Health Information and Quality Authority

An tÚdarás Um Fhaisnéis agus Cáilíocht Sláinte

Health Technology Assessment of Scheduled Procedures

Referral thresholds for patients with upper gastrointestinal symptoms suspected of indicating malignancy

November 2014

Safer Better Care

About the Health Information and Quality Authority

The Health Information and Quality Authority (HIQA) is the independent Authority established to drive high quality and safe care for people using our health and social care services. HIQA's role is to promote sustainable improvements, safeguard people using health and social care services, support informed decisions on how services are delivered, and promote person-centred care for the benefit of the public.

The Authority's mandate to date extends across the quality and safety of the public, private (within its social care function) and voluntary sectors. Reporting to the Minister for Health and the Minister for Children and Youth Affairs, the Health Information and Quality Authority has statutory responsibility for:

- **Setting Standards for Health and Social Services** – Developing person-centred standards, based on evidence and best international practice, for those health and social care services in Ireland that by law are required to be regulated by the Authority.
- **Supporting Improvement –** Supporting health and social care services to implement standards by providing education in quality improvement tools and methodologies.
- **Social Services Inspectorate** – Registering and inspecting residential centres for dependent people and inspecting children detention schools, foster care services and child protection services.
- **Monitoring Healthcare Quality and Safety** – Monitoring the quality and safety of health and personal social care services and investigating as necessary serious concerns about the health and welfare of people who use these services.
- **Health Technology Assessment** – Ensuring the best outcome for people who use our health services and best use of resources by evaluating the clinical and cost effectiveness of drugs, equipment, diagnostic techniques and health promotion activities.
- **Health Information** – Advising on the efficient and secure collection and sharing of health information, evaluating information resources and publishing information about the delivery and performance of Ireland's health and social care services.

Table of Contents

1 Upper gastrointestinal symptoms

1.1 Scope of this health technology assessment

This health technology assessment (HTA) evaluates the appropriateness and potential impact of introducing clinical referral or diagnostic thresholds for people with upper gastrointestinal (GI) symptoms in Ireland. The effectiveness of these investigations may be limited unless undertaken within strict clinical criteria. This report is one of a series of HTAs of scheduled procedures. Details of the background to the request and general methodology are provided in the separate 'Background and Methods' document.[1]

The scope of this HTA is to investigate clinical referral and diagnostic thresholds that can be used in the assessment, referral and diagnosis of adults who are suffering from upper gastrointestinal (GI) symptoms in Ireland. Inputs from an Expert Advisory Group along with a review of the clinical and cost-effectiveness literature were used to inform the criteria. Additionally, the budget impact and resource implications were assessed, as appropriate.

1.2 Background

The upper gastrointestinal (GI) tract consists of the oropharynx (back of the mouth and the throat), the oesophagus (gullet), the stomach, duodenum and jejunum (part of the small bowel). Related structures that can also give rise to symptoms include the liver, gallbladder and pancreas. Symptoms which may indicate pathology of the upper GI tract include difficulty swallowing ('dysphagia'), heartburn ('acid reflux'), indigestion ('dyspepsia' - pain or discomfort in the upper abdomen), blood in the vomit ('haematemesis'), and weight loss.

Dyspepsia is the fourth most common symptom presenting for diagnosis in primary care.[2] It is not in itself a diagnosis, but rather acts as an umbrella term for symptoms including upper abdominal discomfort, bloating, nausea and early satiety. In the UK, it has been estimated that approximately 40% of the population will, at some time, have dyspepsia, about 20% of the population use medications for symptom relief and 2% lose time from work because of dyspepsia.[2]

Gastro-oesophageal reflux disease (GORD) is the most common disorder of the upper GI tract. It results from failure of the gastro-oesophageal sphincter, with reflux of stomach acid into the oesophagus. Postulated risk factors included hiatus hernia, certain foods, alcohol and smoking, pregnancy, obesity and a genetic component.[3;4] Implicit in definitions of GORD is that tissue injury is not necessary to fulfil disease criteria.[5] In Western Countries, 10-40% of the population suffer heartburn, which is

the main symptom of GORD,[6] although it is noted that respiratory symptoms due to GORD (chronic cough, hoarseness, bronchospasm, recurrent aspiration) may occur in the absence of typical heartburn.[4] A community-based study in Teeside, UK, reported a prevalence rate of 28.7% for GORD symptoms; 24.9% had consulted their GP about their symptoms in the previous year (this accounted for 7.9% of the total population in Teeside). Heartburn when lying flat (45.3%) or which woke patients from their sleep (28.8%) and dyspepsia (17.1%) were the most common symptoms reported.[7] In Ireland, medications for acid-related disorders were prescribed over 3.8 million times in 2012 on the General Medical Scheme (GMS) alone; they cost €70.8 million euro and accounted for 7.5% of the total GMS budget spend.[8]

Around 50% of people with GORD also have oesophagitis, which is inflammation of the lower end of the oesophagus. Severe, longstanding GORD can lead to a condition known as Barrett's oesophagus in approximately 10% of individuals;[4] this is characterised by abnormal changes in the cells at the lower end of the oesophagus and is regarded as a precursor for oesophageal adenocarcinoma (see below).[6] It is recognised, however, that GORD symptoms have poor specificity and sensitivity as predictors of cancer risk; approximately 40% of patients who develop oesophageal adenocarcinoma have no heartburn, and the yearly risk among persons aged 50 years or older who have heartburn has been estimated at just 0.04%.[5]

A peptic ulcer is a collective term for ulceration of the stomach or duodenum. Helicobacter pylori (*H. pylori*) is a bacterial agent which is thought to be responsible for 90-95% of duodenal ulcers and 70-80% of stomach ulcers.[6] Prevalence rates for *H. Pylori* infection range from as high as 80% in developing countries to between 20 and 50% in developed countries.[9] Infection with *H. pylori* is a cofactor in the development of three important upper gastrointestinal diseases: duodenal or gastric ulcers (reported to develop in 1 to 10% of infected patients), gastric cancer (in 0.1 to 3%), and gastric mucosa-associated lymphoid-tissue (MALT) lymphoma (in 0.1 to 3%).[10] It is classified as a 'group 1 human carcinogen' for gastric adenocarcinoma (see below).[11] Non invasive methods of detection of *H. pylori* include serology, C-urea breath test, and a test based on the detection of Helicobacter stool antigen.[12] Alternatively, a biopsy can be taken from the stomach and tested for its presence. Non steroidal anti-inflammatory drugs (NSAIDs) are the main cause of *H. pylori*–negative ulcers.[10]

Gastric cancer refers to tumours of the stomach that arise from the gastric mucosa (adenocarcinoma), connective tissue of the gastric wall (gastrointestinal stromal tumours), neuroendocrine tissue (carcinoid tumours), or lymphoid tissue (lymphomas).[13] Gastric adenocarcinoma accounts for more than 90% of cancers of

the stomach.[9] As noted above, *H. pylori* is a recognised risk factor for gastric adenocarcinoma and carries a relative risk of gastric cancer of 3.05 (95% confidence interval 1.92-4.74). It should, however, be noted that the vast majority of patients infected with *H. pylori* will not develop gastric adenocarcinoma; while more than two billion people are infected worldwide, fewer than 0.5% will develop gastric adenocarcinoma.[13] Other risk factors for gastric cancer include cigarette smoking, high alcohol intake, excess dietary salt, lack of refrigeration for food, inadequate fruit and vegetable consumption, and pernicious anaemia.[13] It is twice as common in men as women. It has been noted that 33% of patients with gastric cancer in NHS England present through an emergency route on their way to being diagnosed with cancer.[14]

According to the National Cancer Registry, there are approximately 526 new cases of gastric cancer diagnosed in Ireland each year. These represent 2.7% of all invasive cancers diagnosed, and gastric cancer is the seventh most common invasive cancer diagnosed overall. Incidence rates of gastric cancer in men and women are 15.6 and 7.5 per 100,000 population per year, respectively. The cumulative lifetime risk of gastric cancer in men and women is 1.2% and 0.5%, respectively. Approximately 327 people die of gastric cancer each year. Five-year relative survival from gastric cancer has improved from 17.0% between 1994 and 1999 to 23.9% between 2008 and 2010.[15] Between 2005 and 2011, inclusive, 3,510 people were diagnosed with gastric cancer;[16] their age profile is outlined in Table 1.1. For those in whom the method of detection was known, ≥96% was on the basis of symptoms. Modelling work performed by the National Cancer Registry has suggested that, while incidence is predicted to decrease over time, demographic changes to the population will result in an increase in the number of cases diagnosed annually of gastric cancer between 2010 and 2040; increases of approximately 32%-74% in females and 27%-59% in males were suggested, with proportionate increases in treatment rates.[17]

The two main histological types of oesophageal cancer are adenocarcinoma and squamous cell carcinoma (SCC). The incidence of oesophageal adenocarcinoma has risen more rapidly than that of any other cancer in many Western countries since the 1970s, particularly among white men; the UK has the highest reported incidence worldwide, for reasons yet unknown. The two main risk factors for oesophageal adenocarcinoma are obesity and GORD, whilst those for SCC of the oesophagus are tobacco smoking and alcohol consumption.[18] It has been noted that 22% of patients with oesophageal cancer in NHS England present through an emergency route on their way to being diagnosed with cancer.[14]

According to the National Cancer Registry, there are approximately 384 new cases of oesophageal cancer diagnosed in Ireland each year. These represent 2.0% of all

invasive cancers diagnosed, and oesophageal cancer is the 14th most common invasive cancer diagnosed overall; it is, however, the sixth most common invasive cancer causing death. Incidence rates of oesophageal cancer in men and women are 11.9 and 5.0 per 100,000 population per year, respectively. The cumulative lifetime risk of oesophageal cancer in men and women is 1.0% and 0.4%, respectively. Approximately 359 people die of oesophageal cancer each year. Five-year relative survival from oesophageal cancer has improved from 11.2% between 1994 and 1999 to 15.1% between 2008 and 2010.[19] Between 2005 and 2011, inclusive, 2,594 people were diagnosed with oesophageal cancer;[16] their age profile is outlined in Table 1.1. For those in whom the method of detection was known, at least 96% was on the basis of symptoms. Modelling work performed by the National Cancer Registry has suggested that demographic changes will result in an increase in the number of cases of oesophageal cancer diagnosed annually in Ireland of approximately 84%-123% in females and 112%-160% in males, between 2010 and 2040, with proportionate increases in treatment rates.[17]

Table 1.1 National Cancer Registry Data, Oesophageal and Gastric Cancer, 2005-2011[16]

		Gastric Cancer	Oesophageal Cancer
		No. Diagnosed (%)	**No. Diagnosed (%)**
Year of Diagnosis	2005	455	338
	2006	477	343
	2007	494	399
	2008	506	363
	2009	538	378
	2010	545	369
	2011	495	404
	Total	**3,510**	**2,594**
Age	<40	69 (2.0%)	26 (1.0%)
	40-49	206 (5.9%)	134 (5.2%)
	50-59	414 (11.8%)	388 (15.0%)
	60-69	810 (23.1%)	707 (27.3%)
	70-79	1,168 (33.3%)	713 (27.5%)
	80+	843 (24.0%)	626 (24.1%)
	Total	**3,510**	**2,594**

Functional gastrointestinal disorders are defined by symptoms in the absence of any structural abnormalities. They are associated with a range of symptoms, including globus (feeling of a lump in the throat), non-cardiac chest pain, functional dyspepsia in the upper GI tract, and irritable bowel syndrome (IBS) in the lower GI tract. These

disorders are characterised by poorly understood abnormalities of gut motility and sensory perception.[6] At least 40% of persons who undergo investigation for upper GI symptoms have no evidence of oesophagitis or gastric or duodenal ulceration and are considered to have non-ulcer or functional dyspepsia.[20] In many instances, however, it is not possible to distinguish between functional disorders and more serious disease without the use of special investigations or tests.[6]

1.3 Procedures, potential complications and alternative treatments

A number of options are available to the clinician when a patient complains of upper GI symptoms. For some patients immediate referral for specialist opinion will be warranted; the vast majority, however, are managed in the first instance with either a 'test and treat' strategy for *H. pylori* or a trial of empirical medical therapy and lifestyle modification(s) such as smoking cessation and reduction of alcohol consumption. This is particularly the case for those suspected of suffering from GORD or dyspepsia; many will have already self-medicated with over-the-counter treatments and will be prescribed a course of 'proton pump inhibitors' (PPI) or H2 receptor antagonists (H2RA) aimed at reducing acid secretion. The patient, and their associated clinical signs and symptoms, will dictate the extent to which further investigation(s) are required.

