatient and inpatient elective, the one-year survival rate was around 50%.

Table 21: One-Year Survival Rate of OG Cancer Patients

Referral Pathway	Mean Value	Distribution Used in PSA	Source
Standard Referral	47%	Beta (53,59)	[1]
2WW Referral	42%	Beta (58,79)	[1]
Emergency Referral	18%	Beta (82,373)	[1]
Inpatient Elective	49%	Beta (51,52)	[1]
Outpatient Elective	50%	Beta (50,49)	[1]

To estimate the long-term survival, we sourced the 10-year OG cancer survival data from Cancer Research UK (CRUK) [4]. The data sourced were not stratified by referral route and for the model use, we stratified it using the 1-year survival estimated by Brookes L et al (2012) (Table 4) [2].

Following equation, provide the mathematical form which we used in the model for deriving 10-year survival by referral route from 10-year OG cancer data.

$$S(t = 2)_{referral} = S(t = 1)_{referral} * \frac{S(t = 2)_{overall}}{S(t = 1)_{overall}}$$

$$S(t = i)_{referral}^{i=2\ to\ 10} = S(t = i-1)_{referral} * \frac{S(t = i)_{overall}}{S(t = i-1)_{overall}}$$

overall: Overall OG cancer survival; referral: standard or TWW or emergency or inpatient or outpatient. Separate equation for each referral pathway.

Based on the CRUK data, the 5-years and 10-years survival of the OG cancer patients are 15.1% and 12.3%, respectively [4]. For extrapolation beyond the 10-year time horizon, we derived the relative hazard from the observed data and found that it is decreasing exponentially over time (Figure 3). We extrapolated the relative hazard beyond 10-years using exponential distribution and estimated the survival distribution from that (Figure 4).

To account for the all-cause mortality in the model in people with and without cancer, we used the UK life tables (2015-17) [5]. For people without cancer, this was used directly to estimate survival distribution. For those with cancer, we compared the hazard from the life tables and the hazard resulting from fitting a parametric function for OG cancer survival. The maximum of the two hazards was used in the model. As per the 1-year survival data estimated by Brookes L et al (2012), the survival for the patients who referred through TWW was lower compared to the patients who were referred through standard pathway [2]. However, to make sure both model arms representing the same set of patients with the same overall level of illness, so it is not valid to assume that a particular individual who sees the GP at a particular time point would have shorter survival if they get referred through 2WW instead of standard referral - in fact the faster referral process might mean longer survival. Hence, for the model, as a scenario analysis, we assumed that the cancer survival rate of the patients who were referred through TWW would be the same as for the standard referred patient.

For the patients who were diagnosed with cancer through the non-referral route, we assumed that they were diagnosed through either outpatient elective or inpatient elective or through emergency presentation. For estimating survival for these patients, we have considered the weighted survival based on the survival estimates from inpatient, outpatient and emergency survival probability and the proportions diagnosed through each referral route [2].

Figure 6: Trend of Hazard Rate Over 10-years from Observed Survival Data of Cancer Research UK

