National Institute for Health and Care Excellence

Dyspepsia (update)
Guideline Consultation Table
2nd April – 19th May 2014

Type	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
SH	Association of Upper Gastrointestinal Surgeons of GB & I	1	NICE	14	1.4.6	Failure to respond to a standard course of PPI should be a prompt to reconsider the diagnosis rather than simply swap to an alternative agent such as H2RA therapy. This is the group who may have a more sinister underlying therapy particularly if over 50 and should be considered for endoscopy	Thank you for your comments. This particular recommendation is not part of this guideline update. It has only been re-edited based on NICE style without changing its intent. Therefore, it is outside the remit of this guideline update to change this particular recommendation.
SH	Association of Upper Gastrointestinal Surgeons of GB & I	2	NICE	15	1.6.7	This is misleading and should be re-written. The implication is that "severe oesophagitis " can be diagnosed clinically. Diagnosis of the severity of oesophagitis can only be made on endoscopy. An appropriate statement should be made in this section which refers to Interventions in GORD	Thank you for your comments. In Recommendation 1.6.7: *"Offer people a full-dose PPI (see table 2 in appendix A) for 8 weeks to heal severe oesophagitis, taking into account the person's preference and clinical circumstances (for example, underlying health conditions and possible interactions with other drugs)"*, no statement referred to the diagnosis of severe oesophagitis. The diagnosis of GORD and oesophagitis are outside the scope of this guideline update.
SH	Association of Upper Gastrointestinal Surgeons of GB & I	3	NICE	16	1.6.11	The statement about discussing individual risk factors should be stronger – males with a long history and change in symptoms should be referred for endoscopy and not simply considered – this is the risk group for adenocarcinoma	Thank you for your comment. Due to the very low quality evidence with high uncertainty, the GDG felt that they were not able to make any strong recommendation other than 'consider'. The issue on high risk groups for adenocarcinoma will be covered by other NICE guideline (Suspected cancer update which is

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							expected to publish in May 2015).
SH	Association of Upper Gastrointestinal Surgeons of GB & I	4	NICE	21	1.11.1	AUGIS is very pleased to see the inclusion of "Consider referral to a specialist service for people: of any age with gastro-oesophageal symptoms that are persistent, non-responsive to treatment or unexplained.	Thank you.
SH	Association of Upper Gastrointestinal Surgeons of GB & I	5	NICE	21	1.12.1	This statement is not acceptable as it is at variance with the BSG Barrett's Guidelines. This statement should not be included and this section should start with 1.12.2	Thank you for your comment. After further discussion, taking into account of stakeholder comments, the GDG agreed to re-adjust the relevant recommendations to the following: *Consider surveillance to check progression to cancer for people who have a diagnosis of Barrett's oesophagus (confirmed by endoscopy and histopathology), taking into account:* • *the presence of dysplasia (also see Barrett's oesophagus - ablative therapy - NICE clinical guideline CG106)* • *the person's individual preferences* • *the person's risk factors (for example, male gender, older age and the length of the Barrett's oesophagus segment).* *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).*
SH	Association of Upper Gastrointestinal Surgeons of GB & I	6	NICE	23	2.2	This subject is very broad as without careful physiology assessment simple lack of response to optimal PPI therapy is not an indication for surgery. This should be qualified to ensure exclusion of those conditions which may be	Thank you for your comments. This is a research recommendation, not a clinical guideline recommendation on indications for surgery.

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						made worse by surgery such as disorders of motility Also there is the opportunity here within research to consider assessment of some of the newer devices be promoted for GORD such as Endostim	This research recommendation is attempting to address the current lack of evidence on the effectiveness of fundoplication for patients who do not respond to optimal proton pump inhibitor (PPI) treatment. The GDG do not think that the effectiveness of Endostim is a priority for a research recommendation at this time.
SH	Biohit HealthCare Ltd	1	Full	153	31	• Long term acid suppression is not always appropriate for H pylori negative patients because of the risk of GI infections, gastric cancer and pulmonary infections, specifically linked to hypochlorhydria. • The same applies to patients with corpus predominant atrophic gastritis who bear a greater risk from receiving acid suppression therapy.	Thank you for your comments. The whole section 4.7.18 in the Full guideline (from page 153 to 162) is from the original guideline (2004), which is outside the scope to be updated in this specific guideline update, and therefore was not part of this public consultation. Hence, it is outside the NICE process to respond to these comments.
SH	Biohit HealthCare Ltd	2	Full	163	17	• H pylori serology tests only give rise to false positive results if successful eradication has been achieved.	Thank you for your comment. The whole sub-section 4.7.18 in the Full guideline (from page 163 to 165) is from the original guideline (2004), which is outside the scope to be updated in this specific guideline update, and therefore was not part of this public consultation. Hence, it is outside the NICE process to respond to these comments.
SH	Biohit HealthCare Ltd	3	Full	163	30	• There should be a clause that stipulates the need to withdraw from acid suppression therapy prior to testing, and an advisory note that certain gastric conditions can limit the sensitivity of H pylori tests (gastric ulcer, atrophic gastritis etc)	Thank you for your comment. The whole sub-section 4.7.18 in the Full guideline (from page 163 to 165) is from the original guideline (2004), which is outside the scope to be updated in this specific guideline update, and therefore was not part of this public

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SH	Biohit HealthCare Ltd	4	Full	239	9	The key concerns of the GDG included people at risk of developing GI cancers were not identified early. • There is insufficient emphasis on, or links to, guidance on pre-referral testing to enable early identification of patients at risk of gastric disease other than H pylori infection alone. • Referral based on 'persistent symptoms' may not speed up the diagnosis. • Furthermore, for clarity when recommending referral to a specialist, 'Persistent' should be clearly defined (e.g. time interval/min number of visits to GP)	Thank you for your comments. The accuracy of pre-referral testing to enable early identification of patients at risk of gastric disease other than *H pylori* infection alone is outside the scope of this particular update. After further discussion, the GDG decided to remove the term 'persistent' from the recommendation as they agreed that the phrase in the recommendation 'non-responsive to treatment' has already covered the meaning of persistent symptoms. Regarding the time interval/min number of visits to GP before referral to specialist services, these have already covered by other recommendations in the guideline (please see Section 4.3 to 4.6 in the Full guideline). Under these sections, there are already recommendations for primary care practitioners for treating different types of dyspepsia and at what point (also illustrated by the treatment flow-charts in the Full guideline) they should consider treatment as 'non-responsive. Appropriate links and interfaces of all these recommendations will be further clarified after the NICE Pathways are completed after guideline publication.
SH	British Medical Association, General Practitioners	1	NICE	General	General	In general, this draft guidance seems reasonable however we are concerned by the removal of the cancer risk paragraphs. Whilst we appreciate that suspicious symptoms may be	Thank you for your comments. We share the same concerns. More editorial work will be carried out to appropriately cross

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	Committee					better dealt with by reference to the alternate NICE guidance, we feel it would be both helpful and safer to continue to remind doctors that dyspepsia can be a serious / malignant symptom. If the cancer risk paragraphs are removed, the link(s) to alternative NICE guidance need to be highlighted much more clearly.	refer to the NICE Suspected cancer update, which is expected to publish in May 2015.
SH	British Medical Association, General Practitioners Committee	2	NICE	10	1.3.1	Same day referral for people presenting with dyspepsia together with significant acute gastrointestinal bleeding; it is not clear if this means an admittance or referral (when although the letter may go that day, an appointment may be some time later) and clarification would therefore be welcomed.	Thank you for your comment. Recommendation 1.3.1 in the NICE version is outside the scope to be updated in this specific guideline update, and therefore was not part of this public consultation. Hence, it is outside the NICE process to update these recommendations at this time.
SH	British Medical Association, General Practitioners Committee	3	NICE	21	1.12.2	Surveillance for people with Achalasia is not mentioned however, the risks are similar to Barrett's oesophagus; we feel perhaps Achalasia ought to be included in the draft guideline too.	Thank you for your comment. Diagnosis and management of Achalasia is outside the scope of this guideline update.
SH	British Society of Gastroenterology	1	Full	15	11	New recommendations have been added for the specialist management and surveillance of Barrett's oesophagus. This is very confusing since the BSG updated guidelines (NICE accredited) have been published in Gut in 2014; 63:7-42. It would be simplest to refer to these guidelines (this was the view of the majority of BSG oesophageal committee) or else be modified so that there is no contradiction which will cause confusion.	Thank you for your comments. After further discussion, taking into account of stakeholder comments, the GDG agreed to re-adjust the relevant recommendations to the following: *Consider surveillance to check progression to cancer for people who have a diagnosis of Barrett's oesophagus (confirmed by endoscopy and histopathology), taking into account:* • *the presence of dysplasia (also see Barrett's oesophagus - ablative therapy - NICE clinical guideline CG106)*

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							• *the person's individual preferences* • *the person's risk factors (for example, male gender, older age and the length of the Barrett's oesophagus segment).* *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).*
SH	British Society of Gastroenterology	2	Full	16	20	These recommendations are slightly at odds with the BSG guidelines in Gut in 2014; 63:7-42. There we recommend: "Endoscopic screening can be considered in patients chronic GORD symptoms and multiple risk factors (at least three of age 50 years or older, white race, male sex, obesity). However, the threshold should be lowered in the presence of family history including at least one first degree relative with Barrett's or oesophageal adenocarcinoma (Recommendation grade C)" Since GPs will need toknow whom to refer in practice having consistent recommendations would be most helpful.	Thank you for your comments. NICE produces guidance independently based on rigorous, systematic and transparent processes and methodology. In essence, both NICE and the BSG guideline recommend to 'consider' endoscopy based on particular 'risk factors'. The inconsistency between the two guidelines is due to the different 'risk factors' in the recommendations. Different information was used to inform the recommendations which may explain this inconsistency NICE has used a different evidence-base to draw the recommendations on risk factors compared to the BSG guideline because the methodology used differed in 2 key respects. The 2 key methodological issues are outlined below: • To address the 'clinical prediction' question (i.e. risk factors to predict who with GORD are more likely to develop Barrett's), NICE only included studies that used a 'multivariate regression model' in the

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							analysis. This approach was taken to ensure the 'risk factors' of interest were appropriately 'adjusted' to other confounding factors that may, or could, have a 'modifying' or 'moderating' effect to the associations between the 'risk factors' of interest and the dependent variable, (in this case, those who developed Barrett's) in order to minimise the risk of bias. For this reason prevalence studies, or studies that only provided univariate analyses, were not included in the NICE systematic reviews. • Secondly, NICE did not 'meta-analyse' or pool the 'adjusted OR' from different individual studies as this was considered to be technically inappropriate, The approach taken by NICE was that the 'adjusted OR' should only be interpreted based on what has been 'adjusted' in that particular study. In order to pool the different adjusted OR from different studies an underlying assumption would need to be that all these studies have adjusted exactly the same baseline characteristics and confounding factors. This was not the case for the studies included in the NICE review. NICE considers that the most appropriate method to meta-analyse these kinds of studies is to conduct an Individual Patient Data meta-analysis (IPD meta-analysis) where all individual raw data points from all individual patients in all individual studies are obtained to construct such IPD meta-analysis. In this case, it was not possible to perform an IPD meta-analysis, as there were no published IPD available in order to do so.