Upper GI endoscopy, otherwise known as a gastro-oesophago-duodenoscopy (OGD), involves the passage of a flexible endoscope through the mouth, throat, oesophagus, stomach, and duodenum, and is generally performed as a day case under sedation or with topical anaesthesia to the oropharynx. This procedure facilitates visualisation of the gastrointestinal mucosa and, where a suspicious lesion is seen, it also allows biopsies to be taken for definitive diagnosis. In patients with signs or symptoms severe enough to merit endoscopy, 40% have functional or non- ulcer dyspepsia, 40% have GORD and 13% have some form of ulcer.[3] Large series report adverse event rates of 1 in 200 to 1 in 10,000 and mortality rates ranging from none to 1 in 2,000.[21] Cardiopulmonary adverse events related to sedation and analgesia account for approximately 60% of complications following upper GI endoscopy, with a rate in large, national studies of between 1 in 170 and 1 in 10,000.[21] Prospective multicentre registries, meanwhile, report rates of oesophageal perforation of between 1 in 2,500 and 1 in 11,000; this complication is associated with a mortality rate of between 2 and 36%.[21]

Potential alternatives to upper GI endoscopy include a barium swallow test (an X-ray examination of upper GI structures using contrast material called barium), capsule endoscopy and abdominal ultrasound scan. Oesophageal pH monitoring may be used

to diagnose GORD. Oesophageal manometry – which assesses movement (peristalsis) and pressure within the oesophagus may be used in the investigation of achalasia (a disease which causes inability of the oesophageal smooth muscle to relax, leading to dysphagia). A full assessment of the relative merits of these investigations is beyond the scope of this report.

1.4 Current practice in Ireland

Patients with upper GI symptoms are generally referred by their general practitioner (GP) or by another hospital specialist to a gastroenterologist, general or upper GI surgeon. In some cases, patients with these symptoms may also be referred to an otolaryngologist. Referral or treatment thresholds (similar to those discussed in Section 2 below) may be used by GPs, gasteroenterologists and surgeons in Ireland to identify eligible candidates for referral or treatment. However, it is unclear if such thresholds are being used, or how consistently they are being applied. It is also unclear the extent to which initial management of symptomatic patients varies according to geographic location or clinician specialty; this particularly relates to the availability and use of the urea breath test in the diagnosis and management of *H. pylori.*

Upper GI endoscopy is a routine scheduled diagnostic procedure within the publicly-funded healthcare system in Ireland. The Hospital In-Patient Enquiry (HIPE) system was employed during this HTA to assess activity levels in relation to upper GI endoscopy. This procedure may be coded as the principal procedure or as a secondary procedure. For consistency and completeness, data are reported to include the principal and secondary procedures (that is 'all procedures') with all data presented on this basis. The International Classification of Diseases (ICD) intervention codes used to retrieve this data are listed in Appendix 1.1.

The HIPE system reports that there were approximately 73,914 patients who underwent upper GI endoscopy in 2012. Of these, 60,030 (81.2%) patients were admitted for their procedure on an elective (planned procedure) basis. This data captures procedures provided as hospital day case and inpatient procedures, as in the other HTA reports in this series. Of the 60,030 procedures carried out in the pure elective setting 57,793 (96.3%) were reported as being done on a day case basis. A total of 2,237 procedures were carried out on inpatient basis, with an average length of stay (ALOS) of 9.4 days; it is likely that the majority of these patients were admitted for investigation and work-up, and would not have been in hospital for upper GI endoscopy alone. It is also noted that the average length of stay for these patients decreased from 11.2 days in 2005 to 9.4 days in 2012.

The 60,030 elective upper GI endoscopies recorded within the HIPE system in 2012 were performed across 42 different hospital sites (range 2 – 6,200 procedures per hospital). These institutions are categorised according to their hospital groups in Table 1.2. Any variation in practice may be explained by differing catchment sizes or the availability of a particular medical or surgical service, hospital size or specialisation.

Table 1.2 HIPE data for elective upper GI endoscopy in adults per HSE hospital group* (2012)[22]

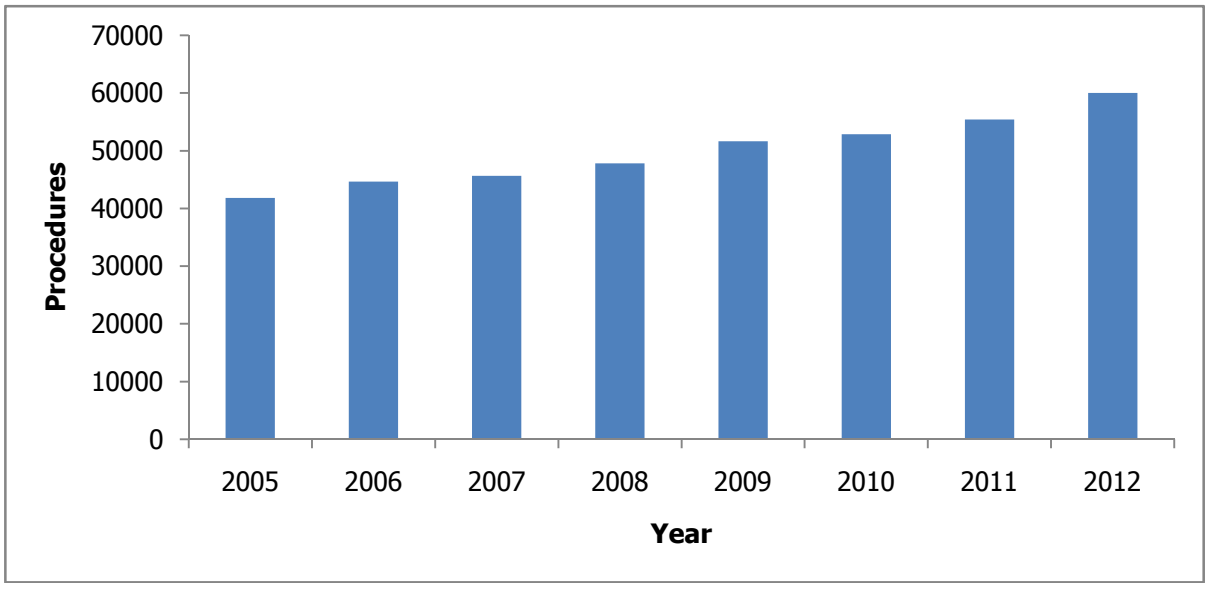
Hospital group	Number (%) (Range)	% Day Case (Range)	Average age (years)
Dublin North East	12,528 (20.9%) (508-3,268)	98.2 (96.6-99.9)	52.8
Dublin Midlands	12,674 (21.1%) (2-6,200)	97.5 (94.6-100)	52.4
Dublin East	11,480 (19.1%) (84-2,787)	97.1 (73.8-98.8)	52.5
South/South West	9,740 (16.2%) (517-2,145)	91.9 (84.9-98.4)	53.2
West/North West	8,995 (15.0%) (531-3,248)	96.8 (94.9-98.3)	53.3
Midwest	3,971 (6.6%) (759-1,572)	96.2 (94.5-99.5)	53.1
Total	60,030 (100)	96.3	52.4

*Key: Range – the range in terms of number of procedures performed in individual institutions within the hospital group. * See Appendix 1.1 for HIPE codes; HIPE data includes all activity in publicly-funded hospitals, including procedures in patients that used private health insurance.*

As part of the HIPE coding process, the principal diagnosis is recorded at the time of procedure, but may not be synonymous with the preoperative diagnosis. In 2012, the principal diagnosis – at the time of elective upper GI endoscopy – was coded as 'gastritis and duodenitis' (22.7%); the next most frequently coded diagnoses were 'diaphragmatic hernia' (12.6%), GORD (9.0%) and 'other disease of the oesophagus' (8.1%).

In addition to the activity levels in public hospitals, there were 329 procedures procured by the public healthcare system via the National Treatment Purchase Fund (NTPF), from private hospitals, between 2005 and 2012. Data on the total number of procedures undertaken in the publicly-funded system are shown in Figure 1.1.

Figure 1.1 Number of elective upper GI endoscopies provided through the publicly-funded healthcare system in Ireland, 2005-2012



Key: Numbers includes all procedures performed in public hospitals and all publicly-funded procedures performed in private hospitals.

The number of elective upper GI endoscopies undertaken in the publicly-funded healthcare system has increased by 44% from 41,803 in 2005 to 60,038 in 2012; there has been an increase of 34% in the number of elective GI endoscopies undertaken in those aged less than 55 years of age, with an increase of 56% in activity in those aged 55 years or older. The average age of patients undergoing upper GI endoscopy in 2012 was 52.4 years; 42.4% were aged less than 50 years, while 24.9% were aged less than 40 years (Table 1.3).

Table 1.3 HIPE data for elective upper GI endoscopy – breakdown by age (2012)[22]

Age	<30	30-39	40-49	50-59	60-69	70-79	≥80
Number Procedures (2012)	7,062	7,849	10,500	11,612	11,898	8,010	3,099
% of Total	11.8	13.1	17.5	19.3	19.8	13.3	5.2

See Appendix 1.1 for HIPE codes; HIPE data includes all activity in publicly-funded hospitals, including procedures in patients that used private health insurance.

The length of time a patient must wait to be reviewed varies according to the referral pathway and the individual hospital and consultant to which a patient is referred. At the end of July 2014, it was reported that there were 360,753 patients on the Outpatient Waiting List database collated by the NTPF, 34.7% of whom were waiting longer than six months, with 10.5% on the list for longer than 12 months.[23] Speciality-specific figures were published at the end of July 2014 – referrals to general surgery (including 'gastrointestinal surgery') constituted 11.3% (37,436) of the total waiting list at that time.[24]

Initiatives are underway by the HSE to standardise the management of outpatient services and to ensure consistent management processes across all publicly-funded healthcare facilities that provide outpatient services. This includes the publication of a protocol for the management of these services by the NTPF in January 2013 that provides the core guidance of the Outpatient Services Performance Improvement Programme.[25] The protocol specifies that patients should be treated based on clinical urgency, with urgent referrals seen and treated first. It is intended that the definition of clinical urgency and associated maximum wait times is to be developed at speciality or condition-level and agreed by the clinical programmes.

In January 2013, the NTPF published a national waiting list management policy that outlines the standardised approach to managing scheduled care treatment for inpatient, day case and planned procedures in all publicly-funded hospitals.[25;26] It outlines a consistent structured approach that must be adopted in the management of the waiting list; monitoring of the implementation of the policy will be routinely undertaken by the NTPF in the form of annual quality assurance reviews. Specifically in relation to GI endoscopy (includes colonoscopy [examination of the bowel] and oesophago-gastro-duodenoscopy (OGD) [examination of the gullet and stomach]), the HSE has stated that no patient should wait more than four weeks for an urgent endoscopy from time of referral; they are also monitoring the number of patients waiting longer than 13 weeks from referral to the time of their procedure.[27] However, the signs and symptoms that constitute an urgent referral have not yet been formally defined. At the end of July 2014, there were 11,521 patients waiting

for GI endoscopy; of these, 3,162 (27.4%) were waiting longer than three months, with 373 (3.2%) patients waiting longer than six months.[28] The HSE's National Performance Assurance Report, meanwhile, reported that at the end of July 2014 there were 3,247 people waiting over 13 weeks following a referral for a routine colonoscopy or upper GI endoscopy. While it did not comment on those patients referred for urgent upper GI endoscopy, it did report that no patient referred for an urgent colonoscopy was waiting for longer than four weeks.[23]

Direct access endoscopy (DAE) is now offered at some institutions in Ireland. This has been defined as "an endoscopic procedure requested by a general practitioner and carried out without selection by a hospital consultant";[29] however, it is noted that it is standard practice in most endoscopy centres for all referral letters to be triaged by the hospital consultant with consideration given as to the type of procedure to be undertaken, the timing of the procedure (within 4 or 13 weeks) and whether the patient should be initially reviewed as an outpatient. A report by the Irish College of General Practitioners published in 2013, noted that 64% of GPs surveyed reported having direct access to endoscopy (57% within public system, 85% within private system).[30]

In 2013, Beaumont Hospital, Dublin published findings from its DAE service over a seven-year period from its implementation in 2004. Over this time, 4,262 patients were referred for DAE by their general practitioner; oesophageal cancer was diagnosed in seven patients and gastric cancer in 27 patients, representing a diagnostic yield overall of 0.8% (34/4,262) for upper GI cancers. The report highlighted the fact that 27 of these 34 patients with upper GI cancer were over the age of 55 years of age; hence, the diagnostic yield of identifying an upper GI cancer in patients over 55 years through the DAE program was 2.25% and conversely, in the under 55 age group, the diagnostic yield was 0.3%. Other diagnoses included peptic ulcer disease (4.3%) and Barrett's oesophagus (3.5%); 3,734 (87.6%) of patients had a normal upper GI endoscopy.[29]

2 Clinical referral/treatment threshold

2.1 Review of the literature

A comprehensive review of the literature was conducted during April 2014 to identify international clinical guidelines and health policy documents describing diagnostic thresholds that are in place in other healthcare systems. It also considered systematic reviews and economic evaluations examining the effect of the introduction of those thresholds. The approach and general search terms are

described in Appendix 1 in the 'Background and Methods' document, and a summary of the results is included in Table 2.1. A summary of the clinical guidelines identified from the search and thresholds in use elsewhere are provided in Appendices 1.2-1.4 and 1.6, respectively.