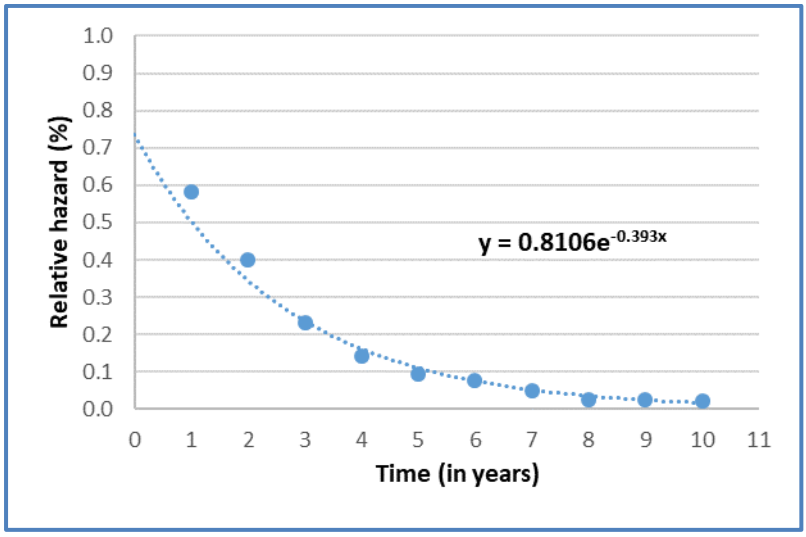
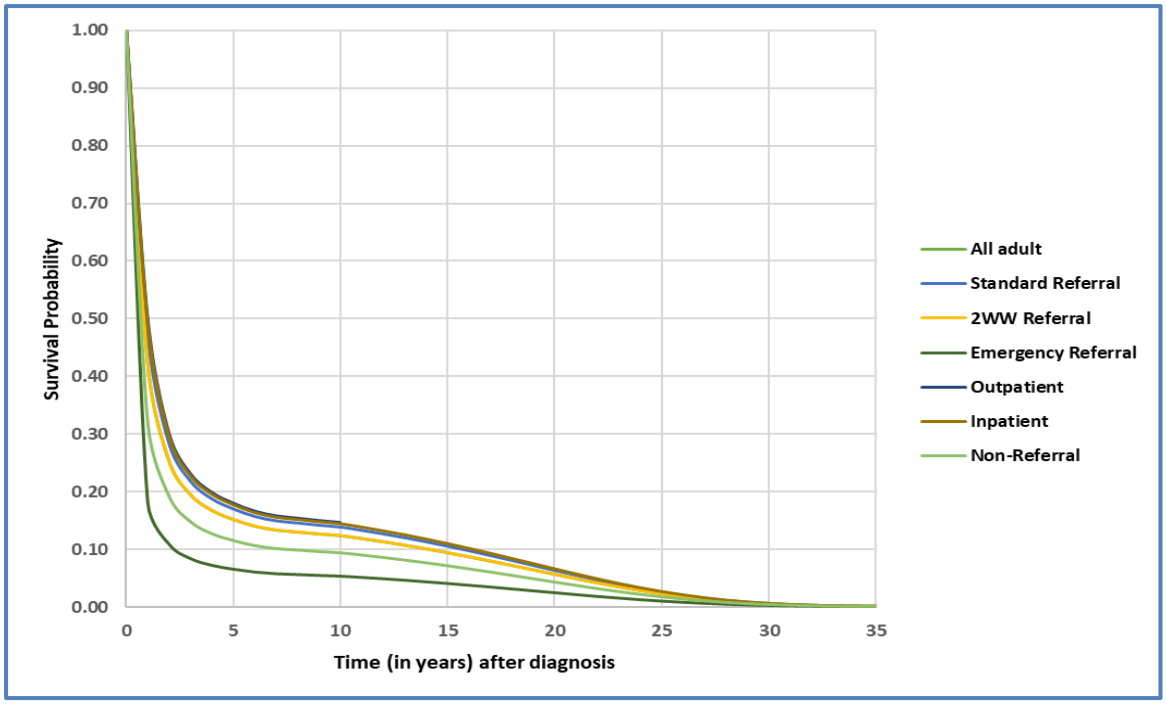


Figure 7: OG cancer Survival by Referral Pathway



4.2.4 Cost Inputs

The cost of gastroscopy for different referral pathways was sourced from NHS reference costs [6]. We assumed that the cost associated with standard GP referral would be the same as the cost of outpatient referral mentioned in the NHS reference cost database. For the TWW referral pathway, we have assumed it to be 10% more compared to the cost of standard referral pathway and we have varied this in a sensitivity analysis. For the emergency referral, the cost of A&E facility cost was added to the inpatient referral cost, as it would be an additional cost, should a patient be referred through an emergency route. The cost associated with gastrointestinal bleeding was also considered in the model and sourced from the NHS reference cost database. In NHS reference cost, a single cost for gastrointestinal bleeding was not provided and for the model, it was calculated as a weighted mean of certain procedures.

