National Institute for Health and Clinical Excellence
Barrett's Oesophagus – Ablative therapy Guideline Consultation Comments Table
10 March – 7 April 2010

Stakeholder	Document	Section No	PageNo	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
Department of Health	Full	General	General	Thank you for the opportunity to comment on the draft for the above clinical guideline. I wish to confirm that the Department of Health has no substantive comments to make, regarding this consultation.	Thank you for your comment.
NETSCC referee 1	Full	General	General	**1.1 Are there any important ways in which the work has not fulfilled the declared intentions of the NICE guideline (compared to its scope – attached)**	
NETSCC referee 1	Full	General	General	No	
NETSCC referee 1	Full	General	General	**2.1 Please comment on the validity of the work i.e. the quality of the methods and their application (the methods should comply with NICE's Guidelines Manual available at http://www.nice.org.uk/page.aspx?o=guidelinesmanual).**	
NETSCC referee 1	Full	General	General	I feel less comfortable to comment on validity of the work before my concerns listed below are addressed.	We hope that the responses below alleviate these concerns
NETSCC referee 1	Full	General	General	**2.2 Please comment on the health economics and/or statistical issues depending on your area of expertise.**	
NETSCC referee 1	Full	General	General	This model-based economic evaluation compared different ablations for Barrett's Oesophagus (BO). However, the report has not been well organized and presented to make it harder to follow. More importantly, I have several major concerns about the methods used in this evaluation.	The appendix has been rewritten for additional detail. However, it was considered that in an area where data quality was particularly low that an overly detailed approach was most appropriate.

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NETSCC referee 1	Ap. 6	5.1 (5.1)	12 (12)	This model structure in Figure 1 is not an accurate and appropriate illustration for the evaluation. If I understand the text descriptions correctly, this study was to evaluate the cost effectiveness of different strategies in treating BO. These strategies included no surveillance/treatment (i.e. natural progression), surveillance only, different treatments. Natural history will not be followed any more once either surveillance or treatments has been applied. So it was misleading to draw an arrow from treatment to natural history.	The appendix has been amended accordingly. The treatments do not alter the progression of Barrett's oesophagus. Rather they affect the proportion of people who commence the cycles in no Barrett's oesophagus, non-dysplastic Barrett's oesophagus and so on.
NETSCC referee 1	Ap. 6	5 (fig 2 &3) (5)	15 & 17 (15 & 17)	As acknowledged in the report, there were two important but different surgeries considered: oesophagectomy and surgery for cancer. The former was actually one of the comparators, while the latter was the important pathway for all patients except for those who have undergone oesophagectomy based on the assumption that all people who have surgery for HGD cannot have further surgery for adenocarcinoma (see 8.1.6 at page 46). Thus here the surgery should be the "surgery for cancer" and there should be a direct pathway from the patients with oesophagectomy to untreatable cancer (or some other post surgical health states such as well or death) if that makes clinical sense. On a related note, one single figure can present the model structure. Three figures just unnecessarily over represented the model structure.	Thank you for your comment. The appendix amended accordingly. It was attempted to fit the entire model on one diagram, however it was not a readable size font so was split into smaller sections.