During the assessment process, feedback was provided from the expert clinician group regarding a number of conditions for which surveillance is generally not warranted. A critical review of the literature retrieved for GORD and dyspepsia was completed and a further review of the literature was undertaken to retrieve the evidence underpinning these recommendations. The conditions identified by the clinicians were: atrophic gastritis, pernicious anaemia, fundic or hyperplastic gastric polyps, gastric or intestinal metaplasia, and in asymptomatic patients with a history of duodenal ulcer or oesophagitis.

Table 2.1 Summary of literature search results

Publication Type	Number	References
Clinical Guidelines	21	(2-5;31-48)
Commissioning Guidance	3	(49-51)
Cost-Effectiveness Studies	5	(52-56)

2.2 Clinical evidence

The principal aim of this report is to identify a referral threshold for patients with upper GI symptoms which suggest the need for specialist review. The majority of the relevant literature surrounding this topic concerns patients with dyspepsia and, or GORD. Although these symptom complexes are discussed in detail below, the identification of optimal management strategies in primary care is beyond the scope of this report.

Where possible, dyspepsia and GORD are dealt with separately for clarity. It is recognised, however, that there can be significant overlap between dyspepsia and reflux-type (GORD) symptoms. Indeed, the National Institute for Health and Care Excellence (NICE) in the UK has published 2014 updated guidelines for dyspepsia *and* GORD.[3] These state that consideration should be given to referral for a specialist opinion for patients of any age with gastro-oesophageal symptoms that are

persistent, non responsive to treatment or unexplained, for patients with suspected GORD who are thinking about surgery, and for patients with *H. pylori* who have persistent symptoms that have not responded to second-line eradication therapy. Specific recommendations from the NICE report in relation to dyspepsia and GORD are outlined in their respective sections below.

The American Society for Gastrointestinal Endoscopy (ASGE) also published guidelines on the appropriate use of upper GI endoscopy that were not symptom-complex specific.[32] These guidelines are included in Appendix 1.2. In 2005, the Canadian dyspepsia working group (CANDYS) published its recommendations regarding the management of uninvestigated dyspepsia in primary care – its definition of dyspepsia included GORD symptoms; recommendations relevant to this report are also included in Appendix 1.2.[48]

A number of the guidelines discussed in the following sections include information on 'alarm' symptoms which require urgent investigation. These are listed in Appendix 1.3.

Dyspepsia

The NICE guidelines (2014) suggest that, for those who present with dyspepsia, which has not previously been investigated ('uninvestigated'), *H. pylori* testing and treatment has not been demonstrated to produce better patient outcomes than endoscopy with initiation of treatment based on procedure findings, although they note considerable variation in study findings regarding patient outcomes. However, studies have consistently demonstrated that 'test and treat' strategies dramatically reduce the need for endoscopy (by approximately two thirds). For some patients with an inadequate response to therapy, it may become appropriate to refer to a specialist for a second opinion. For those who have previously had an endoscopy, the guidance suggests that, in the absence of any new alarm signs, clinicians should consider continuing management according to previous endoscopic findings. Age is not discussed as a factor when discussing referral.[3]

In its commissioning guidance, meanwhile, the British Society for Gastroenterology (BSG) suggested that the majority (>95%) of dyspepsia should be managed in primary care, with those patients less than 55 years of age without alarm features being managed with *H. pylori* 'test and treat' and empirical PPI strategies. It goes on to state that patients with alarm symptoms need prompt investigation, as do those older than 55 years of age with genuinely new significant dyspepsia.[34] The Maastricht IV/Florence Consensus Report on the management of *H. pylori* concurred with the adoption of a 'test and treat' strategy for uninvestigated dyspepsia in

populations where *H. pylori* prevalence is high (>20%). This later report noted that this approach should be subject to local cost-benefit considerations and is not applicable to patients with alarm symptoms, or older patients (age to be determined locally according to cancer risk).[42]

Allum et al. published guidelines for the management of oesophageal and gastric cancer on behalf of the Association of Upper GI Surgeons of Great Britain and Ireland (AUGIS), the British Society of Gastroenterology (BSG) and the British Association of Surgical Oncology (BASO), in 2011. This states that all patients with recent onset dyspepsia over the age of 55 years and all patients with alarm symptoms (whatever their age) should be referred for rapid access endoscopy with biopsy. Although 'rapid' was not explicitly defined, the paper makes reference to the UK Department of Health guidelines regarding urgent referral which is taken to mean within two weeks.[31]

In 2009, Toward Optimized Practice (TOP), the Alberta, Canada-based guideline development organisation identified four 'alarm' features in its guideline (Appendix 1.3). This document suggests that patients older than 50 years of age with new onset of symptoms, or those with alarm features, or those who fail repeated trials of therapy, warrant careful assessment and timely investigation, preferably including endoscopy, with barium swallow as a potential alternative.[2] Its full guideline algorithm is included in Appendix 1.2 of this report.

The British Columbia Medical Association also published its guidelines in 2009.[33] This separates those with dyspepsia into those with and without alarm features (Appendix 1.2). While referral for upper GI endoscopy is recommended for the former cohort, those without alarm symptoms are deemed to be more appropriately managed in primary care, with management dictated by the extent of symptoms. This was based on the rationale that malignancy is an unlikely diagnosis in the absence of any alarm features, especially in patients under 55 years of age. Those with mild or infrequent symptoms can be managed with non-prescription acid-reducing medications, while those with more persistent symptoms can either be tested and treated for *H. pylori* infection or else treated with empiric therapy.[33]

In 2007, the American Society of Gastrointestinal Endoscopy (ASGE) published its guideline regarding the role of endoscopy in the management of dyspepsia.[38] This states that those patients with dyspepsia:

- who are older than 50 years of age and/or those with alarm features should undergo endoscopic evaluation

- who are younger than 50 years of age and without alarm features may undergo an initial 'test and treat' approach for *H. pylori*
- who are younger than 50 years of age and are *H. pylori* negative can be offered an initial endoscopy or a short trial of PPI acid suppression
- who do not respond to empiric PPI therapy or have recurrent symptoms after an adequate trial should undergo endoscopy.

In 2004, the Scottish Intercollegiate Guidelines Network (SIGN) published its guidelines on the management of dyspepsia.[46] This was followed in 2006 by publication of its guidelines regarding the management of oesophageal and gastric cancer.[47] Both of these documents advocated the need for initial management of uncomplicated dyspepsia (no 'alarm' features, not associated with NSAID use) with a 'test and treat' *H. pylori* policy for those who are less than 55 years old; those with recurrent or persistent symptoms after treatment should be considered for further assessment, including endoscopy. The 2006 document stated that those with GORD in the absence of 'alarm' features (Appendix 1.3) do not require endoscopy.[47] Of importance in the 2004 guidelines, and in contrast to other guidelines, the authors noted that there was no evidence to support the mandatory use of early upper GI endoscopy to investigate patients over 55 years old who present with new onset uncomplicated dyspepsia, and that these patients should only be referred if their symptoms persist *after* initial management with the *H. pylori* 'test and treat' strategy.[46] This guidance was altered in the 2007 Scottish 'referral guidelines for suspected cancer', in which it was stated that urgent referral was warranted for dyspepsia in a patient aged 55 years or more with at least one of the following 'high risk' features (Appendix 1.4):

- onset of dyspepsia less than one year ago
- continuous symptoms since onset.[57]

The 2007 Scottish referral guidelines for suspected cancer also suggested that urgent referral was warranted for those with dyspepsia combined with at least one of the following known risk factors:

- family history of upper GI cancer in more than two first-degree relatives
- family history of colorectal cancer (familial adenomatous polyposis [FAP]), hereditary non-polyposis colorectal cancer [HNPCC])
- Barrett's oesophagus
- pernicious anaemia
- peptic ulcer surgery over 20 years ago
- known dysplasia, atrophic gastritis, intestinal metaplasia.[57]

NICE published its referral guidelines for suspected upper GI cancer in 2005.[43] This categorises patients according to the presence or absence of dyspepsia, and makes recommendations in relation to the indications for urgent referral within both groups (Appendix 1.2). For those patients who are referred for endoscopy, the guidelines suggest that they should ideally be free from acid suppression medication, including PPIs or H2RAs, for a minimum of two weeks, and patients should have a full blood count taken where possible.[43] The 2013/2014, NHS England commissioning guidance states that an urgent referral for endoscopy should be made for patients matching the requirements set out in NICE's 2005 document (Appendix 1.2).[14] Similarly, the guidelines published by the New Zealand Guidelines Group in 2009 adopted the NICE recommendations.[45]

In its 2004 guidelines regarding dyspepsia and heartburn, the New Zealand Guidelines Group advocated a review of lifestyle factors and current medications.[44] For those with heartburn, clinicians were advised to manage patients with measures addressing GORD (PPIs, H2RAs, antacids, alginate). For those with dyspepsia, but no heartburn meanwhile, clinicians were advised to either: offer initial treatment with H2RAs or domperidone, or, if patients were aged less than 50 years and in an area with *H. pylori* prevalence of greater than 30%, clinicians could test and treat for *H. pylori*. In the case of recurrent undifferentiated dyspepsia, the guidelines suggested that patients should be referred for OGD if four to 12 weeks of treatment had failed to bring about a response.

In summary, there exists a clear list of 'alarm' or 'red flag' symptoms that warrant immediate referral for review in secondary care. The consensus emanating from the guidelines discussed thus far is that patients with uncomplicated dyspepsia, in the absence of alarm symptoms, should be managed with a *H. pylori* 'test and treat' policy in primary care in the first instance, with referral for specialist opinion, including endoscopy where indicated, reserved for those who do fail to respond. The caveat to this statement is that those older than 55 years of age, with new onset dyspepsia, should be referred for urgent review within four weeks to secondary care.

GORD

The NICE guidelines (2014) suggest that endoscopy should not routinely be offered to diagnose Barrett's oesophagus, but should be considered if the person has GORD. These guidelines suggest that the person's preferences should be discussed and their individual risk factors (for example, long duration of symptoms, increased frequency of symptoms, previous oesophagitis, previous hiatus hernia, oesophageal stricture or oesophageal ulcers, or male gender) considered.[3]

In 2013, a national commissioning guide for GORD in the UK was jointly published by the Royal College of Surgeons (RCS) and the Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland (AUGIS), with NICE accrediting the process.[49] This guide lists a number of indications for urgent referral (Appendix 1.3). It goes on to suggest that initial management should involve lifestyle changes and medical therapy. Indications for referral for specialist opinion include when the patient's quality of life remains significantly impaired and there are persistent symptoms despite initial management, or if the patient expresses a preference to consider surgery rather than continue long term medical treatment. It is suggested that clinicians should perform a GerdQ Questionnaire (see Appendix 1.5) to identify the degree of symptom burden before onward referral as this can be useful in postoperative follow up.[49]

The American College of Gastroenterology published its guidelines on the diagnosis and management of GORD in 2013.[40] The authors stated that a presumptive diagnosis can be made from typical symptoms of heartburn and regurgitation, and empiric medical therapy with a PPI was recommended in this setting; screening for *H. pylori* was not recommended in patients with GORD and the authors stated that treatment of *H. pylori* infection is not routinely required as part of anti-reflux therapy. The authors also noted that patients with chest pain should have a cardiac cause excluded prior to the commencement of a GI evaluation. Non responders to conservative management should be referred for evaluation. They stated that upper GI endoscopy is *not required* in the presence of typical GORD symptoms, but *is* recommended for those with alarm symptoms and for screening of patients at high risk of complications. Repeat endoscopy was not indicated for patients with Barrett's oesophagus in the absence of new symptoms.[40]

The American College of Physicians published its clinical guidelines regarding upper GI endoscopy for GORD in 2012.[5] These guidelines also suggest that upper GI endoscopy *is* indicated in those with typical GORD symptoms that persist despite a therapeutic trial of four to eight weeks of twice daily PPI therapy. They also stated that it *is* indicated in those with:

- heartburn and alarm symptoms
- severe erosive oesophagitis after a two month course of PPI therapy, to assess healing and rule out Barrett's oesophagus. Recurrent endoscopy after this follow-up examination is not indicated in the absence of Barrett's oesophagus.
- a history of oesophageal stricture who have recurrent symptoms of dysphagia.