For the price of intervention – eRAT, the model assumed that it is a factor of three main components:

1. Cost associated with installation
2. Cost associated with training GPs
3. Cost associated with consultation (due to increase in duration)

Based on the clinical expert advice and study by Porat et al (2017), it was assumed that the consultation length will increase by 2-minutes per patient if the GP used eRAT tool during the consultation [7]. Per minute cost for GP consultation was sourced from PSSRU and the additional 2-minutes cost was estimated to be £6.80 [8]. For the other two components, no detailed costings were available. We therefore performed a threshold analysis and estimated the maximum justifiable cost for installation and training combined, at different willingness to pay thresholds.

The cost associated with cancer treatment was not included in the model as differential cost by referral pathway was not available. Without the inclusion of different costs by referral route, treatment costs (primarily incurred in the first year after diagnosis) will not differ by treatment arm and thus will be differenced out in the incremental cost-effectiveness calculation. In reality,

this means that the model is likely to considerably underestimate the benefits of switching referral pathways and is a significant limitation of the model.

All the costs were inflated to 2019 GBP.

Table 22: Cost Inputs

Cost Parameters	Mean Value	Distribution Used in PSA	Source
Inpatient Referral Gastroscopy	£ 895.00	Uniform (£305, £1,217)	NHS Reference cost (2017-18) Diagnostic Endoscopic Upper Gastrointestinal Tract Procedures, 19 years and over, currency code: FE22Z Lower and upper bounds for uniform distribution were derived from using lower and upper quartile reported in NHS 2016-17 reference cost
Outpatient Referral Gastroscopy	£ 298.00	Uniform (£290, £290) As per NHS 2016-17, same upper and lower quartile were reported and was less than the mean value	NHS Reference cost (2017-18) Diagnostic Endoscopic Upper Gastrointestinal Tract Procedures, 19 years and over, currency code: FE22Z Lower and upper bounds for uniform distribution were derived from using lower and upper quartile reported in NHS 2016-17 reference cost
A & E Facility	£ 149.00	Uniform (£75, £222)	NHS Reference cost (2017-18) Emergency Medicine, No Investigation with No Significant Treatment, currency code: VB11Z Lower and upper bounds for uniform distribution were derived from using lower and upper quartile reported in NHS 2016-17 reference cost
Emergency Referral Gastroscopy	£ 1,044.00	-	Assumption: Inpatient referral + A&E facility
Standard Referral Gastroscopy	£ 298.00	-	Assumption: Same as outpatient referral
2WW Referral Gastroscopy	£ 327.80	-	Assumption: 10% more than the standard referral
Gastrointestinal Bleeding	£ 474	Uniform (£320, £602)	NHS Reference cost (2017-18): Currency code - FD03A, FD03B, FD03C, FD03D, FD03E, FD03F, FD03G, FD03H Lower and upper bounds for uniform distribution were derived from using lower and upper quartile reported in NHS 2016-17 reference cost

4.2.5 Health-Related Quality of Life (HRQoL)

The outcome used in the model were quality-adjusted life years (QALYs). In the model, utility values were used to weight years of life by the quality of life in any given alive health state (cancer and no cancer) in order to estimate QALYs. Generally, EuroQol patient-reported 5-dimension, 3-level instrument (EQ-5D-3L) use to measures generic health status, the results of which converted to population-based utility valuations using published algorithms. It contains five attributes and each attribute has three levels, thus defining 243 possible health states. It is measured on a cardinal scale of 0-1, where 0 indicates death and 1 indicates full health. States worse than death are also accounted for, with such states taking a negative value.

A literature search was undertaken for health utility values for the model. For the patients diagnosed with OG cancer, the utility was sourced from a study by Garside et al (2006) and the mean value considered was 0.675 (standard error 0.19) [9]. For the patients who were not diagnosed with cancer, the utility was sourced from a study by Ara and Brazier et al. (2011) and considered as 0.808 [10].