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							The differences in methodology has resulted in some papers being included in the BSG guideline, for example, 2 meta-analysis papers (Cook et al. 2005; Taylor et.al. 2010), which were excluded, for methodological reasons in the systematic reviews within the NICE guideline. Therefore, we believe that NICE has drawn the recommendations from a rigorous evidence-base, based on a transparent and systematic approach.
SH	British Society of Gastroenterology	3	Full	17	7	Surveillance comes here and again on page 23 with a different emphasis which is confusing,	Thank you for your comment. Page 15 to beginning of page 17 are under the section title "**2.7 Key priorities for implementation**", where the GDG has prioritised 10 recommendations (out of the 62 in total in the guideline) to be implemented in the NHS. While the second half of page 17 to page 23 are the 'full list' of all the 62 recommendations in the guideline. This is the reason why the recommendation on surveillance for Barrett's oesophagus is repeated in 2 different sections.
SH	British Society of Gastroenterology	4	Full	23	20 23	***62. Do not routinely offer surveillance for people with Barrett's oesophagus*** ***63. Consider surveillance to check progression to cancer for people who have a diagnosis of Barrett's oesophagus (confirmed by endoscopy and histopathology) after first talking to the person about their preferences and risk factors (for example, male gender, older age***	Thank you for your comments. Please see responses below in relation to your comments:

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						and the length of the Barrett's segment). I think that the intentions of these statements are laudable i.e. be thoughtful when enrolling patients into surveillance and do not enrol everyone by default. Risk stratify as much as possible. The problem is that many clinicians will simply read statement 62 and conclude that surveillance is not indicated. This may not achieve the desired effect: 1) NICE have recently suggested that RFA should be used in patients with confirmed LGD (NICE IPAC committee out for public consultation). This is on the basis of new RCT evidence in JAMA for a significant reduction in progression to cancer when these patients are ablated. We need to find these individuals and if units stop surveillance we will not find them. Neither will we find the HGD. 2) This statement contradicts the recent NICE accredited BSG guidelines (Gut 2014) and every other international guideline and will therefore cause confusion. In the BSG guidelines we say that surveillance is indicated and we then go to great lengths to help clinicians	<u>For comment 1:</u> The remit of NICE Interventional Procedures Guidance is to only assess the safety and efficacy of an individual interventional procedure, without assessing its relative or comparative effectiveness or cost-effectiveness. Current draft NICE Interventional Procedures Guidance on Endoscopic radiofrequency ablation for squamous dysplasia of the oesophagus only proposed that Endoscopic radiofrequency ablation <u>is safe to be used</u> for squamous dysplasia of the oesophagus; it does not recommend it <u>should be used</u> across the NHS. Please note that RFA is outside of the scope for this guideline. <u>For comment 2:</u> After further discussion, taking into account of stakeholder comments, the GDG agreed to re-adjust the relevant recommendations to the following: *Consider surveillance to check progression to cancer for people who have a diagnosis of*

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						prioritise and risk stratify e.g. short segments of gastric type consider discharge, longer segments more frequent etc.	*Barrett's oesophagus (confirmed by endoscopy and histopathology), taking into account:* • *the presence of dysplasia (also see Barrett's oesophagus - ablative therapy - NICE clinical guideline CG106)* • *the person's individual preferences* • *the person's risk factors (for example, male gender, older age and the length of the Barrett's oesophagus segment).* *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)*.
						3) The data are indeed controversial. Much emphasis is put on the Corley paper in this NICE appraisal of the evidence. However these retrospective data (1995-2007) are problematic. It tells us more about how **not** to do surveillance than how to do it since the cases who progressed and died from cancer had dysplasia detected in previous surveillance procedures (LGD in 67%and HGD in 56%) and yet nothing was apparently done about it. These data were prior to endoscopic therapy being widely available.	<u>For comment 3:</u> We disagree that the Corley paper has been emphasised in the interpretation of the evidence-base. In the Full guideline Section 4.11.5 (Evidence to recommendations), the evidence-base was discussed by the GDG as a whole, no specific reference was made on the Corley paper. Moreover, the GDG discussed and developed the recommendations based on both clinical effectiveness evidence as well as cost-effectiveness evidence, where the latter suggested routine surveillance is not cost-effective for the general population of people with Barrett's oesophagus. The surveillance strategy represented by the economic model is dominated by a no surveillance strategy as it is more costly and generates fewer QALYs. This means that, on balance, the surveillance

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							strategy would cost more than a strategy of no surveillance and may cause patient harm. However, while the GDG acknowledged that indiscriminate surveillance appears to be dominated by no surveillance, it also believed that there is likely to be a subset of patients for whom a surveillance programme would be beneficial. After further discussion, taking into account of stakeholder comments, the GDG agreed to re-adjust the relevant recommendations to the following: *Consider surveillance to check progression to cancer for people who have a diagnosis of Barrett's oesophagus (confirmed by endoscopy and histopathology), taking into account:* • *the presence of dysplasia (also see Barrett's oesophagus - ablative therapy - NICE clinical guideline CG106)* • *the person's individual preferences* • *the person's risk factors (for example, male gender, older age and the length of the Barrett's oesophagus segment).* *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)*.
						An abstract has just been published (Bhat SK et al Gut 2014, Apr 3 Oeosphageal adenocarcinoma and prior diagnosis of Barrett's: a population based study), (I	Thank you for the reference. The technical team has checked this particular paper and it did not meet the inclusion criteria of this review protocol i.e. the paper did not address the question on

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						realise this was since the NICE review). This was larger and population based (cf Kaiser Permanente based review). This suggests that even given its shortcomings surveillance does improve outcome. This would be consistent with some of the previous studies. Hopefully the BOSS trial will bring higher quality data and more clarity. In the meantime we would propose that we either: simply refer to the BSG guidelines OR simply remove recommendation 62 and start "Consider surveillance to check progression…" OR alter the text to bring these recommendations in line with the BSG	the effectiveness of routine surveillance programme compared to no surveillance or opportunistic surveillance. The paper is purely an epidemiological study. The GDG agreed that the BOSS trial (still in development) will bring higher quality data and more clarity to this area. Please see above responses. After further discussion, taking into account stakeholder comments, the GDG agreed to re-adjust the relevant recommendations to the following: *Consider surveillance to check progression to cancer for people who have a diagnosis of Barrett's oesophagus (confirmed by endoscopy and histopathology), taking into account:* • *the presence of dysplasia (also see Barrett's oesophagus - ablative therapy - NICE clinical guideline CG106)* • *the person's individual preferences* • *the person's risk factors (for example, male gender, older age and the length of the Barrett's oesophagus segment).* *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)***.**
SH	British Society of Gastroenterology	5	Full	53	45	The suggestion for GPs to meet patients on acid suppressants once per year in person seems quite costly with no evidence to support this.	Thank you for your comment. This section of the guideline is outside the scope

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						Clearly the GPs should be reviewing meds regularly. This is standard.	to be updated in this guideline update. Therefore, we could not change this recommendation at this time.
SH	British Society of Gastroenterology	6	Full	23	24 Point 63	The BSG guideline is the first of any international guideline to bring in some risk stratification. We present the evidence for male gender but the consensus voting did not include it as we did not feel that the data was strong enough to help suggest how men and women should be surveilled differently in a practical sense.	Thank you for your comment. We interpret the technical term 'risk stratification' as a statistical method with appropriate multivariate regression modelling followed by validation studies with further calibration of the thresholds for the stratifications of different risks (or risk categories). We believe that currently no guideline or primary study have been published that used this appropriate method yet. Whilst the GDG acknowledged the 'consensus voting' of the BSG guideline on the issue of male gender as a risk factor, the GDG believe that based on their expertise and knowledge (and limited evidence), male gender should remain as an example of the risk factors that clinicians should consider when decisions about surveillance for people with Barrett's are made.
SH	British Society of Gastroenterology	7	Full	23	25 Point 63	Older age. Isn't fitness for surveillance and endoscopic intervention more relevant?	Thank you for your comment. Based on the GDG's expertise and knowledge (and limited evidence), the GDG believe that 'older age' (which may also reflect duration of the condition) should remain as an examples of the risk factors that clinicians should consider when decisions about surveillance for people with Barrett's are made.
SH	British Society of Gastroenterology	8	Full	23	24 Point 63	Patient preference is very difficult. Absolutely it should be a dialogue with the patient about the risk and benefits. The patient preference will be heavily influenced by how the evidence is	Thank you for your comment. The developers agree that having an effective dialogue between clinician and patient in order to inform patient preference is a very important

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						presented.	principle to adhere to.
SH	British Society of Gastroenterology	9	Full	270	4 -11	The surveillance intervals used in the model are not in line with current British and other international guidelines	Thank you for your comment. The surveillance intervals used followed the standard schedule within the model in the NICE evaluation of ablative therapy for the treatment of Barrett's oesophagus (http://www.nice.org.uk/nicemedia/live/13096/50243/50243.pdf). The Bhat analysis used as the health economic evidence for the question of surveillance for Barrett's oesophagus, included sensitivity analysis of different surveillance intervals. A change to surveillance time-points did not generate a cost-effective surveillance strategy.
SH	British Society of Gastroenterology	10	Full	General	General	It might be pertinent to point out that I cannot see the age groups to which this guideline refers - is it over 16 years only?	Thank you for pointing this error out. A statement of: *The guideline applies to adults (aged 18 and over) with symptoms suggestive of dyspepsia, symptoms suggestive of gastro-oesophageal reflux disease (GORD), or both'* has been added to the Overview section of the Full guideline. The age group for the guideline was adjusted in part due to an impending future guideline for gastro-oesophageal reflux disease in children and young people.
SH	Department of Health	1	Full	General	General	I wish to confirm that the Department of Health has no substantive comments to make, regarding this consultation.	Thank you.
SH	Health and Social Care Board, Northern Ireland	1	NICE	19	1.9.2	Within this review, among the areas from the original guideline that will not be updated but will appear in the final guideline is "Type of H pylori test (breath, stool, laboratory-based serology)".	Thank you for your comments. *H pylori* testing is outside the scope of this update.

