BALLOON EUSTACHIAN TUBOPLASTY FOR THE TREATMENT OF EUSTACHIAN TUBE DYSFUNCTION

Input from manufacturers, external reviewers and Strand B members on V 2.0 of the pilot rapid assessment

Assessment

Pilot ID: WP5-SB-13

CONTENT

STRAND B MEMBERS

Comments were received from:

Name	Agency
Cari Almazan	AQuAS - Agència de Qualitat i Avaluació Sanitàries
Stefan Sauerland	IQWIG
Marina Cerbo	AGENAS

Comment #	Comment received from	Page	Line number	Comment	Author's reply
Summary					
1	Agenas	7	167	Data on prevalence should be put in „Health condition" part and referred to a specific population (UK ?)	The prevalence has been added to the health problem section and the population the prevalence estimate is taken from is now specified.
2	Agenas	7	168	Check the biblio (reference): it's not 3, but according to lines 552-558, it could be 7.	The reference has been corrected.
3	AQuAS	7	168	I think it's important that the prevalence comes from 1 English study	Additional wording adding to clarify that the prevalence comes from one UK study.
4	Agenas	7	174	It is not the published work that deflated: suggestion to re-word.	This has been reworded.

Comment #	Comment received from	Page	Line number	Comment	Author's reply
5	Agenas	7	207	Reword: Both products have just one version of their product on the market.	This has been reworded.
6	Agenas	8	223	adoclescent	This has been corrected.
7	AQuAS	8	237	I would include what the outcome measures are. Decision makers usually only read the summary, and this information is important.	Outcome measures have now been included in the summary.
8	AQuAS	9	252	It needs a)	Ok.
9	Agenas	9	287	Due to uncertainty in diagnostic of ETD, the eligibility criteria adopted in the different studies should be mentioned, to evaluate their results.	A column on the inclusion criteria in different studies has been added to table 4. A new sentence has been added to the summary about problems related to diagnostic criteria of ETD. The variability of patient populations in different studies has been mentioned in several places in the manuscript.
10	AQuAS	11	329	In the table column: valsalva manoeuvre 67% or 64% as in the line 246?	This has been corrected (64%).
11	AQuAS	11	329	Why do you not include quality of life measures?	Three main outcome measures were selected to be presented in the table plus adverse events. Quality of life was one of the secondary outcome measures. QoL was mistakenly mentioned in abbreviations and has now been removed.
12	IQWIG	11	338	The words "improvement" and "benefit" are being used interchangeably here. It would be more precise to use only the word "improvement", when describing before-and-after changes as observable in case series. The word "benefit"	"Benefit" has been reworded now as "improvement".

Comment #	Comment received from	Page	Line number	Comment	Author's reply
				implies a comparison group, because patients only benefit from therapy if their improvement from therapy is larger than the improvement with no therapy (i.e. the natural course of the disease).	
Clinical effectiveness					
13	IQWIG	30	847	Studies on combined interventions (e.g. tuboplasty + turbinectomy) were excluded during abstract screening but were included when the combined nature of the interventions became apparent on reading the full-text article. This means that probably not all studies on combined interventions were included. The fact that an article abstract contained the word "turbinectomy" determined inclusion or exclusion of a study. It should be described how large the risk of missing other studies on combined interventions was.	As the flow chart shows, the exclusion of studies based on combined treatments at the abstract reading phase was the case only for one study (Businco LDR et al. Balloon dilatation tuboplasty and tubal ostium shrinkage in the treatment of Eustachian tube dysfunction J Int Adv Otol 2012;8:354-9). In that study, molecular quantic resonance treatment was used for all patients. According to the protocol, combined interventions should be excluded. This rule was followed when reading the abstracts. However, on closer examination of the selected studies it was found that some patients had procedures performed concomitantly. With combination therapy, an additional treatment for ETD is meant whereas for concomitant therapies, there must not necessarily be an etiological reasoning meaning that this therapies are not directed to the treatment of ETD. We included 2 studies (Catalano et al. 2012, and McCoul et al 2012) where some patients had concomitant procedures. In the McCoul study the results have been discussed and it was concluded that