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NETSCC referee 1	Ap. 6	5.2.1 (5.2.1)	20 (20)	Priors for natural history transition matrix: An uninformative prior value of 0.12 (Table 7) was relatively too high compared to the probability of varying from 0.001 to 0.013 in Table 6. This will make priors dominate the estimations. Although the authors stated this value was chosen due to calculation errors in Excel, what errors should be detailed (not necessary in the main text, but could be in an Appendix) before this can be accepted.	The appendix amended accordingly. The error in excel was a "NUM!" error due to the numbers being too small therefore the priors were increased. However, to maintain the relative difference between the priors and observed data all observed data were increased a 100 times. The final values were compared to the inputted data and they were consistent while allowing for the GDGs prior beliefs.
NETSCC referee 1	Ap. 6	5.2.2 (5.2.2)	22 (22)	Transition matrix in Table 9 was not consistent with that in Figure 3. Since "people can transit to death from all states (in Figure 3, Page 17)", the probability, for example, from well (asymp) to well (asymp) should be (0.908 *(1-Age). Currently the probabilities will not sum to one within the same row.	Thank you. The appendix amended accordingly.
NETSCC referee 1	Ap. 6	5.2.3.2 (5.2.3.2 & 5.2.3.3)	23 (23)	It is much clearer using "oesophagectomy" instead of "surgery". In the second paragraph of this session, "surgery for asymptomatic, symptomatic and perforations…" here is the surgery for cancer.	Thank you. The appendix amended by splitting section into surgery for cancer and oesophagectomy.
NETSCC referee 1	Ap. 6	5.2.3.3 (5.2.3.4)	24 (24)	Across this page, midpoints were used when multiple studies reported the same parameters were identified. Why not pool all these estimates together by taking into consideration sample sizes and variations among these studies. The pooled estimates and corresponding variation can subsequently be used in reference case and PSA, respectively.	The clinical review concluded that evidence synthesis was not appropriate because the studies were of very low quality often being cohort studies and highly heterogeneous. Therefore only the highest quality studies were used.

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NETSCC referee 1	Ap. 6	5.2.4 (5.2.4)	26 (26)	Inconsistency in Tables 11 and 12. The proportions of patients in NBO and BO were determined in Table 11. However, these were not corresponding to the numbers in the column of NBO and Bar in Table 12, at least I did not understand the information from these two tables. I guess "Per' stands for perforation. But perforation was not a health state in the model, what the transitions were for?	Thank you. The appendix amended to provide clarity. The difference in tables is due to the difference in the total proportion achieving complete ablation of dysplasia (table 11) and then of these how many achieved complete ablation of Barrett's
NETSCC referee 1	Ap. 6	6.1.7 (6.1.7)	33 (33-34)	A detriment was applied for surgery here. However, it is not clear what time length was used to calculate QALY (or QALMonth) for surgery. It is important to make this explicit as the duration of surgery is assumed to be short.	The decrement is a utility which then went into the calculation of a QALY value.
NETSCC referee 1	Ap. 6	6.1.12 (6.1.12)	35 (37)	Both complication and surgery were associated with utility decrements in Table 15. Could it be double-counting? Utility decrement associated with surgery may already account for the impact by complications (Note: the duration for complications was assumed to be one month in this study). All numbers represented absolute utility values with the exception of the two decrements for stricture and photosensitivity. This should be consistent or at least using different headings here. The same problem in Table 21 (page 50)	Thank you for your comment. The breakdown of QALYs indicated that complications are relatively small contributing factor to the final results. In addition, the surgery utility was calculated from people who did not experience complications.
NETSCC referee 1	Ap. 6	7.1.2.8 (7.1.2.8)	43 (45)	Considering "inoperable cancer", it seems better than untreatable cancer as the costs for treatments were incurred for patients staying in the state of untreatable cancer. This is a minor point.	Thank you for this comment. The terminology was used as it was consistent with previous analyses (Garside et al 2006), therefore has not been amended.