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						The group felt that this section of the guidance should be reviewed due to the publication of recent evidence to indicate that the stool antigen test (SAT) is suitable for test of eradication. The group felt that this was the right direction of travel for NI HSC due to the clinical utility and suitability of the test, its low cost and potential to be a sustainable solution.	Your information has been passed to the surveillance team for further consideration.
SH	Health and Social Care Board, Northern Ireland	2	NICE	19	1.9.5	Offer people who are allergic to penicillin and who have had previous exposure to clarithromycin and a quinolone a 7-day, twice-daily course of treatment with: • a PPI (see table 3 in appendix A) and • clarithromycin and • metronidazole. [new 2014] If a patient has previous exposure to clarithromycin, surely this would NOT be in the regime?	Thank you for pointing out the error. This has now been corrected to: *1.9.5 Offer people who are allergic to penicillin a 7 day, twice-daily course of treatment with:* • *a PPI (see table 3 in appendix A) and* • *clarithromycin and* • *metronidazole.*
SH	London Cancer pathway board	1	NICE	21	1.12.1	This statement is confusing and should be entirely removed. In 1.12.1 it is stated 'Do not routinely offer surveillance for Barrett's oesophagus'. However, in 1.12.2 it is stated 'Consider surveillance…for Barrett's oesophagus (BE).' This second statement makes sense and is in line with the new British Society of Gastroenterology guidelines as well as those from other international specialist groups. The point about risk stratifying patients is well made and lies at the heart of the arguments about who should be surveyed. The first statement appears to directly contradict it. Further, many doctors will not even think once they see a bald statement about not routinely surveying.	Thank you for your comments. Please see the following responses in relation to your comments: <u>For comment 1:</u> We assume you are referring to the current draft NICE Interventional Procedures Guidance on Endoscopic radiofrequency ablation for squamous dysplasia. The remit of NICE Interventional Procedures Guidance is to only assess the safety and efficacy of an individual interventional procedure, without assessing its relative or comparative effectiveness or cost-effectiveness. Current draft NICE Interventional Procedures Guidance on Endoscopic radiofrequency ablation for squamous dysplasia

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						NICE now mandates endoscopic intervention for patients with high grade and low grade dysplasia in BE (new 2014). If units see that they don't need to survey BE patients, they will discharge them even if they are at significant risk. We will lose the opportunity to treat these patients. A great deal of weight appears to have been placed on the Corley paper – this paper is now old and has some significant weaknesses. The data were retrospective and really tells us about how not to do surveillance as most of those who actually developed cancer were found to have dysplasia but did not have it treated. These days, we would be offering HALO radiofrequency ablation. The national registry led by Dr Laurence Lovat (into which NICE is recommending that all patients with low grade dysplasia should be entered when treated) shows that the success rate of ablation is almost 90% and has long term durability. This discounts the arguments made by Corley et al.	of the oesophagus only proposed that Endoscopic radiofrequency ablation is safe to be used for squamous dysplasia of the oesophagus, it does not recommend it should be used across the NHS. Therefore, we disagree with your statement regarding NICE mandating endoscopic intervention for patients with high grade and low grade dysplasia in BE. For comment 2: We disagree that the Corley paper has been emphasised in the interpretation of the evidence-base. In section 4.11.5 Evidence to recommendations of the Full Guideline, the evidence-base was discussed by the GDG as a whole, no specific reference was made on the Corley paper. Moreover, the GDG discussed and developed the recommendations based on both clinical effectiveness evidence as well as cost-effectiveness evidence, where the latter suggested routine surveillance is not cost-effective for the general population of people with Barrett's. The surveillance strategy represented by the economic model is dominated by a no surveillance strategy as it is more costly and generates fewer QALYs. This means that, on balance, the surveillance strategy is certain to cost more than a strategy of no surveillance and may cause patient harm. However, while the GDG acknowledged that indiscriminate surveillance appears to be dominated by no surveillance, it also believed that there is likely to be a subset of patients for whom a surveillance programme would be

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							beneficial. After further discussion, taken into account of stakeholder comments, the GDG agreed to re-adjust the relevant recommendations to the following: *Consider surveillance to check progression to cancer for people who have a diagnosis of Barrett's oesophagus (confirmed by endoscopy and histopathology), taking into account:* • *the presence of dysplasia (also see Barrett's oesophagus - ablative therapy -NICE clinical guideline CG106)* • *the person's individual preferences* • *the person's risk factors (for example, male gender, older age and the length of the Barrett's oesophagus segment).* *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)*. Regarding the national registry data you mentioned, we suggest that these data should be published in a peer-reviewed journal so that it could be appraised as part of the evidence-base in the next update.
						A newer, larger, study has just come out in abstract form this year (Bhat SK …Murray LJ – Gut 2014). It suggests that surveillance does improve cancer outcomes, even though cancer risk is low. The new BSG guidelines now help us	Thank you for the reference. The technical team has checked this particular paper and it did not meet the inclusion criteria of this review protocol i.e. the paper did not address the question on the effectiveness of routine surveillance

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						to risk stratify our patients. They will significantly reduce the number of wasted endoscopies on very low risk patients.	programme compared to no surveillance or opportunistic surveillance.
SH	London Cancer pathway board	2	FULL	235	4.8.6	Need to add 'Patients with incomplete control of reflux symptoms'	Thank you for your comment. After further discussion, the GDG felt that as the evidence on the effectiveness of fundoplication was from trials that only included patients who had adequate symptom control with acid suppression therapy, they could not make any recommendation regarding fundoplication for patients who do not respond to acid suppression therapy. The GDG felt that this specific subgroup of patients is adequately covered by recommendations in section 4.9 Referral to specialist services, where it stated: *"Consider referral to a specialist service for people of any age with gastro-oesophageal symptoms that are non-responsive to treatment or unexplained".* The recommendations have been further modified to: *Consider laparoscopic fundoplication for people who have:* • *a confirmed diagnosis of acid reflux and adequate symptom control with acid suppression therapy but do not wish to continue with this therapy long term* • *a confirmed diagnosis of acid reflux and who are responding to PPI but cannot tolerate acid suppression therapy.*

Type	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
SH	NHS Choices, Digital Assessment Service	1	Full	General	General	Welcome the guideline and have no comments on its content.	Thank you.
SH	NHS England	1	NICE version	16	1.6.11	Obesity is a risk factor for the development of Barrett's Oesophagus and therefore for the ongoing development of dysplasia and malignancy. Therefore obesity should be included in the list of clinic parameters that might trigger a referral for endoscopy.	Thank you for your comments. From the systematic review, there is conflicting and inconclusive evidence regarding obesity as a risk factor. Moreover, the list of 'risk factors' in the recommendation is only an example, it does not meant to be an exhaustive list.
SH	NHS England	2	NICE version	21	1.12.2	Obesity is a risk factor for the development of Barrett's Oesophagus and therefore for the ongoing development of dysplasia and malignancy. Therefore obesity should be included in the list of clinic parameters that might trigger a referral for endoscopy.	Thank you for your comments. From the systematic review, there is conflicting and inconclusive evidence regarding obesity as a risk factor. Moreover, the list of 'risk factors' in the recommendation is only an example, it does not meant to be an exhaustive list.
SH	Northern Region Endoscopy Group	1	Full	16	20	Suggest rephrasing as when read superficially, this may be confused with Barrett's SURVEILLANCE	Thank you for your comment. The recommendation stated: *"Do not routinely offer endoscopy to diagnose Barrett's oesophagus…."*, we think the phrase is very clear that it is about 'to diagnose' Barrett's oesophagus rather than 'surveillance' for Barrett's oesophagus.
SH	Northern Region Endoscopy Group	2	Full	17	6	We recommend this guideline simply signposts the more comprehensive BSG/NICE Barrett's guideline published in 2014, or summarises it. Otherwise there is great potential for confusion. We would advocate a simple statement something like "Barrett's surveillance should be offered in line with the recommendations within the BSG/NICE guideline…"	Thank you for your comments. NICE produces guidance independently based on rigorous, systematic and transparent process and methodology. It is not appropriate to cross refer to recommendations in guidance produced by other organisations.