The guideline also suggested that upper GI endoscopy *may* be indicated:

- In men older than 50 years with chronic GORD symptoms (symptoms for more than five years) and additional risk factors (nocturnal reflux symptoms, hiatal hernia, elevated body mass index, tobacco use, and intra-abdominal distribution of fat) to detect oesophageal adenocarcinoma and Barrett's oesophagus.
- For surveillance evaluation in those with a history of Barrett's oesophagus. In men and women with Barrett's oesophagus and no dysplasia, surveillance examinations should occur at intervals no more frequently than three to five years. More frequent intervals are indicated in patients with Barrett's oesophagus and dysplasia.

In 2011, the Gastroenterological Society of Australia (GESA) published the fifth edition of its guidelines on GORD in adults. This concurs with the guidance of the American College of Gastroenterology in that it states that young patients who have longstanding mild, typical reflux symptoms and no alarm symptoms may be given a trial of therapy without investigation. It goes on to suggest that further investigation is warranted if the diagnosis is unclear, symptoms are persistent or refractory to treatment, complications are suspected or alarm symptoms are present. Specifically in relation to upper GI endoscopy, the guidelines state that early endoscopy is indicated for patients with alarm symptoms (see Appendix 1.3); endoscopy may also be indicated where: there is diagnostic uncertainty such as mixed, non-specific or atypical symptoms; symptoms are refractory to initial treatment; it forms part of preoperative assessment; and where provision of reassurance is required when verbal reassurance is inadequate. It further states that endoscopy should be considered for those with longstanding frequent troublesome symptoms, to tailor drug treatment, and to detect and manage Barrett's oesophagus.[37]

The British Columbia Medical Association noted the influence of obesity as a risk factor in its guidelines on GORD, published in 2009.[4] These guidelines note that in the absence of alarm features (see Appendix 1.3), barium X-ray and endoscopy are frequently normal and are thus not recommended. Noting that it may take between four and eight weeks to see a response to conservative measures, the guidelines note that endoscopy is the investigation of choice for those who fail to respond.

In 2008, the American Gastroenterological Association (AGA) published its position statement on the management of GORD.[39] This report recommended endoscopy and biopsy for patients with oesophageal GORD syndrome with troublesome dysphagia, and for those with suspected oesophageal GORD syndrome who have not responded to an empirical trial of twice daily PPI therapy. The position statement noted that endoscopically monitoring patients with chronic GORD symptoms has not been shown to diminish the risk of cancer, and that this practice was discouraged.[39]

In 2007, the ASGE suggested that if the patient's history is typical for uncomplicated GORD, an initial trial of empiric medical therapy is appropriate prior to endoscopy in most patients. They stated that endoscopy at presentation should be considered in patients who have symptoms suggestive of complicated disease or those at risk for Barrett's oesophagus. A number of other indications for endoscopy were also noted (Appendix 1.2).[41] In a separate report in 2012, the ASGE stated that an initial screening endoscopy may be appropriate in selected patients with multiple risk factors for Barrett's oesophagus and oesophageal adenocarcinoma (for example, male sex, white race, age older than 50 years, family history of Barrett's oesophagus, increased duration of reflux symptoms, smoking, and obesity), but patients should be informed that there is insufficient evidence to affirm that this practice prevents cancer or prolongs life.[36]

As noted in the section on dyspepsia, the New Zealand Guidelines Group recommended initial management of GORD (excluding those with 'alarm' symptoms or aged greater than fifty years at first presentation) with PPIs, H2RA, antacids and alginate.[44] They suggested that treatment should continue for between three and six months, with upper GI endoscopy recommended for those who fail to respond or whose symptoms recur within one month after ending treatment.

The use of referral thresholds by primary care trusts (PCT) in the English NHS has been common practice for several years. As part of the changes to the NHS brought about by the Health and Social Care Act 2012, PCTs and strategic health authorities (SHAs) ceased to exist on 31 March 2013. Their responsibilities were taken over by clinical commissioning groups and the NHS Trust Development Authority, and a number of national commissioning guidelines have been published including the one on GORD discussed above.[49] However, the thresholds that were previously developed by these trusts are likely to represent ongoing practice at a local level while new commissioning guides are being established. Examples of two local clinical commissioning guides are included in Appendix 1.6.

For patients with GORD-dominant symptoms, there is thus a consensus that, in the absence of alarm symptoms, patients should be trialled on a course of empiric PPI therapy and advised in relation to appropriate lifestyle change; referral should then be considered for those who fail to respond to this initial management, if the diagnosis is unclear, or if patients voice a preference for surgery over long-term medical therapy.

Other conditions

As noted, during the assessment process expert clinician feedback was provided recommending that surveillance endoscopy is generally not indicated for the following conditions: atrophic gastritis; pernicious anaemia; fundic or hyperplastic gastric polyps; gastric intestinal metaplasia; and in asymptomatic patients with a history of duodenal ulcer or oesophagitis. The evidence to support this recommendation was sought from the international clinical guidelines and health policy documents that describe diagnostic and surveillance thresholds that are in place in other healthcare systems.

In 2012, the American Society of Gastrointestinal Endoscopy (ASGE) published its appropriate use of endoscopy guideline based on a critical review of available information and broad clinical consensus.[32] They state that sequential or periodic esophagogastroduodenoscopy (EGD) is generally not indicated for:

- Surveillance for malignancy in patients with gastric atrophy, pernicious anemia, fundic gland or hyperplastic polyps, gastric intestinal metaplasia, or previous gastric operations for benign disease.
- Surveillance of healed benign disease, such as esophagitis and gastric or duodenal ulcer.

The NICE guidelines (2014) emphasise that the harms of endoscopic surveillance may outweigh the benefits in people who are at low risk of progression to cancer.[3] The 2006 guidance from the Scottish Intercollegiate Guidelines Network (SIGN) states that there is limited evidence to support endoscopic surveillance for pernicious anaemia noting that it has not been appraised in a randomised controlled trial and that case series studies in patients with pernicious anaemia generally do not support the use of endoscopic surveillance to try to identify early cancers.[47] Similarly guidelines from New Zealand (2004) note that they do not currently recommend endoscopy surveillance for intestinal metaplasia.[44] Allum et al. published guidelines (Improving Outcomes Guidance [IOG]) for the management of oesophageal and gastric cancer on behalf of the Association of Upper GI Surgeons of Great Britain and Ireland (AUGIS), the British Society of Gastroenterology (BSG) and the British Association of Surgical Oncology (BASO), in 2011. This noted that individuals at increased risk of oesophago-gastric cancer on the basis of a premalignant condition (including pernicious anaemia, intestinal metaplasia of the stomach or previous gastric surgery) may be considered for endoscopic monitoring, but that decisions are complex and should be determined by balancing the magnitude of the benefits against the perceived clinical risks of the procedure and patient preferences.[31] This is not inconsistent with the 2013 AUGIS commissioning guideline which presents a care pathway which suggests urgent referral for patients with atrophic gastritis or intestinal metaplasia if they present with worsening reflux.[58] Finally, while the

European Society of Gastrointestinal Endoscopy (2012) recommends that there is no evidence to support surveillance for patients with mild to moderate atrophy or intestinal metaplasia restricted to the antrum, they note endoscopic surveillance should be offered to patients with extensive atrophy and, or intestinal metaplasia.[35]

Therefore there is broad consensus in clinical guidelines that surveillance with endoscopy is generally not indicated for patients with atrophic gastritis or pernicious anaemia, fundic or hyperplastic gastric polyps, gastric intestinal metaplasia and in asymptomatic patients with a history of duodenal ulcer or oesophagitis. However, it is noted that decisions are complex and should be determined by balancing the potential clinical benefits and risks of the procedure, with consideration given to the referral of patients who develop new or progressive symptoms.

2.3 Cost-effectiveness evidence

A number of cost-effectiveness analyses have been published that have examined the relative value of various initial management strategies, for example, comparing an initial test and treat strategy with empirical PPI therapy in patients with uncomplicated dyspepsia.[52;53] However, the management of dyspepsia in the primary care setting is beyond the scope of the present work. The NICE guidelines (2014) regarding dyspepsia and GORD note that no cost-utility analyses were identified that assessed the benefits and harms of endoscopy in previously uninvestigated patients who, following some treatment, remain symptomatic or develop new symptoms.[3] Three economic evaluations were retrieved that examined the role of early (prompt) endoscopy in patients with dyspepsia; these are discussed in detail below. An evidence table summarising the data extracted is included in Appendix 1.7. For ease of review, all costs presented have been inflated using the local consumer price index for health to 2013 values and then converted to Irish Euro using the latest Purchasing Power Parities.

A 2009 study by Vakil et al.[54] aimed to determine the prevalence of upper GI malignancies and other serious abnormalities in primary care patients with uncomplicated dyspepsia, and to determine the cancer yield and cost of setting different age thresholds for early endoscopy, in a multinational population of dyspeptic patients. The cost of upper GI endoscopy was calculated using three values - €93, €280, and €466, corresponding to a low, intermediate, and high cost environment. The authors studied 2,471 patients who underwent endoscopy; abnormalities were detected in 635 patients (23%) and the prevalence of upper GI malignancy was 0.22%. The authors reported that if early endoscopy was limited to all dyspeptic patients aged 50 years or older, one oesophageal cancer and no gastric cancers would have been missed; with an age cut off set at age 55 years, three

patients with cancer (2 gastric and 1 oesophageal) would have been missed. If the age threshold for early endoscopy were set at 50 years, at a cost of €466/endoscopy, it would cost €77,289 (95% CI, €33,297 €233,079) to detect each case of cancer; a limitation of this study was that stage of cancer and resectability were not recorded, and thus a formal analysis of the cost-effectiveness of endoscopy could not be undertaken.[54]

In 2005, Ford et al.[55] published a meta-analysis comparing *H. Pylori* test and treat with prompt upper GI endoscopy for the management of dyspepsia using data from 1,924 patients across five randomised controlled trials (RCTs). Although the authors noted that the latter was associated with a small, but statistically significant, benefit in terms of symptom resolution, over a 'test and treat' approach, they concluded that the prompt endoscopy strategy is not cost-effective at a realistic level of willingness-to-pay for cure of dyspepsia.[55]

A 2003 Cochrane review, considered the cost-effectiveness of four different initial management approaches for patients with dyspepsia: initial pharmacological therapy (including endoscopy for treatment failures), early endoscopy, testing for *H. pylori* and endoscope only those with a positive finding, and *H. pylori* eradication therapy with or without prior testing.[56] The authors concluded that it is unlikely that early endoscopy would result in a reduction in overall economic costs of managing dyspepsia over only one year. Although the authors suggested that it is more likely that an initial excess cost would be incurred that may be recouped in some prescribing and consultation reductions in subsequent years, the point at which early endoscopy may become cost neutral, if at all, could not be determined. In contrast to the study by Ford et al., the Cochrane review reported no differences between the strategies in terms of symptom outcome.[56]

To summarise, the limited economic literature available suggests that a *H. pylori* 'test and treat' strategy is at least as cost-effective as a prompt endoscopy approach in patients with dyspepsia. This, of course, is a general statement, and does not pertain to particular patient subgroups, nor does it refer to patients with alarm symptoms.

2.4 Budget impact and resource implications

The number of elective upper GI endoscopies provided through the publicly-funded healthcare system has increased by approximately 43.7% since 2005. The current estimated annual national cost of elective upper GI endoscopies is €44.2 million, with an average weighted cost per inpatient case of €7,719, and an average weighted cost per day case patient of €466, based on the latest Casemix costs (Appendix 1.8). This markedly higher cost for inpatients reflects the previously noted reality that

many of these patients are in hospital for reasons other than their endoscopy, and many will have a protracted length of stay. The estimated annual national cost of elective upper GI endoscopies performed solely in the day case setting is €29.9 million.