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NETSCC referee 1	Ap. 6	8 (8)	45 (47)	It would fit better if placing the assumption session right after the model session 5.	Thank you for your comment. Assumptions should be based on evidence identified and therefore should be placed after evidence has been reviewed not before.
NETSCC referee 1	Ap. 6	9 (9)	48 (50)	Here a formula is missing.	Appendix amended
NETSCC referee 1	Ap. 6	9.1 (9.1)	48 (50)	What clinical data were used to validate the model? Please provide references here.	Thank you. The appendix has been amended with references added
NETSCC referee 1	Ap. 6	9.4 (9.4)	51 (53)	Age-specific utilities and starting age were actually parameters used in the model, rather than structural-related.	Thank you. The appendix has been amended with analysis moved to parameter sensitivity analysis
NETSCC referee 1	Ap. 6	9.5 (9.5)	52 (54)	Non specialist centre's…?	Sorry we are unclear over comment; analysis referred to what would happen if treatments given in a non-specialist centre.
NETSCC referee 1	Ap. 6	9.6 (9.6)	52 (54)	Population EVPI and EVPPI were also calculated, but it is not clear where the population estimate came from. The information should be placed in this paragraph.	The estimates are stated in section 9.6
NETSCC referee 1	Ap. 6	10.2 (10.2)	56-61 (57-58)	All tables in this page range used utilities which should be QALY or QALMonth. This is conceptually different!	Thank you. The appendix has been amended to state QALY.
NETSCC referee 1	Ap. 6	10.2 & 10.4 (10.2 & 10.4)	56 & 61 (57 & 63)	The results from the deterministic base case should be very close to PSA base case, though some calculation errors due to random sampling are acceptable. Surprisingly the current difference is so big! I would strongly recommend to check with the Excel file. This could be a serious fatal mistake!	This has been explored extensively and is not due to an error in the model. Examination of parameter distributions from the PSA was examined as was removing surveillance. The cause was discovered to be the inclusion of surveillance. In this case the incremental QALYs are distributed across the origin. In addition they are not perfectly normal around the origin with a tail on the negative side. This produces a very small incremental benefit and therefore increases the ICER exponentially.
NETSCC referee 1	Ap. 6	10.7.2 (10.7.2)	76 (78)	What was the WTP threshold used to derive these EVPPI in Figure 9?	Thank you. The appendix has been amended with willingness to pay threshold added (£30,000)

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NETSCC referee 1	Full	General	General	**3.1 How far are the recommendations based on the findings? Are they a) justified i.e. not overstated or understated given the evidence? b) Complete? i.e. are all the important aspects of the evidence reflected?**	
NETSCC referee 1	Full	General	General	Unable to comment until the above important comments have been addressed	We hope responses to previous comments have addressed these concerns
NETSCC referee 1	Full	General	General	**3.2 Are any important limitations of the evidence clearly described and discussed?**	
NETSCC referee 1	Full	General	General	There was a reasonable limitation session	Thank you for your comment added section on the issue of surveillance.
NETSCC referee 1	Full	General	General	**4.1 Is the whole report readable and well presented? Please comment on the overall style and whether, for example, it is easy to understand how the recommendations have been reached from the evidence.**	
NETSCC referee 1	Full	General	General	No, this report has not been well presented. Many typos bothered my reading. Such a large amount of information could have been presented in a more organized and logic way.	Due to time constraints of the short clinical guidelines process and an attempt to produce as comprehensive and detailed report as possible a full editorial check was not possible. The appendix has now been fully proofread and typos identified and corrected.
NETSCC referee 1	Full	General	General	**4.2 Please comment on whether the research recommendations, if included, are clear and justified.**	
NETSCC referee 1	Full	General	General	Not able to comment before my concerns were addressed	We hope responses to previous comments have addressed these concerns
NETSCC referee 1	Full	General	General	**Section five – additional comments**	
NETSCC referee 1	Full	General	General	A necessary quality and editorial check would be very helpful for external review in the future.	Thank you for your comment the appendix has now been proof read and checked for editorial errors.
NETSCC referee 2	Full	General	General	**1.1 Are there any important ways in which the work has not fulfilled the declared intentions of the NICE guideline (compared to its scope – attached)**	