Type	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
SH	Northern Region Endoscopy Group	3	Full	General	General	There seem to be a lot of inconsistencies – advising in one place that all people with reflux symptoms have gastroscopy, in another that everyone with any form of dyspepsia is treated symptomatically.	Thank you for your comment. The guideline does not recommend all people with reflux symptoms to have endoscopy. The guideline only recommends 'consider' endoscopy if the person has GORD and has risk factors of developing Barrett's (Rec 1.6.11 of the NICE guideline); and also 'consider' referral to a specialist service (which may or may not include endoscopy) for people with gastro-oesophageal symptoms that are non-responsive to treatment or unexplained (Rec 1.11.1 of the NICE guideline).
SH	Northern Region Endoscopy Group	4	Full	General	General	The guidance doesn't seem to address cancer risk at all clearly. We appreciate that the NICE group on 2WW referral is writing its recommendations at the moment but the potential for a mismatch between the two guidelines, as we saw in 2005, is there once again.	Thank you for your comments. We share the same concerns. More editorial work will be carried out to appropriately cross refer to the NICE Suspected cancer update, which is expected to publish in May 2015.
SH	Oesophageal Patients Association with Action Against Heartburn	1	NICE	General	General	It is very sensible for the document overtly to include GORD in its title	Thank you.
SH	Oesophageal Patients Association with Action Against Heartburn	2	NICE	11	General	The new recommendation about referral for specialist examination regardless of age is strongly supported.	Thank you.
SH	Oesophageal Patients Association with Action Against Heartburn	3	NICE	21	1.12.1	The sentence '*Do not routinely offer surveillance for people with Barrett's oesophagus'* is counter-productive and confusing with its present wording. The practice which should apply is fairly summarised in 1.12.2 so the	Thank you for your comments. Please see the following responses in relation to your comments:

Type	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
			Full Full Full	P 16 P 20 P 23	Para 5 Para 30 Para 62	sentence in 1.12.1 should be omitted. There is sense in not enrolling all cases for surveillance thoughtlessly and by default, but the recently revised BSG Guidelines on Management of Barrett's Oesophagus emphasise the importance of risk stratification and provide a logical basis for that. The sentence is at odds with NICE guidance out for consultation about radio frequency ablation treatment for patients with low grade dysplasia. There are findings reported in *JAMA* for a significant reduction in progression to cancer when patients have undergone ablation. If we do not conduct surveillance we will not detect dysplasia or oesophageal adenocarcinoma.	 For comment 1: We interpret the technical term 'risk stratification' as a statistical method with appropriate multivariate regression model followed by a validation study with further calibration of the thresholds for the stratifications of different risks (or risk categories). We believe that currently no guidelines or studies have been published that used this appropriate method yet. For comment 2: The remit of NICE Interventional Procedures Guidance is to only assess the safety and efficacy of an individual interventional procedure, without assessing its relative or comparative effectiveness or cost-effectiveness. Current draft NICE Interventional Procedures Guidance on Endoscopic radiofrequency ablation for squamous dysplasia of the oesophagus only proposed that Endoscopic radiofrequency ablation is safe to be used for squamous dysplasia of the oesophagus; it does not recommend it should be used across the NHS. Regarding the JAMA paper you referred to, we are unable to identify it as no full reference was provided.

Type	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						The sentence contradicts NICE accredited BSG, and indeed international, guidelines.	For comment 3: After further discussion, taking into account of stakeholder comments, the GDG agreed to re-adjust the relevant recommendations to the following: *Consider surveillance to check progression to cancer for people who have a diagnosis of Barrett's oesophagus (confirmed by endoscopy and histopathology), taking into account:* • *the presence of dysplasia (also see Barrett's oesophagus - ablative therapy - NICE clinical guideline CG106)* • *the person's individual preferences* • *the person's risk factors (for example, male gender, older age and the length of the Barrett's oesophagus segment).* *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).*
						The approach may be relying on the Corley paper where the data were relevant for a period before more modern treatments were available. A paper by Bhat SK and others concludes that prior identification of Barrett's Oesophagus is associated with an improvement in survival of patients with oesophageal adenocarcinoma . http://gut.bmj.com/content/early/2014/04/03/gutjnl-2013-305506.abstract	For comment 4: We disagree that the Corley paper has been emphasised in the interpretation of the evidence-base. In the Full guideline section 4.11.5 Evidence to recommendations, the evidence-base was discussed by the GDG as a whole, no specific reference was made on the Corley paper. Moreover, the GDG discussed and developed the recommendations based on both clinical effectiveness evidence as well as cost-effectiveness evidence, where the latter

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							suggested routine surveillance is not cost-effective for the general population of people with Barrett's. . The surveillance strategy represented by the economic model is dominated by a no surveillance strategy as it is more costly and generates fewer QALYs. This means that, on balance, the surveillance strategy is certain to cost more than a strategy of no surveillance and may cause patient harm. However, while the GDG acknowledged that indiscriminate surveillance appears to be dominated by no surveillance, it also believed that there is likely to be a subset of patients for whom a surveillance programme would be beneficial. After further discussion, taken into account of stakeholder comments, the GDG agreed to re-adjust the relevant recommendations to the following: *Consider surveillance to check progression to cancer for people who have a diagnosis of Barrett's oesophagus (confirmed by endoscopy and histopathology), taking into account:* • *the presence of dysplasia (also see NICE clinical guideline CG106 - Barrett's oesophagus - ablative therapy)* • *the person's individual preferences* • *the person's risk factors (for example, male gender, older age and the length of the Barrett's oesophagus segment.* *Emphasise that the harms of endoscopic surveillance may outweigh the benefits in people*

Type	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
							who are at low risk of progression to cancer (for example people with stable, non-dysplastic Barrett's oesophagus).
						The risk factors for developing adenocarcinoma are variable within the Barrett's Oesophagus population, and one cannot legitimately exclude some people from surveillance unless there is a proper risk assessment. The very nature of a pre cursor condition demands surveillance of some kind.	<u>For comment 5:</u> We agree that the risk factors for developing adenocarcinoma are variable within the Barrett's Oesophagus population. Therefore NICE recommendation 1.12.2 recommends to consider surveillance for people who have specific risk factors. The GDG agreed that surveillance should not be offered as a blanket strategy to all people with Barrett's because firstly, it is not clinically or cost-effective and secondly, surveillance does carry certain risk of harm (e.g. perforation) particularly for those patients without any 'risk factors'. Therefore, the trade-off between benefits and harms needs to be considered particularly for those patients who do not have specific risk factors.
						There are numerous reports of earlier stage cancer detected during surveillance programmes (Peters et al, 1994; Wright et al, 1996; Van Sandick et al, 1998).	<u>For comment 6:</u> A full systematic review on *"Should surveillance be used for patients with Barrett's oesophagus to detect progression to cancer, and improve survival?"* has been conducted (please see Section 4.11 in the Full guideline). The critical appraisal and interpretation of all the available evidence, as well as the health economic evaluation have been detailed in section 4.11. The decision making process and the GDG's interpretation of the evidence are also clearly documented in the Full guideline.

Type	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						From a patient's standpoint, having been told they have a condition with a risk of progression to cancer, many will find it unacceptable not to be considered for endoscopic surveillance, particularly in view of papers quoted above. It would also undermine the strategy for earlier diagnosis in the Government's Cancer Strategy, and the recent *Be Clear on Cancer* campaign on oesophagogastric cancer - in NE England region, and hopefully on a national basis in 2015.	<u>For comment 7:</u> Recommendation 1.12.2 (recommendation 1.12.1 in the consultation version of the guideline) does now say to consider surveillance for Barrett's oesophagus. <u>For comment 8:</u> Dyspepsia as a possible cancer symptom will be covered by the NICE Suspected cancer update
SH	Oesophageal Patients Association with Action Against Heartburn	4	NICE	21	1.12.2	Patient preference can be heavily influenced by how the clinician presents the issues involved. Age in itself may be less relevant than the length of time suffering from symptoms of GORD, or a change in pattern of symptoms, including unexplained cessation of pain when the protective effect from pain of Barrett's oesophagus is completed. General fitness for endoscopic procedures may be a relevant issue. Transferring evidence about male gender into the context of surveillance decisions may not be justified, once the first endoscopy has been completed and a diagnosis of Barrett's and its extent has been reached.	Thank you for your comments. The GDG believe that based on their expertise and knowledge (and limited evidence), male gender and older age should remain as examples of the risk factors that clinicians should consider to decide surveillance for people with Barrett's. The GDG felt that 'older age' encompassed some degree of duration of the condition in the absence of evidence. Moreover, 'male gender, older age and the length of the Barrett's oesophagus segment' are only 'examples' of the risk factors (rather than an exhaustive list) as clearly stated in the recommendation. The GDG believe that clinicians need to make their clinical judgement on risk factors based on individual patients.
SH	Oesophageal Patients Association with Action Against	5	NICE	3	Para 5, line 5	Delete the word 'possible' in '*and the possible role of GORD….as a risk factor for cancer'.* The landmark study of Lagergen et al (1999) unequivocally defines the link between	Thank you for your comment. The systematic reviews on the evidence-base

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	Heartburn					heartburn, GORD and oesophageal adenocarcinoma	(not just based on one study) on GORD as a potential risk factor for Barrett's oesophagus and cancer did not provide conclusive evidence in this area. Hence, we believe the term 'possible' is the true reflection of the current evidence-base.
SH	Oesophageal Patients Association with Action Against Heartburn	6	NICE	10		Interventions for GORD. It is unclear what is meant here by gastro-oesophageal reflux disease – is this symptomatic reflux or endoscopically diagnosed GORD? Whilst under Recommendations P12 it is stated that GORD means endoscopically confirmed disease, if this applies on P10, it should be stated there.	Thank you for your comments. On page 12, under the section **Recommendations – Terms used in this guideline**, stated: *In this guideline, gastro oesophageal reflux disease (GORD) refers to endoscopically determined oesophagitis or endoscopy-negative reflux disease.* This definition, as stated, applies to GORD in the whole guideline. We therefore think it is not necessary to repeat this definition in every single recommendation that has the term GORD.
SH	Oesophageal Patients Association with Action Against Heartburn	7	NICE	11		Referral to a specialist service –the absence of an age criterion is a welcome development. In stating "gastro-oesophageal symptoms that are persistent", persistent should be defined.	Thank you for your comment. After further discussion, the GDG decided to remove the term 'persistent' from the recommendation as they agreed that the phrase in the recommendation 'non-responsive to treatment' has already covered the meaning of persistent symptoms.
SH	Oesophageal Patients Association with Action Against Heartburn	8	NICE	13	1.3.4	Referral guidance for endoscopy 1.3.4 line 2, word 2 should be "symptoms". *Signs* are physical signs detected by a physician on examination.	Thank you for your comment. This particular recommendation is from the 2004 original guideline which is not part of this guideline update and not part of this public consultation. Hence, it is outside the NICE process for the GDG to further define (or modify) this recommendation.