2.5 Advice on clinical referral/treatment threshold

Taking account of the available evidence that exists in relation to upper gastrointestinal symptoms and the associated risk of malignancy, the following threshold criteria are advised for referral and treatment within the publicly-funded healthcare system in Ireland:

In the absence of alarm features (see below), patients with new onset dyspepsia or GORD should be triaged by age:

- Those aged 55 years or older should be referred for urgent review and, or investigation (including endoscopy where appropriate) within four weeks.
- Those aged less than 55 years should be trialled with a test and treat strategy for *H. Pylori*, or empirical treatment with a proton pump inhibitor for an appropriate length of time, with referral to secondary care considered for those who fail to respond to maximal conservative therapy.

Patients with dyspepsia or GORD, who also present with one or more of the following 'alarm' signs or symptoms should be referred for an urgent review and, or upper endoscopy within four weeks:

- dysphagia ('difficulty swallowing')
- odynophagia ('painful swallowing')
- progressive unintentional weight loss
- haematemesis and, or melaena
- recurrent unexplained vomiting or regurgitation of food
- new onset early satiety
- confirmed and unexplained iron deficiency anaemia
- clarification of an epigastric mass or abnormal finding on radiology imaging
- worsening symptoms with known Barrett's oesophagus.

Patients who present with evidence of a significant acute upper GI bleed or severe acute dysphagia or odynophagia should be referred for an emergency review.

Patients who do not meet the criteria above should remain under the care of the

general practitioner (GP) who will manage conservative treatment of the patient or may be referred to a gastroenterology clinic if appropriate.

Surveillace upper endoscopy is generally not indicated in patients with:

- atrophic gastritis or pernicious anaemia
- fundic or hyperplastic gastric polyps
- gastric intestinal metaplasia
- asymptomatic patients with a history of duodenal ulcer or oesophagitis.

3 Discussion

Referral thresholds have been developed based on a comprehensive review of the literature and international referral guidelines. While referral thresholds may currently be used on an informal basis within the Irish system, this has not been done consistently. The thresholds developed here aim to provide primary care practitioners, surgeons and other clinicians involved in the care of these patients with a template upon which decision making can be standardised.

It is noted that the number of endoscopies undertaken in the publicly-funded healthcare system has increased by 43.7% from 41,803 in 2005 to 60,038 in 2012; 42.4% of those who underwent upper GI endoscopy in 2012 were aged less than 50 years, while 24.9% were aged less than 40 years. Diagnoses of upper GI cancer (oesophageal and gastric) increased by 13.4% between 2005 and 2011, having peaked in 2009 with 916 cases diagnosed; 7.1% of those diagnosed between 2005 and 2011 were aged less than 50 years at the time of diagnosis. Based on projections from the National Cancer Registry Ireland, the absolute number of patients diagnosed with upper GI cancer is expected to continue to increase over the coming years. Hence, it is important to note that the introduction of the threshold above is not expected to impact on the number of patients in whom investigation for upper GI malignancy is undertaken. Rather, it is envisaged that this threshold will provide clarity around the timing of these investigations, and should aid in prioritising those patients who are most in need of urgent review and assessment.

While the HSE has previously acknowledged that patients with worrying symptoms should be referred 'urgently' so that they can undergo OGD within four weeks if appropriate, what constitutes an urgent referral has not yet been defined.

As noted above, activity levels increased markedly between 2005 and 2012. That said, there is evidence of regional variation by hospital group in the percentage of procedures completed as day cases (91.9-98.2%). The reasons for this variation are currently unclear and therefore an analysis of the underlying causative factors would be useful in identifying how existing resources might be better utilised. It is noted however that the average length of stay for those who undergo upper GI endoscopy on an inpatient basis, many of whom will have symptoms and signs necessitating additional investigation and management, decreased from 11.2 to 9.4 days between 2005 and 2012.

There is consensus across a broad range of international guidelines in relation to referral practices for patients who present with symptoms which are suggestive of underlying upper GI malignancy. Similarly, there is general agreement about how patients with dyspepsia or GORD should be managed, and when they should be referred for opinion in secondary care. It is noted that there may be some variation in the adoption of a *H. Pylori* 'test and treat' strategy versus initial management with empiric medical therapy of patients with dyspepsia or GORD. While the relevant merits of one strategy versus the other is beyond the scope of this HTA, it is reasonable to suggest that adoption of one over the other should not be consequent on the availability or otherwise of resources (for example, the urea breath test) in a particular region.

It is noted that while development of this threshold should aid in defining who should be referred for urgent review, the mechanisms around its practical implementation remain to be fully clarified. It is clear that the National Healthlink Project, which permits the secure transmission of clinical patient information between GPs and hospitals, has facilitated improved communication of referrals between primary and secondary care. It is thus suggested that one mechanism through which this referral threshold might be implemented would be through its integration in the form of a standardised referral form into this Project.

It is evident that triage of referrals made to symptomatic upper gastrointestinal services remains a significant component of a consultant's clinical workload in secondary care. It is suggested that this service may be better utilised by resourcing specialist nurses – under the supervision of a lead clinician – to perform this triage function. This system has been implemented successfully for rapid access oncology clinics in other specialties (for example, rapid access lung clinics) and has the potential to free up clinician time for other clinical activities. An alternative, but similar approach, which might be adopted is that taken by BowelScreen, in which each individual scheduled for endoscopy is contacted by phone by a BowelScreen

nurse who coordinates the written consent process as part of the endoscopy pre-assessment process.[59]

In conclusion, the thresholds outlined above are consistent with well established clinical guidelines and published evidence. Hence, they are unlikely to represent a major change from current practice, but rather a standardisation of referral and treatment criteria across all areas of the publicly-funded healthcare system. As with all thresholds, it is imperative that there are opportunities for appeal mechanisms to ensure good governance.

4 References

(1) Health Information and Quality Authority. *A series of health technology assessments (HTAs) of clinical referral or treatment thresholds for scheduled procedures. Background chapter.* Dublin: Health Information and Quality Authority; 2013.

(2) Toward Optimized Practice. *Diagnosis and Treatment of Chronic Undiagnosed Dyspepsia in Adults* [Online]. Available from: http://www.topalbertadoctors.org/cpgs/?sid=14&cpg_cats=51.

(3) National Institute for Health and Care Excellence (NICE). *Dyspepsia and gastro-oesophageal reflux disease: Investigation and management of dyspepsia, symptoms suggestive of gastro-oesophageal reflux disease, or both. CG184* [Online]. Available from: https://www.nice.org.uk/guidance/CG184.

(4) British Columbia Medical Association. *Gastroesophageal Reflux Disease – Clinical Approach in Adults* [Online]. Available from: http://www.bcguidelines.ca/pdf/gastro.pdf.

(5) Shaheen NJ, Weinberg DS, Denberg TD, Chou R, Qaseem A, Shekelle P. Upper endoscopy for gastroesophageal reflux disease: best practice advice from the clinical guidelines committee of the American College of Physicians. *Ann Intern Med.* 2012; 157(11): pp.808-16. Available online from: PM:23208168.

(6) Williams JG, Roberts SE, Ali MF, Cheung WY, Cohen DR, Demery G, et al. Gastroenterology services in the UK. The burden of disease, and the organisation and delivery of services for gastrointestinal and liver disorders: a review of the evidence. *Gut.* 2007; 56 Suppl 1 pp.1-113. Available online from: PM:17303614.

(7) Kennedy T, Jones R. The prevalence of gastro-oesophageal reflux symptoms in a UK population and the consultation behaviour of patients with these symptoms. *Aliment Pharmacol Ther.* 2000; 14(12): pp.1589-94. Available online from: PM:11121906.

(8) Health Service Executive. *Primary Care Reimbursement Service. Statistical Analysis of Claims and Payments 2012* [Online]. Available from: http://www.hse.ie/eng/staff/PCRS/PCRS_Publications/PCRSannreport12.pdf.

(9) Bhandari A, Crowe SE. Helicobacter pylori in gastric malignancies. *Curr Gastroenterol Rep.* 2012; 14(6): pp.489-96. Available online from: PM:23054813.

(10) McColl KE. Clinical practice. Helicobacter pylori infection. *N Engl J Med.* 2010; 362(17): pp.1597-604. Available online from: PM:20427808.

(11) Infection with Helicobacter pylori. *IARC Monogr Eval Carcinog Risks Hum.* 1994; 61 pp.177-240. Available online from: PM:7715070.

(12) Kazemi S, Tavakkoli H, Habizadeh MR, Emami MH. Diagnostic values of Helicobacter pylori diagnostic tests: stool antigen test, urea breath test, rapid urease test, serology and histology. *J Res Med Sci.* 2011; 16(9): pp.1097-104. Available online from: PM:22973378.

(13) Thrumurthy SG, Chaudry MA, Hochhauser D, Mughal M. The diagnosis and management of gastric cancer. *BMJ.* 2013; 347 p.f6367. Available online from: PM:24191271.

(14) NHS Commissioning Board. *2013/2014 NHS Standard Contract for Cancer: Oesophagael and Gastric (adult)* [Online]. Available from: http://www.england.nhs.uk/wp-content/uploads/2014/03/b11-cancer-oesop-gast.pdf.

(15) National Cancer Registry Ireland. *Cancer Factsheet - Stomach* [Online]. Available from: http://www.ncri.ie/sites/ncri/files/factsheets/FACTSHEET_stomach.pdf.

(16) National Cancer Registry Ireland. *National Cancer Registry Data* [Online]. Available from: http://www.ncri.ie/data. Accessed on: 28 May 2014.

(17) National Cancer Registry Ireland. *Cancer Projections for Ireland 2015 - 2040* [Online]. Available from: http://www.ncri.ie/publications/cancer-trends-and-projections/cancer-projections-ireland-2015-%E2%80%93-2040.

(18) Lagergren J, Lagergren P. Oesophageal cancer. *BMJ.* 2010; 341 p.c6280. Available online from: PM:21112905.

(19) National Cancer Registry Ireland. *Cancer Factsheet Oesophagus* [Online]. Available from: http://www.ncri.ie/sites/ncri/files/factsheets/FACTSHEET_oesophagus.pdf.

(20) North of England Dyspepsia Guideline Development Group (UK)., NICE. *Dyspepsia: Managing Dyspepsia in Adults in Primary Care. CG17* [Online]. Available from: PM:21678625.

(21) American Society for Gastrointestinal Endoscopy. *Adverse events of upper GI endoscopy* [Online]. Available from: http://www.asge.org/assets/0/71542/71544/28549c5c-8b0e-4050-a588-11791c75ceb2.pdf.

(22) Department of Health. *The Establishment of Hospital Groups as a transition to Independent Hospital Trusts. A report to the Minister for Health, Dr James Reilly, TD* [Online]. Available from: http://health.gov.ie/wp-content/uploads/2014/03/IndHospTrusts.pdf.

(23) Health Service Executive. *Management Data Report. July 2014* [Online]. Available from: http://www.hse.ie/eng/services/publications/corporate/performanceassurancereports/July_2014_Management_Data_Report.pdf.

(24) National Treatment Purchase Fund. *The Patient Treatment Register. Outpatient Waiting List. 31 July 2014* [Online]. Available from: http://www.ntpf.ie/home/PDF/OutPatientData_BySpecialty.pdf.

(25) Plunkett O, O'Shaughnessy C, Nugent C, Hegarty I, Burke B. *Protocol for the management of outpatient services. Special Delivery Unit 2013* [Online]. Available from: http://www.ntpf.ie/home/PDF/Protocol%20for%20the%20Management%20of%20Outpatient%20Services%2028%20February%202013.pdf2.pdf.

(26) National Treatment Purchase Fund. *National waiting list management policy. A standardised approach to managing scheduled care treatment for in-patient, day case and planned procedures* [Online]. Available from: http://www.ntpf.ie/home/PDF/NTPF%20WL%20Final%20Print%20version.pdf .

(27) Health Service Executive. *KPI Metadata 2013. Acute Hospitals including Clinical Programmes, National Ambulance Service & National Cancer Control Programme* [Online]. Available from: http://www.hse.ie/eng/services/Publications/corporate/performanceassurancereports/Acutemetadata13.pdf.

(28) National Treatment Purchase Fund. *Hospital Trend Analysis of Waiting Times - GI Endoscopy* [Online]. Available from: http://www.ntpf.ie/home/PDF/GI%20Endoscopy%20Hospital%20Trend%20Analysis.pdf.