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NETSCC referee 2	Full	General	General	No comments provided	Noted.
NETSCC referee 2	Full	General	General	**2.1 Please comment on the validity of the work i.e. the quality of the methods and their application (the methods should comply with NICE's Guidelines Manual available at http://www.nice.org.uk/page.aspx?o=guidelinesmanual).**	
NETSCC referee 2	Full	2.2.1 (1.1.15)	11 (13)	Relevance of 1888 articles identified when only nine studies are included. (Similar issue elsewhere).	Thank you for your comment. The initial searches identified 1888 but 1524 articles did not meet the inclusion criteria at the abstract and title stage and at full article stage, only nine were relevant to the scope. Details of the inclusion and exclusion criteria, study flowcharts are available in the appendix 4-Methods. The guideline has been amended to clarify this.
NETSCC referee 2	Full	General	General	**2.2 Please comment on the health economics and/or statistical issues depending on your area of expertise.**	
NETSCC referee 2	Full	2.2.1 (1.1.15)	12 (15)	(and elsewhere). Confidence intervals for NNTB are confusing when the result is not significant. The interval (-4.74,24.79) should be interpreted as (24.79, infinity) and (-infinity, -4.74) where negative NNTB are to be interpreted as numbers needed to harm (ie reduced benefit).	Thank you. The relevant sections of the guideline have been amended.
NETSCC referee 2	Full	2.2.1 (1.1.15)	12 (17)	Please check that the 74 metachronous lesions reported by Pech (2008) really were cancer as indicated in the table (primary outcome 5). If 21% progressed to cancer that deserves more discussion.	Thank you. The reference has been checked and footnote 'e' amended with more detail.

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NETSCC referee 2	Full	2.2.2.7 (1.1.16)	15 (18)	Prasad (2009) provides a hazard ratio comparing (presumably) surgery to endotherapy over 5 years. The hazards are unlikely to be proportional over 5 years of follow up. One would expect crossing hazards. In these circumstances other methods should be used to compare post treatment survival.	Thank you for your comment. The Prasad (2009) does compare surgery to endotherapy over 5 years and does use Cox proportional hazard modelling to calculate the hazard ratios. One would expect the hazards to not be proportional over time but that is an assumption made in this study and the evidence is considered to be of low quality.
NETSCC referee 2	Full	2.2.2.7 (1.1.16)	15 (18)	The RR is less than 1, but the HR is greater than 1. Have the relative roles of endotherapy and surgery been interchanged or is something odd going on?	The HR was calculated after adjusting for age, sex, length of Barrett's oesophagus, while the RR was not, therefore the difference in values. This is explained in the footnote 'g'.
NETSCC referee 2	Full	2.2.3 (1.1.17)	19 (22)	There are two relative risks in Table 2. What are they relative to?	These are relative to placebo
NETSCC referee 2	Full	2.2.3 (1.1.17)	19 (22)	The decision to reduce the effectiveness to 85% seems arbitrary. Its role in a systematic review is questionable.	The GDG considered that the results of Ell 2007 were not applicable to the UK setting since it was conducted in a highly specialist setting. Therefore, the clinical opinion of the GDG considered that 85% was more realistic to the UK setting. When the estimate was increased to the 99% seen in the trial the ICER was reduced to £12,045 per QALY.
NETSCC referee 2	Full	2.3.3 (1.1.17)	26 (25)	I was surprised to see that the probabilistic ICER in Table 4 is nearly twice the deterministic ICER. This deserves some comment.	Please see response to NETSCC comment 9.24 and section 2.2.3 for detailed response
NETSCC referee 2	Full	2.4.3 (1.1.27)	44 (53)	(Second sentence below Table 8). I assume that the word NOT has been omitted "53% probability of NOT being cost effective". Please check.	The sentence is correct. 53% of the simulations were cost effective at a £30,000 willingness to pay threshold.