The model also considered the disutility associated with gastroscopy and with age. The disutility associated with gastroscopy was sourced from Dorian et al (2014), however, in this study, the major bleed was with anticoagulants rather than gastroscopy [11]. In terms of the utility decrement, the cause of major bleed was not considered important and we assumed it would be the same. The value provided in this study was for 2 weeks, which was converted to a 1-year value and considered as -0.006 for the model. For the disutility associated with the age, the data were sourced from Ara and Brazier et al. (2010) and presented in Table 6 [12].

Table 23: Utility Inputs

Utility Parameters	Mean Value	Distribution Used in PSA	Source
Utility of patients diagnosed with cancer	0.675	Beta (32,15)	Garside et al (2006) [4]
Utility of patients NOT diagnosed with cancer	0.764	Beta (18,5)	Ara and Brazier et al. (2011) [5]
Utility decrement due to gastroscopy	-0.006	Normal (0.006, 0.0016)	Dorian et al (2014) [6]
Age-based disutility (coefficients)			Ara and Brazier et al. (2010) [7]
Age (years)	-0.00026	Normal (0.00026, 0.000026)	
Age^2	-0.00003	Normal (0.00003, 0.000003)	
Male	0.02121	Normal (0.2121, 0.0212)	
Intercept	0.95086	Normal (0.95086, 0.09508)	

4.3 Model Analyses

In the base case, a probabilistic analysis was undertaken to estimate lifetime costs and QALYs of patients in both the intervention (GP used eRAT) and control arm (GP not used eRAT). In probabilistic analysis, each key model parameter was given a theoretical probability distribution. A set of selected model parameters were simultaneously varied based on associated probabilities in multiple iterations of simulation. A random number generator was used to draw parameter values from each distribution, and these values were run through the model to generate estimates for the cost-effectiveness analysis. It was performed using a second-order Monte Carlo simulation and included 10,000 iterations. Whenever available, the standard error of the selected distribution was obtained directly from the same data source that informed the mean value. In the absence of data, the standard error for each parameter was assumed to be equal to 10% of the mean value.

The following preliminary assumptions for input parameter distributions and the standard error (SE)/deviations (SD) were applied:

- Parameters associated with proportions of patients in both arms were assigned a beta distribution. The parameters of beta distribution- number of events and non-events were sourced from the trial data, wherever possible. In the absence of trial data, SE was assumed to be the 10% of mean.
- Utility parameters associated with cancer diagnosis were assigned a beta distribution with assuming SE as 10% of mean.
- Parameters of age-based disutility and utility decrement were sampled from normal distribution with assuming SE as 10% of mean.
- One-year survival input of different referral pathway was assumed to follow beta distribution with SE as 10% of mean value.
- For costs, due to unavailability of published interquartile range in NHS reference costs 2017-18, we derived upper and lower quartile using NHS reference costs 2016-17 and sampled from uniform distribution

In the model, maximum justifiable cost analysis for eRAT was also undertaken and was one of the key outputs of the model. It was not possible to estimate the real-world cost of using the eRAT per person presenting to the GP with symptoms (combining the costs of installation and training), as there were several elements of the trial that would probably not be replicated in practice. Instead, a maximum justifiable cost analysis was carried out to estimate what the maximum cost of installation and training could be whilst still allowing the intervention to be cost-effective.

A one-way sensitivity analysis was also performed to assess the impact of the uncertain parameters upon the model results. The following sensitivity analyses have been undertaken:

1. **Change in discount rate:**

   In the base case, the discount rate of 3.5% was considered for the health outcome, and no discount rate was considered for the cost, as it was assumed that the cost would incur at only first year. We have undertaken the sensitivity analysis over this parameter and varied at a different rate - 0% (undiscounted) and 5%.