(29) Broe M, Barry M, Patchett S, Hill AD. Evaluating the clinical efficacy and cost effectiveness of direct access endoscopy. *Surgeon.* 2013; 11(6): pp.304-8. Available online from: PM:23510705.

(30) O'Riordain M, Collins C, Doran G. *Access to Diagnostics - A key enabler for a primary care led health service. Irish College of General Practitioners* [Online]. Available from: http://www.lenus.ie/hse/bitstream/10147/292726/1/Access%20to%20diagnostics%202013.pdf.

(31) Allum WH, Blazeby JM, Griffin SM, Cunningham D, Jankowski JA, Wong R. Guidelines for the management of oesophageal and gastric cancer. *Gut.* 2011; 60(11): pp.1449-72. Available online from: PM:21705456.

(32) American Society for Gastrointestinal Endoscopy. *Appropriate use of gastrointestinal endoscopy. American Society for Gastrointestinal Endoscopy* [Online]. Available from: http://www.asge.org/assets/0/71542/71544/28549c5c-8b0e-4050-a588-11791c75ceb2.pdf.

(33) British Columbia Medical Association. *Dyspepsia with or without Helicobacter pylori infection - Clinical Approach in Adults* [Online]. Available from: http://www.bcguidelines.ca/pdf/dyspepsiahpylori.pdf.

(34) British Society of Gastroenterology. *Commissioning evidence based care for patients with gastrointestinal and liver disease* [Online]. Available from: http://www.bsg.org.uk/clinical/general/commissioning-report.html.

(35) Dinis-Ribeiro M, Areia M, de Vries AC, Marcos-Pinto R, Monteiro-Soares M, O'Connor A, et al. Management of precancerous conditions and lesions in the stomach (MAPS): guideline from the European Society of Gastrointestinal Endoscopy (ESGE), European Helicobacter Study Group (EHSG), European Society of Pathology (ESP), and the Sociedade Portuguesa de Endoscopia Digestiva (SPED). *Endoscopy.* 2012; 44(1): pp.74-94. Available online from: PM:22198778.

(36) Evans JA, Early DS, Fukami N, Ben-Menachem T, Chandrasekhara V, Chathadi KV, et al. The role of endoscopy in Barrett's esophagus and other premalignant conditions of the esophagus. *Gastrointest Endosc.* 2012; 76(6): pp.1087-94. Available online from: PM:23164510.

(37) Gastroenterological Society of Australia. *Gastro-Oesophageal Reflux Disease in Adults* [Online]. Available from: http://www.gesa.org.au/professional.asp?cid=9&id=121.

(38) Ikenberry SO, Harrison ME, Lichtenstein D, Dominitz JA, Anderson MA, Jagannath SB, et al. The role of endoscopy in dyspepsia. *Gastrointest Endosc.* 2007; 66(6): pp.1071-5. Available online from: PM:18028927.

(39) Kahrilas PJ, Shaheen NJ, Vaezi MF, Hiltz SW, Black E, Modlin IM, et al. American Gastroenterological Association Medical Position Statement on the management of gastroesophageal reflux disease. *Gastroenterology.* 2008; 135(4): pp.1383-91, 1391. Available online from: PM:18789939.

(40) Katz PO, Gerson LB, Vela MF. Guidelines for the diagnosis and management of gastroesophageal reflux disease. *Am J Gastroenterol.* 2013; 108(3): pp.308-28. Available online from: PM:23419381.

(41) Lichtenstein DR, Cash BD, Davila R, Baron TH, Adler DG, Anderson MA, et al. Role of endoscopy in the management of GERD. *Gastrointest Endosc.* 2007; 66(2): pp.219-24. Available online from: PM:17643692.

(42) Malfertheiner P, Megraud F, O'Morain CA, Atherton J, Axon AT, Bazzoli F, et al. Management of Helicobacter pylori infection--the Maastricht IV/ Florence Consensus Report. *Gut.* 2012; 61(5): pp.646-64. Available online from: PM:22491499.

(43) National Institute for Health and Care Excellence (NICE). *Referral Guidelines for Suspected Cancer. CG27* [Online]. Available from: http://www.nice.org.uk/guidance/CG27.

(44) New Zealand Guidelines Group. *Management of Dyspepsia and Heartburn. Evidence based practice guideline* [Online]. Available from: http://www.health.govt.nz/system/files/documents/publications/dyspepsia_guideline_web201.pdf.

(45) New Zealand Guidelines Group. *Suspected Cancer in Primary Care. Guidelines for investigation, referral and reducing ethnic disparities* [Online]. Available from: http://www.health.govt.nz/system/files/documents/publications/suspected-cancer-guideline-sep09.pdf.

(46) Scottish Intercollegiate Guidelines Network (SIGN). *Dyspepsia. A national clinical guideline. SIGN 68* [Online]. Available from: http://sign.ac.uk/pdf/sign68.pdf.

(47) Scottish Intercollegiate Guidelines Network (SIGN). *Management of oesophageal and gastric cancer. A national clinical guideline. SIGN 87* [Online]. Available from: http://www.sign.ac.uk/pdf/sign87.pdf.

(48) Veldhuyzen van Zanten SJ, Bradette M, Chiba N, Armstrong D, Barkun A, Flook N, et al. Evidence-based recommendations for short- and long-term management of uninvestigated dyspepsia in primary care: an update of the Canadian Dyspepsia Working Group (CanDys) clinical management tool. *Can J Gastroenterol.* 2005; 19(5): pp.285-303. Available online from: PM:15915244.

(49) Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland (ASGBI), Royal College of Surgeons (RCS). *Commissioning guide: Gastro-oesophageal reflux disease (GORD)* [Online]. Available from: http://www.rcseng.ac.uk/healthcare-bodies/docs/published-guides/gord.

(50) NHS Referral Support Service Vale of York Clinical Commissioning Group. *Upper GI topic: Dyspepsia* [Online]. Available from: http://www.valeofyorkccg.nhs.uk/rss/dyspepsia.

(51) North West London Commissioning Support Group. *Direct Access for Upper GI Endoscopy* [Online]. Available from: http://www.northwestlondon.nhs.uk/_uploads/~filestore/9222B164-2C41-4BF1-855F-DDAD287BAD1C/Upper%20GI%20(NWL%20Sector)%20S1%20v6.dot.

(52) Ford AC, Moayyedi P, Jarbol DE, Logan RF, Delaney BC. Meta-analysis: Helicobacter pylori'test and treat' compared with empirical acid suppression for managing dyspepsia. *Aliment Pharmacol Ther.* 2008; 28(5): pp.534-44. Available online from: PM:18616641.

(53) Holmes KP, Fang JC, Jackson BR. Cost-effectiveness of six strategies for Helicobacter pylori diagnosis and management in uninvestigated dyspepsia assuming a high resource intensity practice pattern. *BMC Health Serv Res.* 2010; 10 p.344. Available online from: PM:21176158.

(54) Vakil N, Talley N, van Zanten SV, Flook N, Persson T, Bjorck E, et al. Cost of detecting malignant lesions by endoscopy in 2741 primary care dyspeptic patients without alarm symptoms. *Clin Gastroenterol Hepatol.* 2009; 7(7): pp.756-61. Available online from: PM:19364542.

(55) Ford AC, Qume M, Moayyedi P, Arents NL, Lassen AT, Logan RF, et al. Helicobacter pylori "test and treat" or endoscopy for managing dyspepsia: an individual patient data meta-analysis. *Gastroenterology.* 2005; 128(7): pp.1838-44. Available online from: PM:15940619.

(56) Delaney BC, Moayyedi P, Forman D. Initial management strategies for dyspepsia. *Cochrane Database Syst Rev.* 2003;(2): p.CD001961. Available online from: PM:12804417.

(57) Scottish Executive. *Scottish Referral Guidelines for Suspected Cancer. Health Department Directorate of Healthcare Policy and Strategy* [Online]. Available from: http://www.sehd.scot.nhs.uk/mels/HDL2007_09.pdf.

(58) Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland (AUGIS), Royal College of Surgeons (RCS). *Commissioning guide: Gastro-oesophageal reflux disease (GORD)* [Online]. Available from: http://www.rcseng.ac.uk/healthcare-bodies/docs/published-guides/gord.

(59) National Cancer Screening Service. *Guidelines for Quality Assurance in Colorectal Screening* [Online]. Available from: http://www.cancerscreening.ie/publications/Guidelines-for-Quality-Assurance-in-Colorectal-Screening.pdf.

(60) Jones R, Junghard O, Dent J, Vakil N, Halling K, Wernersson B, et al. Development of the GerdQ, a tool for the diagnosis and management of gastro-oesophageal reflux disease in primary care. *Aliment Pharmacol Ther.* 2009; 30(10): pp.1030-8. Available online from: PM:19737151.

(61) Health Service Executive. *National Casemix Programme. Ready Reckoner of Acute Hospital inpatient and daycase activity and costs (summarised by DRG) relating to 2011 costs and activity.* Ireland: 2013.

Appendices

Appendix 1.1 – HIPE ICD-10AM/ACHI list of intervention codes for upper GI endoscopy procedures

Intervention code	Description
4181600	Rigid Oesophagoscopy
3047303	Oesophagoscopy
3047304	Oesophagoscopy with biopsy
3055900	Local excision of lesion of oesophagus
3047300	Panendoscopy to duodenum
3047302	Panendoscopy through artificial stoma
3047307	Panendoscopy to duodenum with tattooing
3047305	Panendoscopy to ileum
3047308	Panendoscopy to ileum with tattooing
3047801	Panendoscopy to duodenum with diathermy
3047802	Panendoscopy to duodenum with heater probe coagulation
3047803	Panendoscopy to duodenum with laser coagulation
3047820	Panendoscopy to duodenum with other coagulation
3047815	Panendoscopy to ileum with diathermy
3047816	Panendoscopy to ileum with heater probe coagulatiOn
3047817	Panendoscopy to ileum with laser coagulation
3047821	Panendoscopy to ileum with other coagulation
3047804	Panendoscopy to duodenum with excision of lesion
3047818	Panendoscopy to ileum with excision of lesion
3047304	Panendoscopy to duodenum with biopsy
3047306	Panendoscopy to ileum with biopsy

Appendix 1.2 – Indications for referral for endoscopy

Guideline	
CANDYS, (2005)[48]	In patients with longstanding or severe (five to ten years, more than three times per week) dominant symptoms of heartburn or regurgitation and/or patients requiring long term maintenance therapy with anti-secretory medications (H2RA, PPI), a once in a lifetime endoscopy is recommended. In patients with dyspepsia who do not have alarm symptoms or symptoms of dominant heartburn or acid regurgitation, and are not using NSAIDS or aspirin, a test for *H. pylori* should be ordered and the patient treated if positive. Patients who have ongoing or recurrent dyspepsia symptoms following *H. pylori* treatment should be tested by urea breath test (Not serology) or undergo endoscopy to determine whether *H. pylori* is present. If, after an initial course of standard-dose acid suppression, a patient does not respond to a further four to eight weeks of high dose PPI, then further investigations, such as endoscopy, may be required.
ASGE, (2007)[41]	GERD symptoms that are persistent or progressive despite appropriate medical therapy Dysphagia or odynophagia Involuntary weight loss >5% Evidence of GI bleeding or anaemia Finding of a mass, stricture, or ulcer on imaging studies Evaluation of patients with suspected extra-esophageal manifestations of GORD Screening for Barrett's oesophagus in selected patients (as clinically indicated) Persistent vomiting Evaluation of patients with recurrent symptoms after endoscopic or surgical anti-reflux procedures
ASGE, (2012)[32]	GI endoscopy is generally indicated: ▪ If a change in management is probable based on results of endoscopy. ▪ After an empirical trial of therapy for a suspected benign digestive disorder has been unsuccessful. ▪ As the initial method of evaluation as an alternative to radiographic studies. ▪ When a primary therapeutic procedure is contemplated. GI endoscopy is generally not indicated: ▪ When the results will not contribute to a management choice. ▪ For periodic follow-up of healed benign disease unless surveillance of a pre-malignant condition is warranted. GI endoscopy is generally contraindicated: ▪ When the risks to patient health or life are judged to outweigh the most favourable benefits of the procedure. ▪ When adequate patient cooperation or consent cannot be obtained. ▪ When a perforated viscus is known or suspected. Sequential or periodic EGD is generally not indicated for: ▪ Surveillance for malignancy in patients with gastric atrophy, pernicious anemia,