Type	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
SH	Oesophageal Patients Association with Action Against Heartburn	9	NICE	21	1.10.1	Laparoscopic Fundoplication - A third indication for consideration of laparoscopic fundoplication should be those patients with proven GORD who do not respond to acid suppression therapy. Para 1.6.10 recognises that a group of GORD patients will have persistent severe oesophagitis despite PPI therapy and some of these will not respond to high dose PPI. This is because many of these patients reflux both acid and duodenal juice, where acid suppression therapy worsens the situation by inhibiting neutralization of the alkaline refluxate. Only fundoplication can reverse the effect of duodenal juice reflux.	Thank you for your comments. After further discussion, the GDG felt that as the evidence on the effectiveness of fundoplication was from trials that only included patients who had adequate symptom control with acid suppression therapy, they could not make any recommendation regarding fundoplication for patients who do not respond to acid suppression therapy. The GDG felt that this specific subgroup of patients is adequately covered by recommendations in Section 4.9 (Referral to specialist services), where it stated: *"Consider referral to a specialist service for people of any age with gastro-oesophageal symptoms that are non-responsive to treatment or unexplained".* The recommendations have been further modified to: *Consider laparoscopic fundoplication for people who have:* • *a confirmed diagnosis of acid reflux and adequate symptom control with acid suppression therapy but do not wish to continue with this therapy long term* • *a confirmed diagnosis of acid reflux and who are responding to PPI but cannot tolerate acid suppression therapy.*
SH	Oesophageal Patients Association with Action Against Heartburn	10	NICE	16	1.6.11	The comments about *Do not routinely offer surveillance..* re 1.12.1 above apply. If the guidance is addressed to primary care, it would in any event be a referral to a specialist team rather than 'offering endoscopy'. Later stage	Thank you for your comments. Recommendation 1.6.11 is for people who have GORD, based on the evidence from the systematic reviews. There is no evidence

Type	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						Barrett's Oesophagus can entail loss of symptoms because of the effect of Barrett's cells protecting the patient from pain, so amend to 'has a history of GORD'	identified for the population who 'has a history of GORD' in the evidence review. Hence, we do not think it is appropriate to extend the recommendation for this subgroup in the absence of evidence.
SH	Pfizer Ltd.	1	NICE	General	General	Pfizer supports recommendations about the role of Community Pharmacy in the management of dyspepsia/GORD, including advice about OTC medication (recommendation 1.1). Pfizer also supports the recommendations to offer PPI therapy as the initial treatment option throughout this guideline. Whilst recognising that these recommendations are unchanged from previous versions of the Guideline, we are concerned that the Guideline Committee was not aware of the recent approval of a PPI therapy (Nexium [esomeprazole magnesium]) as an over-the-counter (OTC) medication at the time of drafting the new guideline. Pfizer is also seeking approval for Nexium (esomeprazole magnesium) to be included on the general sales list (GSL) and a decision is expected in August 2014. With the availability of PPI therapy now as an OTC, we suggest that it would be appropriate to develop and/or strengthen recommendations in this guideline relating to the role of pharmacy and self-care in the treatment of dyspepsia/GORD with a PPI. Self-treatment is well established for heartburn; indeed 95% of heartburn treatments are bought	Thank you. Thank you for the information. This will be considered by the NICE Surveillance Programme to assess the need for further update. The section on to the role of pharmacy and self-care in the treatment of dyspepsia/GORD with a PPI is outside the scope to be updated in this specific guideline update, and therefore was not part of this public consultation. Hence, it is outside the NICE process to update these recommendations at this time. The section on the role of pharmacy and self-care in the treatment of dyspepsia/GORD with a

Type	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						via GSL channels (IRI data November 2013). In line with DH and MHRA policy, a stronger focus on self-care and pharmacy-led care will enable the 'expert' patient to take ownership of their condition. Furthermore, the introduction to the guideline states that: "*Some of the costs associated with treating dyspepsia are decreasing, but the overall use of treatments is increasing. As a result, the management of dyspepsia continues to have potentially significant costs to the NHS".* Pfizer suggests that a recommendation to try an OTC PPI prior to consulting a primary care physician may help to reduce the burden of minor ailments in primary care and also help with the diagnostic process. Similarly, we suggest that recommendations relating to the role of Community Pharmacy and self-care in the longer-term, maintenance treatment with a PPI should also be added.	PPI is outside the scope to be updated in this guideline update, and therefore was not part of this public consultation. Hence, it is outside the NICE process to update these recommendations at this time. The section on to the role of Community Pharmacy and self-care in the longer-term, maintenance treatment with a PPI is outside the scope to be updated in this specific guideline update, and therefore was not part of this public consultation. Hence, it is outside the NICE process to update these recommendations at this time.
SH	Pfizer Ltd.	2	NICE	13	1.2.5	The draft guideline currently states: "Encourage people who need long-term management of dyspepsia symptoms to reduce their use of prescribed medication stepwise: by using the effective lowest dose, by trying 'as-needed' use when appropriate, and by returning to self-treatment with antacid and/or alginate therapy (unless there is an underlying condition or comedication that needs continuing treatment). **[2004, amended 2014]**". Pfizer would like to highlight to NICE that alternative treatments are available over-the-counter (OTC), such as PPI therapy, so giving	Thank you for your comments. This particular recommendation is not part of this guideline update. It has only been re-edited based on NICE style without changing its intent. Therefore, it is outside the remit of this guideline update to change this particular recommendation.

Type	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						an alternative to antacid and/or alginate treatment. Pfizer would like to see PPI's mentioned and added to the recommended list**.**	
SH	Pfizer Ltd.	3	NICE	14	1.5.2	The draft guideline currently states: "Advise people that it may be appropriate for them to return to self-treatment with antacid and/or alginate therapy (either prescribed or purchased over-the-counter and taken as needed). **[2004, amended 2014]**". Pfizer would like to highlight to NICE that alternative treatments are available over-the-counter (OTC), such as PPI therapy, so giving an alternative to antacid and/or alginate treatment. Pfizer would like to see PPI's mentioned and added to the recommended list**.**	Thank you for your comments. This particular recommendation is not part of this guideline update. It has only been re-edited based on NICE style without changing its intent. Therefore, it is outside the remit of this guideline update to change this particular recommendation.
SH	Pfizer Ltd.	4	NICE	16	1.6.9	We note that section 1.6.9 states the following: "*Offer a full-dose PPI (see table 2 in appendix A) long-term as maintenance treatment for people with severe oesophagitis, taking into account the person's preference and clinical circumstances (for example, tolerability of the PPI, underlying health conditions and possible interactions with other drugs), and the acquisition cost of the PPI. [new 2014]*" With the availability of PPI therapy over-the-counter, we would urge the Committee to add a recommendation that clinicians consider the role of pharmacy and self-care in the long-term treatment of patients, particularly given the request to take acquisition cost of the PPI into account.	Thank you for your comments. This recommendation refers to people with 'severe oesophagitis' rather than the general population with GORD whom could be considered for self-care. Therefore the GDG agreed for this severe population, it is not appropriate to encourage self-care with OTC PPIs.

Type	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
SH	RD Biomed Limited	1	Full	321		Your definition of GORD (page 321) notes 'a condition with predominantly the sensation of **stomach contents** returning past the oesophageal sphincter, prolonging acid and **pepsin** exposure in the lower oesophagus'. With reference to pepsin exposure in the definition of GORD, RD Biomed Ltd are surprised that no further reference was made to the aggressive and damaging effects of pepsin reflux exposure within the draft guideline. There is an extensive scientific and clinical literature describing the role of pepsin in oesophageal damage in general [ref 1-4] and that pepsin remains active until around pH 6.5 and is not irreversibly denatured until above pH 7.8 [ref 5]. We consider that pepsin plays a key role in the aetiology and pathology of dyspepsia/GORD especially in patients that do not respond to acid suppression [ref 6-7]. A recent review published at the end of 2012 "Reflux revisited – advancing the role of pepsin" [ref 8] summarises the pepsin literature and highlights it role in dyspepsia/GORD. We believe that greater attention should be paid to pepsin, this aggressive gastric enzyme. Furthermore, pepsin being an important digestive enzyme and found only in the stomach can be used as a reliable indicator that the stomach contents have refluxed into the lower oesophagus (and also larynx, throat and airways) [ref 9-12]. Reference to the clinical utility of immunological detection of pepsin was first made in the early 1990s [ref 13-14].	Thank you for your comments and references. The role of pepsin in the aetiology of GORD and the diagnosis of GORD are outside the scope of this guideline update but information about pepsin studies will be passed on to the surveillance team for consideration when the guideline is next reviewed for update.