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					concurrent treatment did not have influence on subjective outcomes. These 2 studies have also been included in the earlier systematic review (Llwellyn et al. 2014). The risk of missing studies with combined treatment is very small.
14	IQWIG	31	880	The quality of systematic reviews was assessed by using the PRISMA checklist. However, PRISMA is intended to improve the reporting of systematic reviews. On the PRISMA website (http://www.prisma-statement.org/), one can read: "PRISMA may also be useful for critical appraisal of published systematic reviews, although it is not a quality assessment instrument to gauge the quality of a systematic review." Therefore, it is clearly preferable to assess the quality of systematic reviews by using instruments such as the Oxman-Guyatt checklist, AMSTAR (A MeaSurement Tool to Assess systematic Reviews), or the newly developed ROBIS (Risk of Bias in Systematic Reviews).	We replaced PRISMA with the summary table of the ROBIS tool.
15	IQWIG	32	904	Based on the IHE checklist, three case series were found to have an acceptable quality. On page 63, line 1533, it is mentioned that summary scores ≥ 14 were considered to represent acceptable quality. It should be noted that the authors of the IHE checklist do not propose an overall summary score for their instrument. Furthermore, it should be clarified here why and when the threshold of 14 was chosen.	It is true that the IHE checklist does not propose an overall score for the instrument. However, in their Delphi panel, they also considered studies with 14 or more 'yes' responses (≥ 70%) to be of acceptable quality. We have not presented the overall scores

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					in the table 6 in order not to emphasise "the threshold point".
16	IQWIG	32	919	Tympanometry was selected as primary outcome "since it is an objective measure". Among the other outcomes, otoscopic findings and tubomanometry were also assessed. It is recommended that the clinical relevance of these outcomes is critically reconsidered in light of the EUnetHTA guidance on surrogate endpoints (http://www.eunethta.eu/sites/5026.fedimbo.belgium.be/files/Surrogate%20Endpoints.pdf). A patient simply does not care how his or her tympanic membrane looks like or how high the pressure is in his or her Eustachian tube. Local symptoms, pain, hearing problems, and quality of life are patient-relevant outcomes and should be given more attention. As a minimum, the report should critically discuss the pros and cons of accepting surrogate endpoints. Are there any empirical data that support the validity of these outcomes?	The selection of outcomes was based on earlier literature, discussions with the clinical experts and (lack of) comments received during consultation of the project plan, In the earlier systematic review (Llewellyn et al.) "change in severity and/or frequency of symptoms" was used as primary outcome. This kind of definition has also problems. It is not essential which was taken as "primary" outcome, since main outcomes are all given the table 3 including "patient relevant outcomes". We have now added a paragraph in which problems related to different kinds of outcomes are discussed.
17	IQWIG	31	876	Please replace "design" by "designs".	This has been corrected now.
18	IQWIG	31	901	The word "as" seems to be missing ("…as were the studies…")	This has been corrected now.
19	IQWIG	33	969	The word "turbinectomy" is misspelled.	This has been corrected now.
20	IQWIG	42	1107	In this paragraph, the extreme heterogeneity of 'success rates' (ranging from 28% to 97%) is described, but the authors fail to propose a possible explanation for these results.	We added a sentence stating that conclusions about reasons for heterogeneity cannot be made.

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21	IQWIG	42	-	It would appear appropriate to discuss whether it was useful at all to include studies without a control group in the present assessment. If the present report would have included only controlled studies, the conclusion ("no definite conclusion") would have been exactly the same. What has been the benefit of evaluating case series?	The whole assessment is based on case series since no comparative data is so far available. The question whether technologies having just case series data should be evaluated remains a question of debate. Since this is the case in many new technologies, what would be the alternative? Not to do assessments at all before at least comparative data is available (and sometimes never will). And let the market take over? One benefit is that this report can be used as a base once new data becomes available.
General remarks/Other					
22	Agenas	12	351	Cite evidence for this statement "Furthermore, the natural course of ETD is poorly documented and known to have favorable outcomes without interventions."	A reference has been added.