2. **Change in cost of gastroscopy when referred via TWW pathway:**

   In the model for the base case, we have taken an assumption that the cost of gastroscopy, when referred via TWW pathway, would be 10% more costly compared to the patients referred via standard pathway. To check the uncertainty around this assumption, we have varied it and conducted sensitivity analysis by assuming 1) cost of gastroscopy (TWW) would be same as of cost of gastroscopy (standard), and 2) cost of gastroscopy (TWW) would be 50% more costly compared to the patients referred via standard pathway.

3. **Assuming 2WW and standard referral pathway has same survival**

   In the base case we assumed the survival in TWW, and standard referral pathway are different based on the evidence from Brookes L et al (2012). However, in real-world scenario in longer term, the survival of the patients who referred through TWW may be better or equal compared to the patients who referred through standard referral pathway. This is because that the patients in TWW got access to cancer diagnosis earlier than the patients who referred through standard referral. Hence, as a scenario, we assumed TWW and standard referral pathway has same survival.

4. **No complication with gastroscopy**

   In the base case, the model assumes that the patients would have complication during the gastroscopy. However, as a scenario we have tested the model results by removing any complications and assumed patients would go through the gastroscopy with ease.

4.4 Results

4.4.1 Base-Case Analysis:

Table 7 presents the results of long-term probabilistic model (time horizon: lifetime). The model predicted that the QALY was not significantly different in eRAT and control arm . The QALY estimated in eRAT arm was 9.73 (95% CrI: (7.51, 11.30)) and in control arm was 9.70 (95% CrI: (7.48, 11.27)) with incremental gain in eRAT arm as 0.0281 (95% CrI: (-0.0145, 0.0708)) .

The eRAT is also projected to prevent 17 (95% CI: 3; 216) emergency referrals per 10,000 individuals consulting the GP with symptoms. The maximum justifiable cost for eRAT installation and training per person consulting the GP with symptoms is estimated to be £568 (95% CI: -£265; £1,402) assuming a willingness to pay threshold of £20,000 per QALY. The 95% credible intervals indicate that the results are highly uncertain and there is a 9.7% probability that the eRAT produces a QALY loss and an 8.8% probability that any cost at all for eRAT installation and training would be too high to enable the eRAT to be cost-effective at the £20,000 willingness to pay threshold.

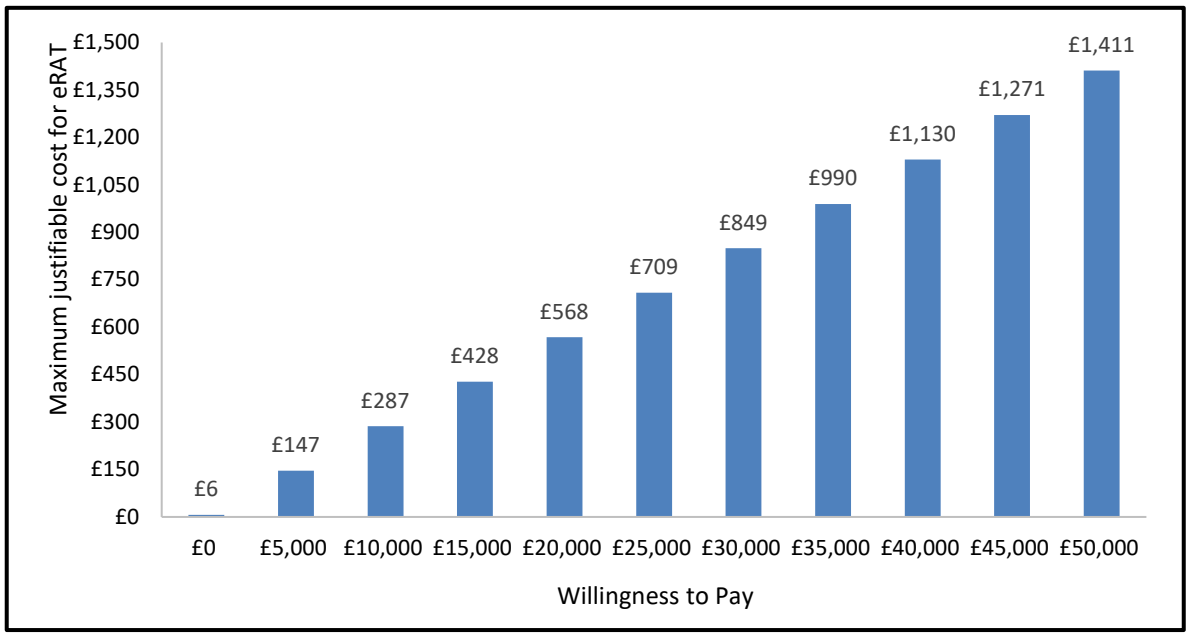
Table 24: Base Case Analysis Result (Probabilistic)