Type	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						More recently a medical device has been launched (Peptest) based on two unique human anti-pepsin monoclonal antibodies which can rapidly detect the presence of pepsin in saliva/sputum clinical samples and be used to diagnose the presence of reflux. This completely non-invasive lateral flow device has undergone validation in various patient groups and has sensitivity of 69-95% and specificity of 63-100% [ref 15-19]. The test is rapid, non-invasive and cost effective especially when compared to other invasive diagnostic procedures. Suggested key references : [1] Goldberg et al. (1969) *Gastroenterology* **56** (2):223- 230 [2] Gotley et al (1992) *Aust NZ J Surg* **62** (7):569-575 [3] Tobey *et al.* (2001) *Am J Gastroenterol* **96** (11):3062-3070 [4] Nagahama *et al.* (2006) *Dig Dis Sci* **51** (2):303-309 [5] Johnston et al (2007) *Laryngoscope* **117** (6):1036-1039 [6] Roberts (2006) *Aliment Pharmacol Therap* **24** (suppl 2):2-9 [7] Tack (2006) *Aliment Pharmacol Therap* **24** (suppl 2):10-16 [8] Bardhan KD, Strugala V, Dettmar PW. (2012) *Int J Otolaryngol* **2012**:doi:10.1155/2012/646901 [9] Yuksel et al (2012) *Laryngoscope* **122** (6):1312-1316 [10] Potlurri et al (2003) *Dig Dis Sci* **48** (9):1813-1817 [11] Knight et al (2005) *Laryngoscope* **115** (8):1473-1478	

Type	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						[12] Samuels & Johnston (2010) *Annals Otol Rhinol Laryngol* **119** (3):203-208 [13] Coan et al (1994) *Dig Dis Sci* **39** (4):893-895 [14] Blackburn et al (1991) *Gut* **32** :A1257 [15] De Bortoli et al (2012) *Gut* **61** (Suppl3):A199 [16] Bor et al (2012) *Gut* **61** (Suppl 3) A83 [17] De Bortoli et al (2013) *Gastroenterology* **144** (5 Suppl 1): S118 [18] Hayat et al (2013) *UEG Journal* **1** (5 Suppl 1) A112 [19] Hayat et al (2014) *Gut* in press	
SH	RD Biomed Limited	2	Full	11	24 -27 32-34	The NHS constitution states the importance of taking into account a patients individual needs, preferences and to offer a good patient experience. Should this therefore drive the need to discuss other patient-led options in dyspepsia/GORD pathways? In a recent survey "Patient led approach to understanding the patient experience of reflux" conducted by CPD[4] Health Innovation (Dr Elaine McNichol, April 2013) patients were interviewed relating to the complete patient experience from first seeing their GP to secondary care consultation and the various diagnostic procedures which they were given. The learning from this comprehensive survey can help support the NICE initiative and guidance for good patient experience. Dyspepsia and GORD clearly impacts patients' lives and can take several months and in some cases years to reach a satisfactory diagnosis. The early diagnosis of dyspepsia/GORD is essential for the patient and if this can be	Thank you for the information. The developer agrees that patient experience and individual preference is important. The diagnosis of dyspepsia and GORD are outside the scope of this particular guideline update.

Type	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						achieved rapidly, non-invasively and easily understood this is added advantage for the patient. We wish to draw attention to NICE that the diagnosis of GORD could be speeded up by the introduction of a simple, rapid and non-invasive procedure such as Peptest, a simple lateral flow device that can detect the presence of pepsin refluxed from the stomach, above the upper oesophageal sphincter, and into the oesophagus, larynx, throat and airways. The need for invasive tests such as endoscopy could be reduced or inappropriate long-term prescription of PPIs could be avoided with the consideration of the early use of Peptest.	
SH	RD Biomed Limited	3	Full	18	24	Why has the option of early non-invasive diagnostic tests (such as salivary detection of pepsin antigens) not been considered by NICE to answer the obvious question as to whether dyspepsia symptoms are due to GORD ?	Thank you for your comment. Diagnosis and assessment of GORD are outside the scope of this guideline update.
SH	RD Biomed Limited	4	Full	19	20 21	Should NICE not suggest additional alternative treatments to just increased acid suppression for GORD if PPI response is inadequate? Raft–forming alginate suspensions are effective options that should be considered.	Thank you for your comment. The recommendation you referred to in the Full guideline (page 19, line 20-21) is the original recommendation in the original guideline (2004) which is outside the scope to be updated in this guideline update. Therefore, it is outside our scope and process to re-consider this particular recommendation.
SH	RD Biomed Limited	5	Full	279	1 -10	We wish to draw attention of NICE to a newly accepted paper in Gut [ref 19] that may assist in helping target the Research Recommendation section 5.5 Specialist investigations. Using a salivary pepsin diagnostic test subjects	Thank you for the information. Diagnosis of GORD is outside the scope of this guideline update.

Type	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						all underwent pH-impedance (MII-pH) testing to define controls, real GORD, hypersensitive oesophagus and functional heartburn (symptoms but normal MII-pH). This study showed that those with functional heartburn had the same pepsin prevalence as controls but GORD and HO were much higher. Thus there is the opportunity to review this data to help drive your suggested research question. [19] *Hayat, Gabieta-Somnez, Yazaki, Kang, Woodcock, Dettmar, Mabary, Knowles, Sifrim Pepsin in saliva for the diagnosis of gastro-oesophageal reflux disease.* Gut in press	
SH	RD Biomed Limited	6	Full	279	1	We would like to suggest that a further Research Recommendation is considered relating to the potential for early use of non-invasive diagnostic tools within Dyspepsia /GORD, for example Peptest is a licensed in vitro diagnostic that detects pepsin as a biomarker of reflux . Early primary care identification of those with objective evidence of reflux of gastric contents (pepsin and acid) and therefore GORD can offer several benefits: • Targeted PPI therapy in those warranted rather than using as an empirical test in itself (side effects of pharmacological agents, cost) • Reduction in the need to refer for endoscopy (This offers the potential to release free endoscopy sessions for more urgent cancer screening) • A more patient-centred approach The in vitro diagnostic medical device Peptest is based on two unique human anti-pepsin	Thank you for your comments. Based on NICE Guideline Manual (2012), research recommendations should be developed by the GDG to address clinical areas with uncertainty or where there is a gap in current evidence-base, based on the scope of the guideline. As the diagnosis of dyspepsia and GORD are outside the scope of this guideline update, it is not appropriate to consider an additional research recommendation that is not within the scope of this update.

Type	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						monoclonal antibodies which can rapidly detect the presence of pepsin in saliva/sputum clinical samples and be used to diagnose the presence of reflux. This completely non-invasive lateral flow device has undergone validation in various patient groups and has sensitivity of 69-95% and specificity of 63-100% [ref 15-19]. The test is rapid, non-invasive and cost effective especially when compared to other invasive diagnostic procedures. References [15] De Bortoli et al (2012) *Gut* **61** (Suppl3):A199 [16] Bor et al (2012) *Gut* **61** (Suppl 3) A83 [17] De Bortoli et al (2013) *Gastroenterology* **144** (5 Suppl 1): S118 [18] Hayat et al (2013) *UEG Journal* **1** (5 Suppl 1) A112 [19] Hayat et al (2014) *Gut* in press	
SH	RD Biomed Limited	7	Full	39	15 -17	Review question: When (and with what indications) should patients with investigated dyspepsia be referred for endoscopy for further investigations and review of treatment plan? RD Biomed Ltd wish to draw to the attention of NICE that a simple, rapid, non-invasive diagnostic test exists that can be used first line before endoscopy in those patients with investigated dyspepsia with no other risk factors to confirm or deny the existence of GOR. Peptest diagnoses reflux disease using a simple lateral flow device by detecting the presence of pepsin in a saliva/sputum clinical sample provided by the patient. In patients known to have GORD (against a	Thank you for your comments and references. This review question is aimed to investigate 'referral criteria' for further investigation, not about investigating the diagnostic accuracy of tests. Diagnosis of GORD is outside the scope of this guideline update.

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						'gold-standard' diagnostic, [ref 15-19]) Peptest has a sensitivity of 69-95% and a positive predictive value of 61-100% and thus a high likelihood that GORD is causing the symptoms. In those patients where no pepsin was detected (specificity 63-100%) there is a negative predictive value of 57-80% indicating that symptoms were probably not due to GORD and further diagnostic investigation by endoscopy would then be the next step in the diagnostic plan. References [15] De Bortoli et al (2012) *Gut* **61** (Suppl3):A199 [16] Bor et al (2012) *Gut* **61** (Suppl 3) A83 [17] De Bortoli et al (2013) *Gastroenterology* **144** (5 Suppl 1): S118 [18] Hayat et al (2013) *UEG Journal* **1** (5 Suppl 1) A112 [19] Hayat et al (2014) *Gut* in press	
SH	RD Biomed Limited	8	Full	general	general	This is a detailed list of all peer reviewed manuscripts and abstracts pertaining specifically to Peptest for your information. 1. Hayat JO, Yazaki E, Kang J-Y, et al. Pepsin in saliva and gastroeophageal reflux monitoring in 100 healthy asymptomatic controls. Gastroenterology 2013;144(5 (Suppl 1)):S-118. 2. Hayat JO, Woodcock A, Dettmar P, et al. Is pepsin detected in saliva of healthy individuals? Gut 2013;62(suppl 1):A108-109. 3. Hayat JO, Gabieta-Gomez S, Yazaki E, et al. Pepsin in saliva and gastroesophageal reflux monitoring in 100 healthy asymptomatic subjects and 65 patients with significant heartburn/regurgitation. UEG Journal	Thank you for your references. Diagnosis of dyspepsia and GORD are outside the scope of this particular guideline update.