MANUFACTURES

Comments were received from:

Name	Company
Susanne Ferfers	Spiggle & Theis Medizintechnik GmbH
Michael McCormack	Acclarent Inc. (part of Johnson&Johnson family of companies)

Comment #	Comment received from	Page	Line number	Comment	Author's reply
Health problem and current use of the technology					
1	Michael McCormack	General		At the current time, the only treatment modalities available to patients suffering from chronic ETD unresponsive to medical management are repeated myringotomies and BET.[15] Repeated myringotomies are not free of risk, may lead to conductive hearing loss and permanent tympanic membrane damage requiring tympanoplasty.[16] Without BET, however, repeat myringotomy become the only treatment option for these patients. Therefore, based on the overall favorable outcomes reported to date and the lack of options for these patients, it may be appropriate to enable patient access to BET while level-1 evidence is being developed.	The manufacturer's comment regarding the lack of alternative treatment options is reasonable. However, patients should not be undergoing an unproven treatment in the absence of evidence, simply because there isn't an alternative. This assessment is about collating the evidence and making an assessment on that evidence – so while the manufacturer's comment may be appropriate as a concluding point in the assessment, it is not a point to be made in the section on current use of the technology.
2	Michael McCormack	General		The mechanism of action by which BET may contribute to the clinical improvement of patients with ETD has also recently been described.[17] In summary, BET	We have amended the text to reflect this additional information from this newly published

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				results in a reduction of mucosal inflammation within the ET, and through its tissue-preserving action, allows for rapid healing. This additional information is important because it provides an explanation how BET works and supports the clinical findings described to date.	article.
Clinical effectiveness					
3	Michael McCormack	8	240, 243, 246	The 2011 study by Poe *et al* is discussed in several areas within the Clinical Effectiveness section as a study with potentially mixed outcomes. This study was conducted as a pilot, Phase I trial, to evaluate the safety of the procedure. All 11 patients treated in this study had chronic ETD with a history of repeated tympanostomies. The only therapeutic option available for these patients at the time of the study was yet another tympanostomy with eventual repair of tympanic membrane. This point is important as it stresses the severity of the disease in the patients included in this study. Of these 11 severe cases, 100% (11 of 11) could self-insufflate by Valsalva post-operatively, and it is only at the last follow-up visit (6 to 14 months post-operatively) that this count decreased to 7 out of 11. (Please add post-operative time frame on Line 246 – it currently simply reads that "the ability to do the Valsalva maneuver postoperatively ranged from 64%..."). In addition, whereas it is correct that type A tympanograms were observed in 4 / 11 cases post-operatively, the criteria for success of the BET procedure ought to include normal hearing in asymptomatic patients, with or without normal	Details of the Valsalva results of Poe et al 2011 study are given in Table 3. We have added the postoperative time frame to the results.

Comment #	Comment received from	Page	Line number	Comment	Author's reply
				tympanograms. Thus, while this study was neither designed nor powered to demonstrate clinical effectiveness, this study did show in 11 severe cases, a significant success rate.[7]	
4	Michael McCormack	9	249 -250	The outcomes "Eustachian Tube Score" (ETS) described on lines 249-250 are significant as they provide a reference point of disease severity before and after surgery. As shown in a recent validation study, a value of ETS=5 is an appropriate cut-point for disease identification: ETS< 5 being indicative of ETD whereas ETD>5 suggesting functional Eustachian tubes.[18] At 12 and 24 months post-BET, the average ETS was greater than 5, suggesting on average functional tubes in these large patient cohorts.	This information was not given in the article. We have added information about the ETD 5 "cutpoint" to the text, so the results are easier to understand.
5	Michael McCormack	42	1101-1102	"All studies showed benefits from the treatment of Eustachian tube dysfunction with BET. The postoperative improvement was observed both in objective and subjective measures." Thank you for recognizing that the available evidence on BET does show positive clinical benefits using a variety of objective and subjective outcomes measures. As stated above, the clinical community is actively discussing many of the issues presented in the assessment and working to address them through clinical research and studies. This vetting of the disease and treatment methodologies should be allowed to continue to ensure that potentially appropriate treatments are available to the affected	Many weaknesses were found in the studies and in reporting. Hopefully, future studies will have better designs and quality.