	fundic gland or hyperplastic polyps, gastric intestinal metaplasia, or previous gastric operations for benign disease. ▪ Surveillance of healed benign disease, such as esophagitis and gastric or duodenal ulcer.
NICE, (2005)[43]	Those with dyspepsia – an urgent endoscopy is indicated when patients (of any age) also have any of the following: ▪ chronic gastrointestinal bleeding ▪ dysphagia ▪ progressive unintentional weight loss ▪ persistent vomiting ▪ iron deficiency anaemia ▪ epigastric mass ▪ suspicious barium meal result ▪ are over 55 years and the dyspepsia is of recent onset. In patients with unexplained worsening of their dyspepsia, an urgent referral should be considered if they have any of the following known risk factors: ▪ Barrett's oesophagus ▪ known dysplasia, atrophic gastritis or intestinal metaplasia ▪ peptic ulcer surgery more than 20 years ago. Those without dyspepsia - An urgent referral for endoscopy or other investigations is indicated when patients also have any of the following: ▪ unexplained weight loss or iron deficiency anaemia ▪ persistent vomiting and weight loss ▪ unexplained upper abdominal pain and weight loss, with or without back pain ▪ an upper abdominal mass ▪ obstructive jaundice (depending on the patient's clinical state).
NICE (2014)[3]	Emphasise that the harms of endoscopic surveillance may outweigh the benefits in people who are at low risk of progression to cancer (for example, people with stable non-dysplastic Barrett's oesophagus).
NHS England, (2013)[14]	Urgent referral for endoscopy should be made for those with: ▪ Chronic gastrointestinal bleeding. ▪ Dysphagia. ▪ Progressive unintentional weight loss. ▪ Persistent vomiting. ▪ Iron deficiency anaemia. ▪ Epigastric mass. ▪ Suspicious barium meal result. ▪ Aged 55 years and older with unexplained and persistent recent-onset dyspepsia alone.
AUGIS	High Value Care Pathway for GORD: Refer urgently in accordance with local

(2013)[58]	guidelines to a team specialising in the diagnosis of upper GI cancer if any of the following detected: Worsening reflux with known Barrett's oesophagus/ atrophic gastritis/ intestinal metaplasia/ dysplasia or previous peptic ulcer surgery /family history of upper GI cancer in more than two first-degree relatives.
ESGE (2012)[35]	Endoscopic surveillance should be offered to patients with extensive atrophy and/or intestinal metaplasia (i.e., atrophy and/or intestinal metaplasia in the antrum and corpus) (evidence level 2++, recommendation grade B); 91% of voters stated that they would apply this statement; 80% of those representing national societies mentioned that it would be applicable in their countries. Patients with extensive atrophy and/or intestinal metaplasia should receive follow-up every 3 years after diagnosis (evidence level 4, recommendation grade D); 90% of voters stated that they would apply this statement; 80% of those representing national societies mentioned that it would be applicable [70%] or widely applicable [10%] in their countries.) For those patients with mild to moderate atrophy/intestinal metaplasia restricted to the antrum there is no evidence to recommend surveillance(evidence level 4, recommendation grade D).
Improving Outcomes Guidance (IOG) (2011)[31]	Individuals at increased risk of oesophago-gastric cancer on the basis of family history (tylosis) or a premalignant condition (Barrett's oesophagus, pernicious anaemia, intestinal metaplasia of the stomach or previous gastric surgery) may be considered for endoscopic monitoring. These decisions are complex and should be determined by balancing the magnitude of the benefits against the perceived clinical risks of the procedure and patient preferences.
SIGN (2006)[47]	Case series studies in patients with pernicious anaemia or previous gastric surgery generally do not support the use of endoscopic surveillance to try to identify early cancers. Surveillance has not been appraised in a randomised controlled trial
New Zealand Guidelines (2004)[44]	OGD surveillance of coincidental (normal macroscopic appearance) short-segment Barrett's oesophagusand intestinal metaplasia in the area of the gastric cardia is not recommended currently.

Appendix 1.3 – Alarm features warranting immediate or urgent referral

Guideline	'Alarm' features
TOP (2009)[2]	Vomiting, bleeding/anaemia, abdominal mass/unexplained weight loss, dysphagia (difficulty swallowing)/odynophagia (painful swallowing).
British Columbia, (2009)[33]	Gastrointestinal blood loss, weight loss, early satiety, dysphagia, persistent vomiting, symptom onset after age 55 years
American College of Physicians, (2012)[5]	Dysphagia, bleeding, anaemia, weight loss, and recurrent vomiting
British Columbia, (2009)[4]	Dysphagia, weight loss, gastrointestinal blood loss (acute or chronic), persistent vomiting or failure to respond to an adequate trial of therapy
New Zealand Guidelines Group, (2004)[44]	Family history of gastric cancer (onset <50 years), severe or persistent dyspeptic symptoms, previous peptic ulcer disease, particularly if complicated, ingestion of NSAIDs in those at risk, unexplained weight loss, gastrointestinal bleeding (haematemesis or melaena), anaemia, dysphagia (difficulty swallowing), coughing spells or nocturnal aspiration, protracted vomiting or persistent regurgitation of food, palpable abdominal mass. NB: All symptoms should be regarded as more serious in people who are aged >50 years when presenting for the first time.
RCS, AUGIS, (2013)[49]	Dysphagia Progressive unintentional weight loss Persistent vomiting Dyspepsia or reflux and Iron deficiency anaemia, or chronic gastrointestinal bleed Epigastric mass/suspicious barium meal >55 years with unexplained and persistent (>4–6 week) recent-onset reflux Worsening reflux with known Barrett's oesophagus/ atrophic gastritis/ intestinal metaplasia/ dysplasia or previous peptic ulcer surgery /family history of upper GI cancer in more than two first-degree relatives
BSG, (2014)[34]	Dysphagia, early satiety, weight loss, anaemia
GESA, (2011)[37]	Include dysphagia, odynophagia, weight loss, haematemesis, anaemia
ASGE, (2007)[38]	Age >50 years, with new onset symptoms, family history of upper GI malignancy, unintended weight loss, GI bleeding or iron deficiency anaemia, progressive dysphagia, odynophagia, persistent vomiting, palpable mass or lymphadenopathy, jaundice
SIGN, (2006)[47]	Dysphagia, recurrent vomiting, anorexia, weight loss, GI blood loss

Appendix 1.4 – Scottish referral guidelines for suspected cancer. Indications for urgent referral[57]

Dysphagia – food sticking on swallowing (any age)

Dyspepsia at any age combined with one or more of the following 'alarm' symptoms:

- weight loss
- proven anaemia
- vomiting

Dyspepsia in a patient aged 55 years or more with at least one of the following 'high risk' features:

- onset of dyspepsia less than one year ago
- continuous symptoms since onset

Dyspepsia combined with at least one of the following known risk factors:

- family history of upper GI cancer in more than 2 first degree relatives
- family history of colorectal cancer (familial adenomatous polyposis,
- hereditary non-polyposis colorectal cancer)
- Barrett's oesophagus
- pernicious anaemia
- peptic ulcer surgery over 20 years ago
- known dysplasia, atrophic gastritis, intestinal metaplasia

Jaundice

Upper abdominal mass

Back pain and weight loss

Appendix 1.5 - GerdQ Questionnaire[60]

When you think of the symptoms you have had in the past 7 days, how did you experience the following?				
Answer the questions by setting a cross in one square in each row.	0	1	2-3	4-7
How often did you have a burning feeling behind your breastbone (heartburn)?	□(0)	□ (1)	□ (2)	□ (3)
How often did you have stomach contents (liquid or food) moving upwards to your throat or mouth (regurgitation)?	□(0)	□ (1)	□ (2)	□ (3)
How often did you have a pain in the middle of your upper stomach?	□(0)	□ (1)	□ (2)	□ (3)
How often did you have nausea?	□(3)	□ (2)	□ (1)	□ (0)
How often did you have difficulty getting a good night's sleep because of difficulty with your heartburn/regurgitation?	□(0)	□ (1)	□ (2)	□ (3)
How often did you take additional medication for your heartburn and/or regurgitation other than what the physician told you to take?	□(0)	□ (1)	□ (2)	□ (3)

The GerdQ questionnaire for assessing reflux disease. The patients complete the questionnaire themselves. Scores for the different responses are given in red in brackets. The points are added together. A score of ≥ 8 means a high probability of reflux disease. A change in score such that none of the questions 1, 2, 5 or 6 scores more than 1 is regarded as a good response to treatment.

Appendix 1.6 – Example of Clinical Commissioning Group Referral Thresholds

Vale of York Clinical Commissioning Group[50]– Dyspepsia

Exclude Red Flag Symptoms

Endoscopy (and hence secondary care referral) is not indicated for dyspepsia without alarm symptoms (red flags) or risk factors for cancer

- Weight loss (unintentional)
- Iron deficiency anaemia
- Vomiting – persistent
- Dysphagia
- Evidence of GI bleeding (blood loss from upper GI tract is a prokinetic agent so may be reflected in change in bowel habit and/or stool colour change.
- Epigastric mass
- Patients aged over 55 with unexplained, persistent and recent onset dyspepsia***

***Unexplained = No obvious reason found in the history for dyspepsia
Persistent = Continuation of symptoms/signs beyond a period that would normally be associated with self-limiting problems (usually regarded as 4-6 weeks)
Recent = New onset and not recurrent symptoms.

Risk factors for cancers: In addition to the red flags above, a lower threshold for referral is suggested in those with a history of Barrett's oesophagus, pernicious anaemia, intestinal dysplasia, peptic ulcer surgery or a family history of upper GI cancer.

Management

The incidence of upper GI cancer in those under the age of 55 years without red flags is 1 per million population per year.
The majority of cases of dyspepsia can be treated in primary care.
Long term PPI use is safe (but should be used at the minimum effective dose).

North West London Commissioning Support Unit[51]- Direct access for upper GI endoscopy

Alarm Features (ANY AGE) – complete 2 week cancer referral form

- Progressive Unintentional Weight Loss

- Iron Deficiency Anaemia
- Dysphagia
- Persistent Vomiting
- Epigastric Mass

THRESHOLDS FOR ENDOSCOPY: Patients must meet at least one of the following criteria:

Patients with dyspepsia

Please refer to the NICE and SIGN guidance on treating dyspepsia

http://www.sign.ac.uk/pdf/qrg68.pdf

http://guidance.nice.org.uk/nicemedia/live/10950/29458/29458.pdf

Dyspepsia* + > 55 years with:

- Unexplained, persistent recent onset dyspepsia in the absence of any other features
- Unexplained worsening of dyspepsia with
- Barrett's Oesophagus
- Known dysplasia
- Atrophic gastritis
- Intestinal metaplasia
- Peptic Ulcer surgery >20 years ago

Any age with a change of or persistent dyspepsia symptoms despite PPI therapy and treatment for HP, with a history of Barrett's oesophagus, metaplasia, dysplasia, recent NSAID use, previous gastric surgery or strong family history

Patients without dyspepsia – any age:

- Dysphagia
- Unexplained Weight loss or Iron deficiency anaemia
- Palpable Upper GI Mass or incidental mass found on imaging
- Obstructive Jaundice
- Persistent vomiting without dyspepsia
- Patients with Liver disease to detect oesophageal varices
- For confirmatory biopsy of coeliac disease
- Post treatment for cancer/Barrett's oesophagus surveillance
- Repeat endoscopy following gastric or oesophageal ulcer treatment
- Screening in polyposis – familial adenomatous polyposis
- Oesophageal dilatation follow-up.