Type	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						2013;1(Suppl 1):A112. 4. Faruqi S, Woodcock AD, Dettmar PW, Morice AH. Pepsin detection in expectorated saliva: a useful marker of airway reflux? Thorax 2013;68(Suppl 3):A19-20. 5. Dudziak JM, Crooks MG, Woodcock AD, et al. Salivary pepsin as a biomarker of airway reflux in idiopathic pulmonary fibrosis - an observational study. Thorax 2013;68(Suppl 3):A18-19. 6. Crossfield GL, Krishnan A, Lordan J, et al. Gastric aspiration into the CF lung - relationship with reflux symptoms and lung function. Journal of Cystic Fibrosis 2013;12(Suppl 1):S5. 7. Crossfield GL, Jackson W, Burke J, et al. Pepsin detection despite the use of acid suppressant medication in patients with airway reflux related chronic cough. Thorax 2013;68(Suppl 3):A19. 8. Yuksel ES, Hong S-KS, Strugala V, et al. Rapid salivary pepsin assay: blinded assessment of test performance in GERD. Laryngoscope 2012;122(6):1312-1316. 9. Woodcock A, Li S, Zhang C, et al. The effect of meal intake and physical activity on pepsin concentrations detected in the saliva of free-living, healthy individuals. J Gastroenterol Hepatol 2012;27(Suppl 5):319. 10. Hayat JO, Yazaki E, Moore AT, et al. Novel techniques for assessing oesophagopharyngeal reflux in patients with hoarseness and suspected laryngopharyngeal reflux. Gut 2012;61(Suppl 2):A260. 11. Hayat JO, Kang J-Y, Dettmar PW, et al. Do patients with hoareness and endoscopic signs of of LPR have abnormal esophago-pharyngeal	

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						reflux? A study using simultaneous impedance-pHmetry, oro-pharyngeal pH monitoring (Restech) and pepsin measurement in saliva. Gastroenterology 2012;142(5 (Suppl 1)):S-411-S-412. 12. de Bortoli N, Savarino E, Furnari M, et al. Evaluation of a non-invasive pepsin diagnostic test to detect GERD: correlation with MII-pH in a series of suspected NERD patients. A pilot study. Gut 2012;61(Suppl 3):A199. 13. Brownlee IA, Woodcock A, Zhang C, et al. Assessment of the potential of a novel detection method for measuring pepsin as a biomarker of reflux. J Gastroenterol Hepatol 2012;27(Suppl 5):319. 14. Bor S, Capanoglu DS, Yildirim E, et al. The validation of Peptest a new non-invasive technology for the diagnosis of laryngopharyngeal relfux (LPR). Gut 2012;61(Suppl 3):A83. 15. Fahim A, Dettmar PW, Morice AH, Hart SP. Gastroesophageal reflux and idiopathic pulmonary fibrosis: a prospective study. Medicinia (Kaunas) 2011;47(4):200-205. 16. Strugala V, Faruqi S, Dettmar PW, Morice AH. Detection of pepsin in sputum and exhaled breath condensate: could it be a useful marker for reflux-related respiratory disease? Eur Resp J 2009(abstract in press). 17. Strugala V, Dettmar PW, Morice AH. Detection of pepsin in sputum and exhaled breath condensate: could it be a useful marker for reflux-related respiratory disease? Gastroenterology 2009;136(5 (Suppl 1)):S1895. 18. Hong S-KS, Dettmar PW, Slaughter JC, et al. Salivary pepsin in patients with refractory	

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						GERD: double blind assessment of test sensitivity, specificity, positive and negative predictive values. Gastroenterology 2009;136(5 (Suppl 1)):382. 19. Strugala V, McGlashan JA, Morice AH, Dettmar PW. Use of a noninvasive pepsin diagnostic test for reflux: a series of case studies. J Clin Gastroenterol 2008;42(Suppl 1):S8. 20. Strugala V, Printza A, Triaridis S, Dettmar PW. Detection of pepsin after longitudinal sampling of sputum from patients with extra-oesophageal reflux disease. Gut 2007;56(Suppl III):A212. 21. Strugala V, McGlashan JA, Watson MG, et al. Detection of pepsin using a non-invasive lateral flow test for the diagnosis of extra-oesophageal reflux - results of a pilot study. Gut 2007;56(Suppl III):A212. 22. Strugala V, McGlashan JA, Watson MG, et al. Evaluation of a non-invasive pepsin dipstick test for the diagnosis of extra-oesophageal reflux – results of a pilot study. Gastroenterology 2007;132(4 (Suppl 2)):A99-A100. 23. Strugala V, Leonard JC, Dettmar PW. The effect of storage conditions on the stability of human pepsin. Gut 2007;56(Suppl III):A233. 24. Strugala V, Farndale AJ, Jacob J, Dettmar PW. Diagnosis of reflux using pepsin as a marker. Logopedics Phoniatrics Vocology 2005;110(Suppl 1):16-17. 25. Farndale AJ, Dettmar PW, Strugala V. Effects of centrifugation on human saliva samples in reducing sample variability in specific pepsin measurement. Logopedics Phoniatrics Vocology 2005;30(Suppl 1):36-37.	

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SH	Royal College of Nursing	1	Full	General	General	This is to inform you that the Royal College of Nursing have no comments to submit to inform on the above guideline consultation at this time.	Thank you.
SH	Royal Pharmaceutical Society	1	Full	General	General	The Royal Pharmaceutical Society welcomes this update of the NICE clinical guideline on dyspepsia and supports the acknowledgement of the important role that community pharmacists have in offering initial and ongoing advice to patients with dyspepsia and GORD symptoms.	Thank you.
SH	Torax Medical Inc	1	Full	General	General	There is no mention of the LINX Reflux Management System as a surgical alternative to laparoscopic fundoplication. I would be happy to supply clinical data on this relatively new method of treating refractory GORD patient.	Thank you for your comments. The LINX Reflux Management System is outside the scope of this particular guideline update.
SH	University College Hospitals NHS Foundation Trust	1	NICE	21	1.10.1	I suggest adding in to the first reason for considering lap fundoplication 'a confirmed diagnosis of acid reflux with adequate symptom control….' This prevents unscrupulous surgeons from hiding behind a poorly worded NICE recommendation that anyone who responds to PPIs should have this surgery. Clearly many people who *do not* have GORD respond to PPIs!	Thank you for your comments. After further discussion, taking into account of stakeholder comments, the GDG agreed to re-adjust the relevant recommendations to the following: *Consider surveillance to check progression to cancer for people who have a diagnosis of Barrett's oesophagus (confirmed by endoscopy and histopathology), taking into account:* • *the presence of dysplasia (also see Barrett's oesophagus - ablative therapy - NICE clinical guideline CG106)* • *the person's individual preferences* • *the person's risk factors (for example, male gender, older age and the length of the Barrett's oesophagus segment).* *Emphasise that the harms of endoscopic*

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							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).
SH	University College Hospitals NHS Foundation Trust	2	NICE	21	1.11.1	The middle recommendation is to Consider referring anyone who is thinking about surgery to a specialist service. I would argue that for this indication, the recommendation should be stronger (ie Refer…). There are still surgeons who dabble in this type of surgery, without properly investigating their patients. I regularly see people who should never have been operated on but who were not properly investigated prior to surgery.	Thank you for your comments. Due to a lack of good quality evidence in referral criteria, the GDG felt that they could not make a strong recommendation other than 'consider'.
SH	University College Hospitals NHS Foundation Trust	3	NICE	21	1.12.1	This statement is confusing and **should be entirely removed**. In 1.12.1 you say Do not routinely offer surveillance for Barrett's oesophagus. However, in 1.12.2 you state 'Consider surveillance…for Barrett's oesophagus (BE).' This second statement makes sense and is in line with the new British Society of Gastroenterology guidelines as well as those from other international specialist groups. The point about risk stratifying patients is well made and lies at the heart of the arguments about who should be surveyed. The first statement appears to directly contradict it. Further, many doctors will not even think once they see a bald statement about not routinely surveying.	Thank you for your comments. Please see the following responses in relation to your comments: <u>For comment 1:</u> After further discussion, taking into account of stakeholder comments, the GDG agreed to re-adjust the relevant recommendations to the following: *Consider surveillance to check progression to cancer for people who have a diagnosis of Barrett's oesophagus (confirmed by endoscopy and histopathology), taking into account:* • *the presence of dysplasia (also see Barrett's oesophagus - ablative therapy - NICE clinical guideline CG106)* • *the person's individual preferences* • *the person's risk factors (for example, male gender, older age and the length of the*

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							Barrett's oesophagus segment). *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).*
						NICE now mandates endoscopic intervention for patients with high grade and low grade dysplasia in BE (new 2014). If units see that they don't need to survey BE patients, they will discharge them even if they are at significant risk. We will lose the opportunity to treat these patients.	<u>For comment 2:</u> We assume you are referring to the current draft NICE Interventional Procedures Guidance on Endoscopic radiofrequency ablation for squamous dysplasia. The remit of NICE Interventional Procedures Guidance is to only assess the safety and efficacy of an individual interventional procedure, without assessing its relative or comparative effectiveness or cost-effectiveness. Current draft NICE Interventional Procedures Guidance on Endoscopic radiofrequency ablation for squamous dysplasia of the oesophagus only proposed that Endoscopic radiofrequency ablation <u>is safe to be used</u> for squamous dysplasia of the oesophagus; it does not recommend it <u>should be used</u> across the NHS. Therefore, we disagree with your statement regarding NICE mandate endoscopic intervention for patients with high grade and low grade dysplasia in BE.
						My question to myself is why NICE has made statement 1.12.1 As I understand it, a great deal of weight has been placed on the Corley paper – this paper is now old and has some	<u>For comment 3:</u> We disagree that the Corley paper has been emphasised in the interpretation of the evidence-base. In the Full guideline section

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						significant weaknesses. The data were retrospective and really tells us about how *not* to do surveillance as most of those who actually developed cancer were found to have dysplasia but did not have it treated. These days, we would be offering HALO radiofrequency ablation. The national registry which I lead (into which NICE is recommending that all patients with low grade dysplasia should be entered when treated) shows that the success rate of ablation is almost 90% and has long term durability. This really discounts the arguments made by Corley et al. A newer, larger, study has just come out in abstract form this year (Bhat SK …Murray LJ – Gut 2014). It suggests that surveillance *does* improve cancer outcomes, even though cancer risk is low. The new BSG guidelines now help us to risk stratify our patients. They will significantly reduce the number of wasted endoscopies on very low risk patients.	4.11.5 Evidence to recommendations, the evidence-base was discussed by the GDG as a whole, no specific reference was made on the Corley paper. Moreover, the GDG discussed and developed the recommendations based on both clinical effectiveness evidence as well as cost-effectiveness evidence, where the latter suggested routine surveillance is not cost-effective for the general population of people with Barrett's. The surveillance strategy represented by the economic model is dominated by a no surveillance strategy as it is more costly and generates fewer QALYs. This means that, on balance, the surveillance strategy is certain to cost more than a strategy of no surveillance and may cause patient harm. However, while the GDG acknowledged that indiscriminate surveillance appears to be dominated by no surveillance, it also believed that there is likely to be a subset of patients for whom a surveillance programme would be beneficial. Thank you for the reference. The technical team has checked this particular paper and it did not meet the inclusion criteria of this review protocol i.e. the paper did not address the question on the effectiveness of routine surveillance programme compared to no surveillance or opportunistic surveillance.
SH	University College	4	NICE	21	1.12.2	Risk stratification is an excellent idea. The first real attempt to do this in national guidelines is	Thank you for your comments.