	Intervention Arm GP used eRAT (95% CrI)	Control Arm GP NOT used eRAT (95% CrI)
Long term model (lifetime time horizon) – Discounted		
Total cost per person (assuming eRAT installation + training cost = £0)	£540 (£358, £734)	£547 (£355, £742)
Total life-years per person	12.1970 (12.1474,12.2282)	12.1890 (12.1371, 12.2230)
Total QALY per person	9.7270 (7.5018, 11.2984)	9.6989 (7.4795, 11.2612)
Cost- difference (assuming eRAT installation + training cost = £0)	-£ 6 (-£53, £29)	
LY-difference	0.0081 (-0.0142, 0.0346)	
QALY - difference	0.0281 (-0.0145, 0.0708)	
Maximum Justifiable Costs of eRAT installation and training at Willingness to Pay of £20,000	£568 (-£265, £1,402)	
Emergency referral prevented (per 10,000 people)	17 (3,216)	

4.4.2 *Maximum Justifiable Cost for eRAT installation and training*

Figure 5 presents the results of probabilistic threshold analyses conducted for the estimation of the maximum justifiable cost for eRAT per person who had symptoms of OG cancer and presented to the GP. The Y-axis of the bar chart shows the cost of eRAT installation and training per person presented to GP with oesophagus cancer symptoms and the Y-axis shows the willingness to pay (maximum allowed cost per unit QALY gained). At the willingness to pay of £20,000/QALY, the maximum allowed cost of eRAT installation and training per person was found to be £568 and anything more than this would make eRAT arm not cost-effective.

Figure 8: eRAT Maximum Justifiable Cost



4.4.3 *One-Way Sensitivity Analysis:*

To assess the robustness of the model results, one-way sensitivity analyses (OWSAs) were conducted by varying one model input or assumption at a time. Table 8 summarises the variables assessed and the resulting outcome.

Across the one-way sensitivity analyses, the maximum justifiable cost of eRAT installation and training per person ranged from £481 (with 5% discount rate) to £881(with no discounting). The OWSAs results are consistent with the model base-case probabilistic results.

When discount rate of 5% was considered, the eRAT is projected to save 0.024 QALY and 0.007 life-years per person with maximum justifiable cost for eRAT installation and training per person as £481 (95% CrI: -£219; £1,185) assuming a willingness to pay threshold of £20,000 per QALY. With not applying discounting, eRAT arm saved 0.044 QALYs and 0.011 life-years; with maximum justifiable cost for eRAT installation and training per person as £881 (95% CrI: -£447; £2,200) assuming a willingness to pay threshold of £20,000 per QALY.

Varying cost of gastroscopy when referred via TWW pathway, didn't had much impact on the maximum justifiable cost and was estimated as £567 (95% CrI: -£265; £1,399), if considered the

cost as same as standard referral, and £573 (95% CrI: -£267; £1,414), if cost of TWW referral was assumed to 50% more than the standard referral.

The analyses based on assuming TWW referral survival as same as standard referral survival and not assuming gastroscopy complications had very minimal impact on the results.