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				population.	
General remarks/Other					
6	Susanne Ferfers	General		From November 2014, the legally binding brand name of our balloon catheter will be TubaVent®. Please include this brand name in your assessment. That would be very helpful for us.	We have included the brand names of the available catheters to the report.
7	Michael McCormack	General		Acclarent appreciates the opportunity to comment on this rapid assessment of the relative effectiveness and safety of balloon Eustachian tuboplasty (BET) in the treatment of Eustachian tube dysfunction (ETD) in a population aged > 12 years. However, as stated in previous comments, the body of clinical and economic evidence around the condition in general, and specifically with Acclarent's recently CE-marked technology, is just beginning to be developed. Acclarent therefore believes this assessment of balloon Eustachian tuboplasty may be premature. The clinical community has identified many of the concerns stated in this assessment and is diligently working to address them through clinical research and studies, such as the Acclarent-sponsored study "A Randomized Clinical Study of Safety and Efficacy for the Eustachian Tube Balloon Catheter."	The assessment can be updated once new study results become available. The Acclarent sponsored study is mentioned in the text.
8	Michael McCormack	General		Despite the novelty of the technology, the current body of evidence includes 14 clinical evaluations from 10 different clinical sites and 5 countries, describing clinical outcomes of more than 1,000 distinct patients with Eustachian Tube Dysfunction (ETD) treated with BET.[1-14] The safety profile of the procedure has been consistently reported in all studies and all sites, and all	We agree, BET may be effective but the evidence is still missing. This thought is included the summary discussion.

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				studies report clinically and statistically significant improvements in average patient outcomes, following the procedure. Therefore, whereas there are currently no Level-1 randomized controlled trials confirming the effectiveness of the procedure, the evidence in its entirety suggests, in a large number of patients, sites and diverse geographic locations, that BET may be safe and effective.	
9	Michael McCormack	General		The current report highlights the lack of long-term data for BET. Whereas 2-year results are still being developed for many of these studies,[1] a significant amount of data is now available – and discussed in this report – at the 1 year follow-up time point. Whereas this time point may be considered short, it is important to highlight that the main comparator for BET – tympanostomies – has very limited 2-year data yet is widely considered to be safe and effective.[19] Because of the similar therapeutic impact of both procedures, it may be appropriate to maintain similar evidence standards for BET and tympanostomies.	Comparative studies are missing. In this report, we have not evaluated tympanostomies and cannot make conclusions about that treatment. From the clinical point of view, the argument is understandable. The realization of comparative studies, taking into account long-term data on both BET and tympanastomy would be advisable.
10	Michael McCormack	General		The studies included in this evaluation vary significantly in size, from N=11 to N=351. It may therefore be valuable to weight the results based on study size.	Unfortunately, the study with n=351 provided very little information. The number of patients in a study does not correlate with the quality of the study. Therefore, weighting is not an option here.
11	Michael McCormack	General		Please include the following studies in your list of clinical evaluations available to date. • Businco LR, Laurino S, Cipriani O, Bucci P, Lauriello M. Balloon Dilation Tuboplasty and Tubal Ostium Shrinkage in the Treatment of Eustachian	Businco et al. 2012 was excluded already in the preliminary phase since it is a combination treatment of BET and tubal ostrium shrinkage with molecular quantic resonance for all the