Appendix 1.7 Evidence table summarising the data extracted from the cost-effectiveness literature

Study	Intervention	Analysis Details	Clinical and QALY Outcomes	Costs*	Results
Vakil et al. (2009)[54]	Early endoscopy (effect of varying age thresholds)	Country: US Discount rate: - Perspective: Health care payer Time Horizon: - Model Type: Cost comparison	-	If the age threshold for early endoscopy were set at 50 years, at a cost of €466/endoscopy, it would cost €77,289 (95% CI, €33,297 €233,079) to detect each case of cancer.	A reported limitation was that stage of cancer and resectability were not recorded, and thus a formal analysis of the cost-effectiveness of endoscopy could not be undertaken.
Ford et al. (2005)[55]	Comparison of *H. Pylori* test and treat with prompt upper GI endoscopy for the management of dyspepsia.	Country: US data (UK analysis) Discount rate: Not reported Perspective: Patient Time Horizon: - Model Type: Meta-analysis of five RCTs	RR of remaining symptomatic after 1 year was reduced with endoscopy compared with "test and treat" (RR0.95; 95% CI 0.92– 0.99).	Cost data available for 1,771 patients. The WMD in total cost for all patients was €476 (95% CI: €338 – €614), indicating that prompt endoscopy cost more per patient than a *H. Pylori* test and treat strategy.	Authors noted that prompt upper GI endoscopy for management of dyspepsia associated with small, but statistically significant, benefit in terms of symptom resolution, over a 'test and treat' approach, concluded that prompt endoscopy strategy is not cost-effective at a realistic level of willingness-to-pay for cure of dyspepsia.
Delaney et al., (2003) [56]	4 management approaches: initial pharmacological therapy, early endoscopy, testing for H. pylori and endoscope only those with positive finding, H. pylori eradication therapy with or without prior testing	Country: UK Discount rate: - Perspective: - Time Horizon: - Model Type: Meta-analysis where there were sufficient trials of similar comparisons reporting the same outcomes.	-	-	Concluded unlikely that early endoscopy would result in a reduction in overall economic costs of managing dyspepsia over only one year. Suggest that it is more likely that an initial excess cost would be incurred that may be recouped in some prescribing and consultation reductions in subsequent years, the point at which early endoscopy may

					become cost neutral, if at all, could not be determined.

CI – confidence interval; GI – gastro intestinal; RCT – randomised controlled tiral; UK – United Kingdom; US – United States; WMD – weighted mean difference; RR-relative risk.
**All costs presented have been inflated using the local consumer price index for health to 2013 values and then converted to Irish Euro using the latest Purchasing Power Parities.*

Appendix 1.8 – HSE inpatient and day case acute hospital activity and costs for elective upper GI endoscopy summarised by diagnosis related group (based on 2011 costs and 2012 activity)[61]

DRG code	Description	No. of procedures*	% of total	Cost/ inpatient (€)	Cost/ Day Case(€)
G47C	Other Gastroscopy; Sameday	38,710	64.48	578	403
G46C	Complex Gastroscopy; Sameday	11,478	19.12	942	619
Q61B	Red Blood Cell Disorders W/O Catastrophic or Severe CC	1,810	3.02	2,563	416
Z40Z	Endoscopy W Diagnoses of Other Contacts W Health Services; Sameday	1,784	2.97	423	466
K40C	Endoscopic or Investigative Procedure for Metabolic Disorders; Sameday	787	1.31	516	520
G46B	Complex Gastroscopy W/O Catastrophic CC	522	0.87	5,111	619
G47B	Other Gastroscopy W/O Catastrophic CC	457	0.76	2,920	403
H63B	Disorders of Liver Excep Malig; Cirrhosis; Alcoholic Hepatitis W/O Cat/Sev CC	444	0.74	2,542	531
H64B	Disorders of the Biliary Tract W/O CC	360	0.60	1,629	382
H62B	Disorders of Pancreas Except for Malignancy W/O Catastrophic or Severe CC	273	0.45	2,570	390
H43B	ERCP Procedures W/O Catastrophic or Severe CC	236	0.39	3,479	1,038
G11Z	Anal and Stomal Procedures	228	0.38	3,461	1,130
H60C	Cirrhosis and Alcoholic Hepatitis W/O CC	222	0.37	2,518	729
F74Z	Chest Pain	215	0.36	1,028	570
D66B	Other Ear; Nose; Mouth and Throat Diagnoses W/O CC	192	0.32	1,548	480
E67B	Respiratory Signs and Symptoms W/O Catastrophic or Severe CC	115	0.19	1,347	511
U60Z	Mental Health Treatment; Sameday; W/O ECT	110	0.18	132	244

K40B	Endoscopic or Investigative Proc for Metabolic Disorders W/O Catastrophic CC	78	0.13	7,132	520
G12C	Other Digestive System OR Procedures W/O CC	76	0.13	4,791	1,668
D60B	Ear; Nose; Mouth and Throat Malignancy W/O Catastrophic or Severe CC	75	0.12	5,018	768
G70B	Other Digestive System Diagnoses W/O Catastrophic or Severe CC	75	0.12	1,663	442
H60B	Cirrhosis and Alcoholic Hepatitis W Severe or Moderate CC	69	0.11	5,450	729
Q61A	Red Blood Cell Disorders W Catastrophic or Severe CC	62	0.10	5,474	416
D14Z	Mouth and Salivary Gland Procedures	55	0.09	5,205	1,314
H61B	Malignancy of Hepatobiliary System; Pancreas W/O Catastrophic CC	53	0.09	4,813	824
H05B	Hepatobiliary Diagnostic Procedures W/O Catastrophic CC	52	0.09	8,995	1,631
R61C	Lymphoma and Non-Acute Leukaemia; Sameday	45	0.07	712	846
G12B	Other Digestive System OR Procedures W Severe or Moderate CC	44	0.07	8,536	1,668
D67B	Oral and Dental Disorders Except Extractions and Restorations; Sameday	43	0.07	498	539
D63Z	Otitis Media and URI	41	0.07	1,577	442
G03A	Stomach; Oesophageal and Duodenal Procedure W Malignancy or W Catastrophic CC	39	0.06	26,591	1,905
B81B	Other Disorders of the Nervous System W/O Catastrophic or Severe CC	37	0.06	2,998	492
G03C	Stomach; Oesophageal and Duodenal Procedures W/O Malignancy W/O CC	32	0.05	7,549	1,905
D66A	Other Ear; Nose; Mouth and Throat Diagnoses W CC	31	0.05	4,305	480
H63A	Disorders of Liver Except Malig; Cirrhosis; Alcoholic Hepatitis W Cat/Sev CC	30	0.05	8,868	531
H64A	Disorders of the Biliary Tract W CC	30	0.05	4,134	382

Q60C	Reticuloendothelial and Immunity Disorders W/O Cat or Sev CC W/O Malignancy	28	0.05	4,177	1,036
R62B	Other Neoplastic Disorders W/O CC	28	0.05	4,598	969
J67B	Minor Skin Disorders; Sameday	27	0.04	242	351
D11Z	Tonsillectomy and/or Adenoidectomy	26	0.04	3,261	1,539
D12Z	Other Ear; Nose; Mouth and Throat Procedures	25	0.04	5,206	1,277
G47A	Other Gastroscopy W Catastrophic CC	24	0.04	11,377	403
G02B	Major Small and Large Bowel Procedures W/O Catastrophic CC	22	0.04	13,084	1,324
Q02B	Other OR Procedure of Blood and Blood Forming Organs W/O Cat or Sev CC	22	0.04	4,802	1,071
E42C	Bronchoscopy; Sameday	21	0.03	906	735
H08B	Laparoscopic Cholecystectomy W/O Closed CDE W/O Cat or Sev CC	20	0.03	4,922	2,691
801C	OR Procedures Unrelated to Principal Diagnosis W/O CC	18	0.03	7,379	1,759
A06B	Trach W Vent >95 hours W/O Cat CC or Trach/Vent >95 hours W Cat CC	18	0.03	55,270	-
E71B	Respiratory Neoplasms W/O Catastrophic CC	18	0.03	5,104	696
A06A	Tracheostomy W Ventilation >95 hours W Catastrophic CC	16	0.03	106,948	-
G10B	Hernia Procedures W/O CC	15	0.02	3,727	1,613
J11Z	Other Skin; Subcutaneous Tissue and Breast Procedures	15	0.02	4,211	689
Z64A	Other Factors Influencing Health Status	15	0.02	5,119	304
E60B	Cystic Fibrosis W/O Catastrophic or Severe CC	13	0.02	12,946	1,377
G03B	Stomach; Oesophageal and Duodenal Procedures W/O Malignancy W Sev or Mod CC	12	0.02	11,891	1,905
R03B	Lymphoma and Leukaemia W Other OR Procedures W/O Catastrophic or Severe CC	12	0.02	8,480	1,668

G02A	Major Small and Large Bowel Procedures W Catastrophic CC	11	0.02	27,413	1,324
G46A	Complex Gastroscopy W Catastrophic CC	11	0.02	14,475	619
N62Z	Menstrual and Other Female Reproductive System Disorders	11	0.02	1,058	395
R62A	Other Neoplastic Disorders W CC	11	0.02	6,527	969
G04C	Peritoneal Adhesiolysis W/O CC	10	0.02	5,843	2,299
R61B	Lymphoma and Non-Acute Leukaemia W/O Catastrophic CC	10	0.02	6,906	846
E42B	Bronchoscopy W/O Catastrophic CC	9	0.01	6,343	735
E75C	Other Respiratory System Diagnosis W/O CC	9	0.01	1,999	413
G62Z	Complicated Peptic Ulcer	9	0.01	4,533	375
G67B	Oesophagitis and Gastroenteritis W/O Cat/Sev CC	9	0.01	1,343	211
D62Z	Epistaxis	8	0.01	1,662	362
G12A	Other Digestive System OR Procedures W Catastrophic CC	8	0.01	17,377	1,668
G60B	Digestive Malignancy W/O Catastrophic CC	8	0.01	4,262	722
H01B	Pancreas; Liver and Shunt Procedures W/O Catastrophic CC	8	0.01	15,969	1,614
H06B	Other Hepatobiliary and Pancreas OR Procedures W/O Catastrophic CC	8	0.01	7,627	1,393
H43A	ERCP Procedures W Catastrophic or Severe CC	8	0.01	10,512	1,038
K40A	Endoscopic or Investigative Proc for Metabolic Disorders W Catastrophic CC	8	0.01	20,950	520
T64C	Other Infectious and Parasitic Diseases W/O CC	8	0.01	2,337	434
801B	OR Procedures Unrelated to Principal Diagnosis W Severe or Moderate CC	7	0.01	12,744	1,759
B67C	Degenerative Nervous System Disorders W/O CC	7	0.01	4,974	982
B71B	Cranial and Peripheral Nerve Disorders W/O CC	7	0.01	3,784	820
G64B	Inflammatory Bowel Disease W/O CC	7	0.01	3,081	1,610

H40B	Endoscopic Procedures for Bleeding Oesophageal Varices W/O Catastrophic CC	7	0.01	8,879	980
H60A	Cirrhosis and Alcoholic Hepatitis W Catastrophic CC	7	0.01	12,618	729
I68C	Non-surgical Spinal Disorders; Sameday	7	0.01	202	581
N60B	Malignancy; Female Reproductive System W/O Catastrophic CC	7	0.01	4,729	1,238
Z63B	Other Surgical Follow Up and Medical Care W/O Catastrophic CC	7	0.01	3,391	440
801A	OR Procedures Unrelated to Principal Diagnosis W Catastrophic CC	6	0.01	28,992	1,759
B67A	Degenerative Nervous System Disorders W Catastrophic or Severe CC	6	0.01	13,706	982
B77Z	Headache	6	0.01	1,228	476
F65B	Peripheral Vascular Disorders W/O Catastrophic or Severe CC	6	0.01	2,470	570
G05C	Minor Small and Large Bowel Procedures W/O CC	6	0.01	8,049	1,535
H62A	Disorders of Pancreas Except for Malignancy W Catastrophic or Severe CC	6	0.01	6,950	390
I76B	Other Musculoskeletal Disorders W/O Catastrophic or Severe CC	6	0.01	2,782	741
L62B	Kidney and Urinary Tract Neoplasms W/O Catastrophic or Severe CC	6	0.01	3,324	694
M60B	Malignancy; Male Reproductive System W/O Catastrophic or Severe CC	6	0.01	4,703	683
R04A	Other Neoplastic Disorders W Other OR Procedures W CC	6	0.01	10,398	1,946
R61A	Lymphoma and Non-Acute Leukaemia W Catastrophic CC	6	0.01	26,223	846
Z60A	Rehabilitation W Catastrophic CC	6	0.01	28,934	1,517
Z60B	Rehabilitation W/O Catastrophic CC	6	0.01	8,443	1,517

*Key: DRG – diagnostic-related group; W – with; W/O – without; CC – complication or comorbidity. Data summary from HSE National Casemix Programme Ready Reckoner, 2013 based on the 2011 inpatient and day case costs reported by 38 hospitals participating in the programme that year. Activity is based on the latest 2012 HIPE data and includes upper GI endoscopy coded as 'all procedures'. *Note the remaining diagnosis-related groups accounted for five or fewer procedures each.*

Published by the Health Information and Quality Authority.

For further information please contact:

Health Information and Quality Authority
Dublin Regional Office
George's Court
George's Lane
Smithfield
Dublin 7

Phone: +353 (0) 1 814 7400
URL: www.hiqa.ie