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NETSCC referee 2	Full	2.5.1 (1.1.30)	50 (63)	There are numerous errors with regards to the 95% confidence intervals for ARR and NNTB in this table. In view of these, someone should check all such results throughout the report! Adverse outcome 7: 1(P). ARR should be 0.29 **(0.18 to 0.41)**, with NNTB 3.68 **(2.45 to 5.41)** Adverse outcome 7: 1(R). ARR should be 0.04 **(-0.01 to 0.10)**, with NNTB 24.5 (**at least 10.4 to benefit, as few as 68.6 to harm**) Adverse outcome 9: 1(P) RR= 0.53 (0.13 to **2.26**) ARR=**0.07 (-0.07 to 0.21)** NNTB=13.7 **(at least 4.65 to benefit, as few as 14.4 to harm)**	Thank you. The guideline was checked and amended accordingly.
NETSCC referee 2	Full	2.5.2.8 (1.1.31)	52 (65)	Confidence intervals for NNTB (as above)	Thank you. The guideline was checked and amended accordingly.
NETSCC referee 2	Full	General	General	**3.1 How far are the recommendations based on the findings? Are they a) justified i.e. not overstated or understated given the evidence? b) Complete? i.e. are all the important aspects of the evidence reflected?**	
NETSCC referee 2	Full	2.2.5 (1.1.19)	23 (27)	Recommendation 1.1.2 is sensible, but not clear that it follows from the evidence presented. It should also be a requirement that is treatment of unproven worth are to be offered that the individual is entered into a registry of such treatment with required follow-up for outcome (including adverse outcomes)	Thank you for comment. The GDG felt that there was enough evidence though of low or very low quality to offer endotherapy as an alternative to surgery.
NETSCC referee 2	Full	2.3.5 (1.1.24)	28 (33)	Recommendation 1.1.4: "Use … with care …", why not "Avoid using …"?	'Avoid using' would change the meaning of the recommendation. Circumferential EMR can be used and the recommendation emphasises using it with care.

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NETSCC referee 2	Full	2.3.5 (1.1.24)	28 (33)	Recommendation 1.1.5. Not sure about the evidence for repeated endoscopic resection. I would have thought recommendation should include a caution about risk of strictures.	EMR is repeated to determine any residual disease and for treatment of residual disease.
NETSCC referee 2	Full	2.6.4 (1.1.38)	57 (71)	These recommendations may be sensible, but I don't think they are evidence based. How are clinicians supposed to provide good information on the efficacy and safety of the different treatment options, when the evidence for these does not exist!	Thank you for your comments. The GDG has to make recommendations on the best available evidence, which in this case was of low quality.
NETSCC referee 2	Full	General	General	**3.2 Are any important limitations of the evidence clearly described and discussed?**	
NETSCC referee 2	Full	General	General	Yes – I think so. The stunning lack of evidence for choice between treatments should perhaps be highlighted.	Thank you. The relevant sections in the guideline were amended to clarify the choice of treatments.
NETSCC referee 2	Full	General	General	**4.1 Is the whole report readable and well presented? Please comment on the overall style and whether, for example, it is easy to understand how the recommendations have been reached from the evidence.**	
NETSCC referee 2	Full	General	General	Text readable. GRADE profile difficult to read and of questionable value.	Thank you. The GRADE table has been amended to improve its readability.
NETSCC referee 2	Full	General	General	**4.2 Please comment on whether the research recommendations, if included, are clear and justified.**	
NETSCC referee 2	Full	3 (2)	58 (71)	Lack of recommendation regarding research into predictors of adverse outcomes with the different treatments. Implicit acceptance of "fit for surgery", but QALY choice between treatments may depend on an individual's risk of various adverse treatment outcomes.	Thank you. The GDG however regarded the listed research recommendations as of higher priority.

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NETSCC referee 2	Full	3.3 (2.3)	59 (72)	Over emphasis of RCTs. It would appear that outcome data only exist for a tiny fraction of patients who have received these treatments. The first objective must be to record and publish outcomes for large series of patients treated using different technologies. RCTs would be great but it is unlikely that the numbers required to differentiate between all these treatments will be recruited in the foreseeable future. Five-years follow up would be nice, but most outcomes will be apparent within 12 months of treatment and good quality trials and even case series that focus on short term outcomes would answer many of the open questions.	The relevant sections in the guideline were amended to include well designed studies apart from RCTs. The GDG felt that the 12 months follow-up would detect the early failure rate but the five years follow-up was needed to determine the late failure rate.
NETSCC referee 2	Full	3.4 (2.4)	59 (73)	RCT seems premature. First record what happens with existing surveillance schedules – what is found and when?	Thank you for your comments. It is true that we have little reliable evidence of the merit of long term surveillance in this setting (HGD) and this would be a first step. However, RCTs remain the vehicle for answering the question raised.
NETSCC referee 2	Full	General	General	**Section five – additional comments**	
NETSCC referee 2	Full	General	General	Good job against a difficult remit. Hopefully the outcome will be to raise awareness of the need for more research/evidence in this area.	Thank you for your comments.
Royal College of Nursing	Full	General	General	The draft guideline seems comprehensive. There are no further comments to make on behalf of the Royal College of Nursing.	Thank you for your comment.
Royal College of Physicians & British Society of Gastroenterology	Full	General	General	The RCP and BSG are grateful for the opportunity to comment. We would like to make the following point.	Thank you for your comments.