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				Tube Dysfunction. Int Adv Otol. 2012;8:354-9. • Schroder S, Lehmann M, Sauzet O, Ebmeyer J, Sudhoff H. A novel diagnostic tool for chronic obstructive eustachian tube Dysfunction-The eustachian tube score. In press Laryngoscope. 2014 • Kivekas et al., Histopathology of Balloon-Dilation Eustachian Tuboplasty, Laryngoscope, DOI: 10.1002/lary.24894.	patients. According to the protocol, combined interventions should be excluded. This rule was followed when reading the abstracts. Schröder et al. 2014 has been published after our literature search, 2 other recent publications from the Bielefeld group have, however, been included. (Schröder et al. 2013, Sudhoff et al. 2013) We have added the study of Kivekas et al.
12	Michael McCormack	General		While not currently in press, the following presentations made at leading society meetings may be informative in EUnetHTA's review of BET. • Dalchow C, Jowett N, Kappo N, Boettcher A, editors. First Clinical Results of the Dilatation of the Eustachian Tube in Patients with Tubal Dysfunction. American Academy of Otolaryngology; 2013; Vancouver. • Donaldson A, McCoul E, Somasegar BS, Anand V. Long-term Follow Up on Eustachian Tube Balloon Dilation Surgery. Presented at American Rhinologic Society (ARS) 2014 – Orlando.	Abstracts are not used as references in EunetHTA assessments.

Comment #	Comment received from	Page	Line number	Comment	Author's reply
13	Michael McCormack			**References:** 1. Donaldson A, McCoul ED, Somasegar BS, Anand VK, editors. Long-term follow-up on Eustachian Tube Balloon Dilation Surgery. American Rhinologic Society; 2014; Orlando. 2. Bast F, Frank A, Schrom T. Balloon dilatation of the Eustachian tube: postoperative validation of patient satisfaction. ORL J Otorhinolaryngol Relat Spec. 2013;75(6):361-5. 3. Businco LR, Laurino S, Cipriani O, Bucci P, Lauriello M. Balloon Dilation Tuboplasty and Tubal Ostium Shrinkage in the Treatment of Eustachian Tube Dysfunction. Int Adv Otol. 2012;8:354-9. 4. Catalano PJ, Jonnalagadda S, Yu VM. Balloon catheter dilatation of Eustachian tube: a preliminary study. Otol Neurotol. 2012;33(9):1549-52. 5. Dalchow C, Jowett N, Kappo N, Boettcher A, editors. First Clinical Results of the Dilatation of the Eustachian Tube in Patients with Tubal Dysfunction. American Academy of Otolaryngology; 2013; Vancouver. 6. McCoul ED, Anand VK. Eustachian tube balloon dilation surgery. Int Forum Allergy Rhinol. 2012;2(3):191-8. 7. Poe DS, Silvola J, Pyykko I. Balloon dilation of the cartilaginous eustachian tube. Otolaryngol Head Neck Surg. 2011;144(4):563-9. 8. Schroder S, Reineke U, Lehmann M, Ebmeyer J, Sudhoff H. [Chronic obstructive eustachian tube dysfunction in adults: long-term results of balloon eustachian tuboplasty]. Hno. 2013;61(2):142-51. 9. Silvola J, Kivekas I, Poe DS. Balloon Dilation of the Cartilaginous Portion of the Eustachian Tube. Otolaryngol Head Neck Surg. 2014;151(1):125-30. 10. Ockermann T, Reineke U, Upile T, Ebmeyer J, Sudhoff HH. Balloon dilatation eustachian tuboplasty: a clinical study. Laryngoscope. 2010;120(7):1411-6. 11. Sudhoff H, Schroder S, Reineke U, Lehmann M, Korbmacher D, Ebmeyer J. [Therapy of chronic obstructive eustachian tube dysfunction: evolution of applied therapies]. Hno. 2013;61(6):477-82. 12. Tisch M, Maier S, Maier H. [Eustachian tube dilation using the Bielefeld balloon catheter: clinical experience with 320 interventions]. Hno. 2013;61(6):483-7.	Thank you for these references. It must be mentioned that we have used several publications as background material. Not all of them have been included as references.