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	Hospitals NHS Foundation Trust					the new BSG guidelines. They very carefully did *not* include male sex or age. Male sex – the evidence was not strong enough. Age – the issue is fitness for endoscopic therapy not age. I have treated many octagenarians who have lived for a decade or longer after treatment in good health. Patient preference – this will be greatly influenced by how the evidence is presented. I would therefore suggest that this statement is modified to: …. After talking to the person about their preferences and risk factors (and leave out the details entirely)	We interpret the technical term 'risk stratification' as a statistical method with appropriate multivariate regression modelling followed by validation studies with further calibration of the thresholds for the stratifications of different risks (or risk categories). We believe that currently no guideline or primary study have been published that used this appropriate method yet. Whilst the GDG acknowledged the 'consensus voting' of the BSG guideline on the issue of male gender and age as risk factors, the GDG believe that based on their expertise and knowledge (and limited evidence), male gender and older age should remain as examples of the risk factors that clinicians should consider for decide surveillance for people with Barrett's. Essentially, the recommendation stated 'consider' older age as a risk factor, it doesn't state to exclude older people with the assumption that older people will have less fitness.
SH	University College Hospitals NHS Foundation Trust	5	NICE	24	2.4	The research question is good. In describing research goals, you are suggesting that patients with symptoms but no diagnosed reflux might benefit from amitryiptylene. Whilst this is true, there is also a group of people who have proven reflux but do not respond completely to PPIs. These people sometimes do rather well on amitriptyline also. So I think the section on 'Why this is important' needs to be broadened in scope.	Thank you for your comments. The GDG felt that this specific group of patients are already covered in Section 2.9.8 Interventions for functional dyspepsia, in the Full guideline (which is outside the scope to be updated in this particular guideline update).

These organisations were approached but did not respond:

AbbVie

Aintree University Hospital NHS Foundation Trust

Airedale NHS Trust

Alder Hey Children's NHS Foundation Trust

Allocate Software PLC

Association of Anaesthetists of Great Britain and Ireland

Association of British Healthcare Industries

Association of Surgeons of Great Britain and Ireland

Astrazeneca UK Ltd

Barrett’s Oesophagus Campaign

Boehringer Ingelheim

Bolton Hospitals NHS Trust

Boots

Boston Scientific

Bradford District Care Trust

British Acupuncture Council

British Association for Psychopharmacology

British Dietetic Association

British Geriatrics Society - Gastroenterology and Nutrition Special Interest Group

British Geriatrics Society

British Infection Association

British Medical Journal

British National Formulary

British Nuclear Cardiology Society

British Nuclear Medicine Society

British Pain Society

British Psychological Society

British Red Cross

British Society for Antimicrobial Chemotherapy

British Society of Gastrointestinal and Abdominal Radiology

British Society of Paediatric Gastroenterology Hepatology and Nutrition

British Specialist Nutrition Association

BSPGHAN

BUPA Foundation

Cambridge University Hospitals NHS Foundation Trust

Camden Link

Capsulation PPS

Care Quality Commission

Central London Community Health Care NHS Trust

Clarity Informatics Ltd

Coeliac UK

Company Chemists Association Ltd

Covidien Ltd.

Croydon Clinical Commissioning Group

Croydon Health Services NHS Trust

Croydon University Hospital

Dako UK Ltd

Department of Health, Social Services and Public Safety - Northern Ireland

Device Access UK Ltd

Digestive Disorder Foundation

Ealing Hospital NHS Trust

East and North Hertfordshire NHS Trust

East Kent Hospitals University NHS Foundation Trust

Economic and Social Research Council

Eisai Ltd

Eli Lilly and Company

Equalities National Council

Ethical Medicines Industry Group

Faculty of Dental Surgery

Faculty of Public Health

Fighting Oesophageal Reflux Together

Five Boroughs Partnership NHS Trust

Gastroenterology specialist group

General Hypnotherapy Register

General Medical Council

George Eliot Hospital NHS Trust

GlaxoSmithKline

Gloucestershire LINk

GP update / Red Whale

Great Western Hospitals NHS Foundation Trust

Greater Manchester & Beyond Coalition of PLW & HIV

H & R Healthcare Limited

Hafan Cymru

Health & Social Care Information Centre

Health and Care Professions Council

Healthcare Improvement Scotland

Healthcare Infection Society

Healthcare Quality Improvement Partnership

Healthwatch East Sussex

Heartburn Cancer Awareness support

Hermal
Hertfordshire Partnership NHS Foundation Trust
Herts Valleys Clinical Commissioning Group
Hindu Council UK
Hockley Medical Practice
Humber NHS Foundation Trust
Independent Healthcare Advisory Services
Institute of Biomedical Science
Institute of Sport and Recreation Management
Integrity Care Services Ltd.
Janssen
Johnson & Johnson Medical Ltd
Joint Speciality Committee in Gastroenterology and Hepatology, Royal College of Physicians and British Society of Gastroenterology
KCARE
Lancashire Care NHS Foundation Trust
Leeds Community Healthcare NHS Trust
Leeds North Clinical Commissioning Group
Leeds South and East Clinical Commissioning Group
Local Government Association
Luton and Dunstable Hospital NHS Trust
Maidstone and Tunbridge Wells NHS Trust
Maidstone Hospital
Medicines and Healthcare products Regulatory Agency
Ministry of Defence (MOD)
National Association of Primary Care
National Cancer Action Team
National Childbirth Trust

National Clinical Guideline Centre

National Collaborating Centre for Cancer

National Collaborating Centre for Mental Health

National Collaborating Centre for Women's and Children's Health

National Deaf Children's Society

National Institute for Health Research Health Technology Assessment Programme

National Institute for Health Research

National Patient Safety Agency

National Public Health Service for Wales

Neonatal & Paediatric Pharmacists Group

NHS Ashton, Leigh and Wigan

NHS Barnsley Clinical Commissioning Group

NHS Birmingham South and Central CCG

NHS Connecting for Health

NHS County Durham and Darlington

NHS Cumbria Clinical Commissioning Group

NHS Fylde & Wyre CCG

NHS Gloucestershire & NHS Swindon Cluster

NHS Greater Manchester Commissioning Support Unit

NHS Halton CCG

NHS Hardwick CCG

NHS Health at Work

NHS Improvement

NHS Luton CCG

NHS Medway Clinical Commissioning Group

NHS Newham CCG

NHS North Somerset CCG

NHS Pathways

NHS Plus

NHS Sheffield

NHS South Cheshire CCG

NHS Wakefield CCG

NHS Warwickshire North CCG

NHS West Lancashire CCG

NHS West Suffolk CCG

Norgine Limited

North Essex Mental Health Partnership Trust

North of England Commissioning Support

North West London Hospitals NHS Trust

Nottingham City Council

Nottinghamshire Healthcare NHS Trust

Novartis Pharmaceuticals

Nursing and Midwifery Council

Oxfordshire Clinical Commissioning Group

Pancreatic Cancer Action

Parenteral and Enteral Nutrition Group

Peckforton Pharmaceuticals Ltd

PERIGON Healthcare Ltd

Pharmaceutical Services Negotiating Committee

PharmaPlus Ltd

PHE Alcohol and Drugs, Health & Wellbeing Directorate

PrescQIPP NHS Programme

Primary Care Pharmacists Association

Primary Care Society for Gastroenterology

Primrose Bank Medical Centre

Proprietary Association of Great Britain

Public Health England

Public Health Wales NHS Trust

Queen Elizabeth Hospital King's Lynn NHS Trust

Royal Berkshire NHS Foundation Trust

Royal Bolton Financial NHS Trust

Royal College of Anaesthetists

Royal College of General Practitioners

Royal College of General Practitioners in Wales

Royal College of Midwives

Royal College of Obstetricians and Gynaecologists

Royal College of Paediatrics and Child Health

Royal College of Paediatrics and Child Health, Gastroenterology, Hepatology and Nutrition

Royal College of Pathologists

Royal College of Physicians

Royal College of Psychiatrists

Royal College of Radiologists

Royal College of Surgeons of England

Royal Society of Medicine

Scottish Intercollegiate Guidelines Network

Sheffield Teaching Hospitals NHS Foundation Trust

SNDRi

Social Care Institute for Excellence

Society and College of Radiographers

Society for General Microbiology

South East Coast Ambulance Service

South London & Maudsley NHS Trust
South West Yorkshire Partnership NHS Foundation Trust
South Western Ambulance Service NHS Foundation Trust
Southport and Ormskirk Hospital NHS Trust
St Mary's Hospital
Staffordshire and Stoke on Trent Partnership NHS Trust
Stockport Clinical Commissioning Group
Sutton1in4 Network
Teva UK
The Association of the British Pharmaceutical Industry
The British In Vitro Diagnostics Association
The IBS Network
The Patients Association
The Rotherham NHS Foundation Trust
UK Clinical Pharmacy Association
UK Pain Society
University Hospital Birmingham NHS Foundation Trust
Vygon
Walsall Local Involvement Network
Welsh Government
Welsh Scientific Advisory Committee
Western Sussex Hospitals NHS Trust
Westminster Local Involvement Network
Wigan Borough Clinical Commissioning Group
Wirral University Teaching Hospital NHS Foundation Trust
Worcestershire Acute Hospitals Trust
York Hospitals NHS Foundation Trust