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Royal College of Physicians & British Society of Gastroenterology	Full	general	general	We believe this to be an excellent, comprehensive review of the literature and guideline development. It is apparent that the evidence quoted has come from tertiary referral specialist centres around the world. The key elements being appropriate patient selection, diagnostics including endoscopy and pathology, expertise in advanced endoscopic techniques to perform these ablative/resection procedures in a highly skilled manner. This can happen only in a tertiary referral centre for the management of UGI cancer in a multi-disciplinary fashion. It is therefore essential that clinicians performing these procedures are adequately trained and accredited to do these procedures with robust data collection.	Thank you for your comments. Thank you. We have added an introductory sentence prior to the recommendations to reflect this.
Welsh Assembly Government	Full	General	General	Thank you for giving the Welsh Assembly Government the opportunity to comment. Please note that we have no comments to submit at this stage.	Thank you for your comment.

These stakeholder organisations were approached but did not respond:

Association of Educational Psychologists
Association of Laparoscopic Surgeons of Great Britain and Ireland
Association of the British Pharmaceuticals Industry (ABPI)
Barretts Oesophagus Campaign
Bolton PCT
Bowel Screening Wales
Brighton and Sussex University Hospitals Trust
British Association of Otolaryngologists Head and Neck Surgeons (ENT UK)
British National Formulary (BNF)
British Nuclear Medicine Society
British Society of Gastrointestinal and Abdominal Radiology (BSGAR)
British Society of Paediatric Gastroenterology, Hepatology & Nutrition (BSPGHAN)
Cambridge University Hospitals NHS Foundation Trust (Addenbrookes)
Care Quality Commission (CQC)
Commission for Social Care Inspection
Connecting for Health
Cook Medical
Department for Communities and Local Government
Department of Health Advisory Committee on Antimicrobial Resistance and Healthcare Associated Infection (ARHAI)
Department of Health, Social Services & Public Safety, Northern Ireland (DHSSPSNI)
Dorset Cancer Network
Galil Medical
Insitute of Biomedical Science
Leeds PCT
Leicester Royal Infirmary
Luton & Dunstable Hospital NHS Foundation Trust
Medicines and Healthcare Products Regulatory Agency (MHRA)
Ministry of Defence (MoD)
National Patient Safety Agency (NPSA)
National Public Health Service for Wales
National Treatment Agency for Substance Misuse
NHS Clinical Knowledge Summaries Service (SCHIN)
NHS Direct
NHS Knowsley
NHS Plus
NHS Quality Improvement Scotland

NHS Sefton
NHS Sheffield
North East London Cancer Network
North Tees and Hartlepool Acute Trust
North West London Cancer Network
Nottingham University Hospitals NHS Trust
PERIGON Healthcare Ltd
Primary Care Society for Gastroenterology (PCSG)
Queen Alexandra Hospital
Roche Diagnostics
Royal Bolton Hospitals NHS Foundation Trust
Royal College of General Practitioners
Royal College of Paediatrics and Child Health
Royal College of Pathologists
Royal Society of Medicine
Sandwell PCT
Scottish Intercollegiate Guidelines Network (SIGN)
Sheffield PCT
Sheffield Teaching Hospitals NHS Foundation Trust
Social Care Institute for Excellence (SCIE)
Social Exclusion Task Force
Synectics Medical
Teva UK Limited
University of Tasmania
Welsh Scientific Advisory Committee (WSAC)
Western Cheshire Primary Care Trust
Western Health and Social Care Trust
York NHS Foundation Trust