Comment #	Comment received from	Page	Line number	Comment	Author's reply
				13. Wanscher JH, Svane-Knudsen V. Promising results after balloon dilatation of the Eustachian tube for obstructive dysfunction. Danish medical journal. 2014;61(4):A4818. 14. Jurkiewicz D, Bien D, Szczygielski K, Kantor I. Clinical evaluation of balloon dilation Eustachian tuboplasty in the Eustachian tube dysfunction. Eur Arch Otorhinolaryngol. 2013;270(3):1157-60. 15. Adil E, Poe D. What is the full range of medical and surgical treatments available for patients with Eustachian tube dysfunction? Curr Opin Otolaryngol Head Neck Surg. 2014;22(1):8-15. 16. Poe DS, Metson RB, Kujawski O. Laser eustachian tuboplasty: a preliminary report. Laryngoscope. 2003;113(4):583-91. 17. Kivekas I, Chao WC, Faquin W, Hollowell M, Silvola J, Rasooly T, et al. Histopathology of balloon-dilation eustachian tuboplasty. Laryngoscope. 2014. 18. Schroder S, Lehmann M, Sauzet O, Ebmeyer J, Sudhoff H. A novel diagnostic tool for chronic obstructive eustachian tube Dysfunction-The eustachian tube score. Laryngoscope. 2014. 19. Wallace IF, Berkman ND, Lohr KN, Harrison MF, Kimple AJ, Steiner MJ. Surgical treatments for otitis media with effusion: a systematic review. Pediatrics. 2014;133(2):296-311.	

EXTERNAL REVIEWERS

Comments were received from:

Name	Affiliation
Juha Silvola	Oslo University Hospital, MD, PhD
Jussi Jero	MD, Docent, ENT-specialist, Head of Section Otology and Skull Base Surgery, Department of Otorhinolaryngology, Helsinki University

Comment #	Comment received from	Page	Line number	Comment	Author's reply
1	Juha Silvola	General		It is important to inform that Eustachian tube dysfunction is NOT a diagnosis. Dysfuction includes both opening problems and aperta symptoms. This is not defined in the Scope, whereas later, the ICD-10 diagnoses are properly referred.	The problem with the diagnosis has been discussed. A new sentence about the problem has been added to the summary now.
2	Juha Silvola	Results and summary		As to my own article, the tympanic membrane status is defined in tables, but not in text.	The results of type A ears are included in the tympanometry results.
3	Jussi Jero	General		Generally well made analysis of the scientific literature concerning Balloon Eustachian Tuboplasty.	Thank you.
4	Jussi Jero		138	`It typically affects children between three and seven years old…` is not the correct age group of the prevalence of OME. AOM is most prevalent in children between 8 months to 2	The text has been corrected.

Comment #	Comment received from	Page	Line number	Comment	Author's reply
				years and the same situation is with the existence of OME. Thereafter the prevalence is diminishing gradually and between three and seven years old children OME is quite uncommon.	
5	Jussi Jero		187	Using long-term ventilation tubes, carries the risk of permanent perforation…`is true, but the use of real long term ventilation tubes (T-tubes, Goode-tubes) is very uncommon, in Helsinki University Central Hospital district probably 0.1% of the used tubes are long-term. What do the authors mean with long term ventilation tubes? Most commonly used tubes in the treatment of glue ear are Donaldson type made of silicone or Titanium, their risk to cause permanent perforation is very low under 1% and of those perforations most are cured spontaneously. This needs more clarification.	The information about uncommon use very long term ventilation tubes is included now and about low risk of commonly used tubes.
6	Jussi Jero		685	'Balloon Eustachian tuboplasty (BET) involves the passage of a catheter into the Eustachian tube through the pharynx'. Catheter is mainly placed into the epipharynx through the nose (nostrils), it could be placed into the ET through the pharynx too, but this is very uncommon method.	This part of the text has been corrected.
7	Jussi Jero	Table 3.		Clinical effectiveness of balloon Eustachian tuboplasty (BET) In Dennis Poe et al article: 2 (18%) myringotomy for 2 perforated TM is incorrect, should be myringoplasty instead of myringotomy.	This has been corrected now.