Table 25: Mean incremental PSA results for eRAT compared with no eRAT, per person consulting the GP with OG cancer symptoms. Results are presented for the base case and for a series of one-way sensitivity analyses. 95% credible intervals are shown in brackets.

	Δ QALYs (95% CrI)	Δ LYs (95% CrI)	Emergency Referrals Prevented (per 10,000 people)	Max Justifiable Cost (WTP: **£ 20,000)** (95% CrI)
Base case	**0.028 (-0.014, 0.071)**	**0.008 (-0.014, 0.035)**	**17 (3; 216)**	**£569 (-£265; £1,402)**
Discount Rate = 0%	0.044 (-0.024;0.111)	0.011 (-0.020;0.048)	17 (3; 216)	£881 (-£447; £2,200)
Discount Rate = 5%	0.024 (-0.012;0.060)	0.007 (-0.012;0.030)	17 (3; 216)	£481 (-£219; £1,185)
TWW referral cost = standard referral cost.	0.028 (-0.014;0.070)	0.008 (-0.014;0.035)	17 (3; 216)	£567 (-£265; £1,399)
TWW referral cost = 50% higher than standard referral cost.	0.028 (-0.014;0.070)	0.008 (-0.014;0.035)	17 (3; 216)	£573 (-£267; £1,414)
TWW referral survival = standard referral survival	0.028 (-0.014;0.071)	0.008 (-0.014;0.034)	17 (3; 216)	£565 (-£268; £1,401)
Exclude gastroscopy complications	0.028 (-0.014;0.071)	0.008 (-0.014;0.034)	17 (3; 216)	£568 (-£265; £1,402)

4.5 Discussion

The present study estimated the cost-effectiveness of using eRAT by GPs for diagnosis of OG cancer for patients presenting with symptoms. The results indicate that use of the eRAT could lead to improvements in patient health and potentially be cost-effective and even cost saving if the intervention cost (cost of eRAT installation and training) could be minimised. These benefits arise partly due to an overall reduction in unnecessary referrals in people without OG cancer, leading to reduced cost and fewer gastroscopy complications; and partly due to a shift towards diagnosis through standard GP referral pathways in the people who do have OG cancer, rather than missing them at the GP resulting in expensive emergency diagnosis, with poorer survival, at a later date when their cancer has possibly progressed. Information about OG cancer stage at diagnosis was not collected in the ECASS trial, so it was not possible to assess whether individuals missing out on GP referral were indeed being diagnosed at a later stage.

This is a first economic modelling study for assessing the cost-effectiveness of any electronic diagnostic tool in cancer. The model has a simple and transparent structure based on the referral pathway in order to maximise the use of limited available data. Another advantage with the study is that it evaluates both the short term (using decision tree model structure) and long-term (using Markov model structure) costs and outcomes.

The model also has some limitations. The biggest limitation is the lack of data. The proportion of patients going through different referral pathways in each arm were sourced from the ECASS trial. The clinical trial data has a small sample size and thus, there were very few patients diagnosed with cancer. The lack of reliability of the results from the trial (due to small sample size) increase the uncertainty around the model analysis results as evidenced by the 95% credible intervals. In addition, the trial did not collect data on the patients' stages of cancer. Thus, we could not model the natural history of the disease. Another limitation is that we could not source the costs for cancer treatment via different referral pathways, which is likely to have had a substantial impact on the total estimated costs.

This study will guide future research in the area by providing a first estimate of cost effectiveness for eRAT intervention. There is a need of further database analysis to estimate the cost of cancer treatment for each treatment pathway. Also, a larger trial, with more sample size and more data recorded on the outcomes of interests would be helpful in implementing a more comprehensive model, which would include the natural history of the disease. This trial should include data about cancer stages and survival of people diagnosed as well as of people who were not referred by the GPs.

Overall, we have found that eRAT usage by GPs could be cost effective compared to no usage for the diagnosis of OG patients, depending upon the cost of eRAT installation and training. However, these results should be assessed with caution in the light of limited data available at hand, and future research should be done to gather more relevant data to complement the analysis.

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