	Yes	Partly (please specify)	No (please specify)	Other (please specify)
Part I: Methods (see appendix 1 of the pilot assessment)				
1. Are inclusion/exclusion criteria for selection of the studies described in appropriate detail?	2x			
2. Are the quality appraisal tools appropriate?	2x			
3. Is the type/presentation of evidence (e.g. Meta analysis, qualitative synthesis, GRADE) appropriate for this analysis?	2x			
4. Is the risk of bias sufficiently assessed, both on study level and on an outcome level?	2x			
5. Is the choice of study types appropriate to the population, intervention(s), comparison(s) and outcome(s)?	2x			
6. Are the types of studies to be included (randomised trials, quasi-randomised trials or other designs) described?	2x			
7. If it was relevant to include data from indirect comparisons, is this step justified and the methods of indirect comparisons sufficiently described?	2x			
8. Are appropriate methods of measuring each outcome and appropriate time points for measurement identified?	2x			

9. Details on sources of information and literature search strategies provided?

Search strategy	Databases	Year range	Language restriction	Primary data	Other kind of information resources
O	O	O	O	O	O

Comments
Well made overall strategy with sufficient amount of databases.

10. Information on basis for the assessment and interpretation of selected data and information?

Method of data extraction described?	Critical appraisal method (for quality assessment of the literature) described?	Method of data synthesis described?
O	O	O

Comments
No negative comments, well made assessment and interpretation of the data.

	Yes	Partly (please specify)	No (please specify)	Other (please specify)
Part II: Results (See Domain Reports)				
Health problem and current use of the technology				
1. Does the section describe the health issue including incidence and prevalence, how it occurs, who is affected (including high-risk groups, vulnerable/disadvantaged populations, where it occurs, how it is diagnosed, symptoms and consequences)?	2x			
2. Are the supporting references current and do they provide an international picture of the problem?	2x			
Description and technical characteristics of the technology				
3. Does the section describe the intervention under review including how it works and how it may have an impact on potential recipients?	2x			
4. Does the section describe the comparator(s) under review including how it works and how it may have an impact on potential recipients?	2x			
5. Are the supporting references current and do they provide an international picture of the problem?	2x			
Effectiveness and Safety				
6. Is the risk of bias clearly reported?	2x			
7. Is quality of data sufficiently evaluated?	2x			
8. Are both relative and absolute effect measures presented for each dichotomous outcome?	2x			
9. Are continuous data reported according to appropriate statistics (e.g. 'standardised mean difference' or 'weighted mean difference')?	2x			
10. In case of time-to event analysis, are hazard ratios (HR) and ratios of medians presented?	2x			
11. Are measures of the precision of the effect estimates presented or, in case of absence of this essential information, is this fact reported?	2x			
12. Is frequency of adverse events, frequency of occurrence, relative risk or number needed to harm (NNH) presented for the safety data?	2x			

13. In cases where adverse events are incorporated in utility values of quality of life, is the source of quantification accessible?	2x			
14. Was the transformation of the surrogate outcomes into patient-relevant final outcomes considered (if relevant)?	2x			
General				
15. Do you agree that the data extracted are relevant to the research questions formulated in the beginning and that analysed and synthesised data still answer the question?	2x			
16. Can the results be applied to the intended population?				
17. Is the assessment sufficiently transparent and evidence ('facts') distinguished from judgements (including values and preferences)?	2x			
Part III: Summary of Relative Effectiveness				
1. Does the summary present a balanced representation of the content of the report?	2x			
2. Does the discussion of the summary clearly address the uncertainty in the available evidence, the evidence gaps and the applicability of the evidence?	2x			
Part IV: Other Considerations				
1. Have all relevant ethical, organisational, social and legal aspects been considered? (see Appendix 2 of the Pilot assessment)	2x			