TRANSCATHETER IMPLANTABLE DEVICES FOR MITRAL VALVE REPAIR IN ADULTS WITH CHRONIC MITRAL VALVE REGURGITATION

Input from manufacturers, external reviewer and Strand B members on V 1.2 of the pilot rapid assessment

Pilot ID: SB-15

Content

The 2nd version of the Pilot Rapid Assessment on "Transcatheter implantable devices for mitral valve repair in adults with chronic mitral valve regurgitation" was open to review by Strand B members manufacturers and external experts between July 17 and August 7 2015.

Strand B members

Name	Affiliation
Anna Nachtnebel & Julia Mayer	LBI HTA
Felix Gurtner	Swiss Network for Health Technology Assessment

#	Comment received from	Page	Line	Comment	Character	Author's reply
Summary						
1.	LBI HTA	8	138-146	The sentence is very long and hard to understand.	3	Not changed.
2.	LBI HTA	10	230	What do you mean with "integrated by"? Do you mean supplemented with?	2	Amended.
3.	LBI HTA	10-11	237ff	Please expand on „secondary studies were analysed first". What is meant with that and how where these study types selected? Also you mention the different tools for SR and case-series, but despite the fact that you say only comparative designs were accepted you don't provide information on the quality assessment tool for these study designs.	1	Amended.
4.	LBI HTA	11	248	Rephrase: no comparative study meeting the PICO question (or the scope) was found. Also, it would be nice if an overview on all studies eventually **included** for the individual technologies would be provided, including information on the study design, the overall number of patients included, inclusion criteria, follow-up, differences in comparators used, etc.	2	Rephrased as suggested. We were dealing with an assessment for which there were no primary studies fulfilling the inclusion criteria set in the scope for EFF. The studies have been described in paragraphs and used in the attempt to answer the assessment elements. The same has been done for SAF, in which also tables have been provided, together with descriptions in paragraphs. Without such approach, we would have ended up with an "empty report"… Considering that, we do not believe that an overview table with all the studies would add value to the present document.

5.	LBI HTA	11	252 - 274	No study results are presented in this section, neither for SAF nor for EFF. The summary should provide an overview of those. Unclear why you mention the TITAN trial even though it did NOT fulfil the inclusion criteria. Unclear how many were included for MitraClip. The information provided belongs out of my understanding more to the discussion section than to the results section.	1	The section has been completely restructured. See also reply to comment #4.
6.	LBI HTA	12	300	Confusing: now you mention that one comparative study is available for CARILLON – in contrast to your statement in p. 255 that it did not meet inclusion criteria? Please clarify.	1	The section has been restructured and amended accordingly other comments. See also reply to comment #4.
7.	LBI HTA	12	305	Wouldn't it be worthwhile to discuss the different inclusion criteria used in actual studies and the restriction of this assessment to high-risk patients? What was the rational; why are studies then conducted in high-risk patients? Impact on applicability?	1	It seems that all the studies published at now have been derived by the EVEREST framework. Great part of the new studies are using optimal medical therapy as comparator instead of surgery but they are still ongoing. The manufacturers have been claiming the use of the devices on high surgical risk patients or non-surgical candidates and surgery is not mentioned as comparator. This means that the comparative evidence available at now cannot be applied to the ideal target population. Conclusions on the three devices need to be updated once results of the ongoing trials will be published.
8.	Swiss Network for Health Technology Assessment	13	326	In the summary, on page 13 (line 326), the report mentions that MitraClip was implanted in almost 200'000 patients worldwide. In the report itself, on page 39 the exact numbers are given: 19'184 for MitraClip (line 1161). I suppose that this figure is correct, so the figure on page 13 should be changed ("almost 20'000").	1	Amended.
Description and technical characteristics of the technology						
9.	LBI HTA	18	Table 1	The table is incomplete; in case no information is available, please mention that. The name and proprietary name should be given for all technologies.	2	Thank you, changes made accordingly.
10.	LBI HTA	23	576-594	References for the information are missing.	2	Thank you, references were added accordingly.
11.	LBI HTA	26	711f.	I would shift this sentence to the end of the AE; confusing that you start with that sentence and then give information about the reimbursement status.	2	This sentence was deleted.
12.	LBI HTA	27	742ff.	I am still not sure whether these explanations are best placed here to be understood by the readers. Maybe you could include an explanation of your internal discussions in the appendix under overall description of methods/ pilot team?	2	Thank you for suggestion, but still think that should be written here, as very important.
Health problem and current use of the technology						

13.	LBI HTA	34ff.	944-971 and 980 - 1090	It would be nice to have that summarised instead of listed here. Or maybe you can present it in a more reader friendly way..?	2	Not changed.
Clinical effectiveness						
14.	LBI HTA	41	1193f	Could you clarify what is meant searches "were integrated"?	2	Amended.
15.	LBI HTA	42	1211f	As indicated in an earlier comment, please clarify usage/selection of secondary studies= how were they selected, based on which criteria? What does "were analysed first" mean?	1	Unclear comment. Two phases are described: screening of secondary studies and screening of primary studies (to be performed only if secondary studies are not available).
16.	LBI HTA	42	1215-1222	How are the results of the HTAs factored in the results of the assessment; What does HTAs "were discussed qualitatively" mean – where is the according information? I did not find such a discussion? Does this mean that you took the most recent HTA for your assessment or all? Was the quality of the HTAs assessed in any way? Unclear how/why Munkholm-Larson, was selected – please provide an explanation; is it an HTA? Also detailed information on EFF results are missing, inclusion criteria or at least it is not clear which HTA you are referring to with this reference?	1	Only the most recent reports were qualitatively discussed. Quality of HTAs was not assessed (they were not used for answering the assessment elements). The review by Munkholm-Larsen et al. was selected according to the following criteria (already stated at paragraph 4.1): "Systematic reviews were assessed according year of publication, time range, scope, and population to identify the most recent review that overlapped with the scope of the present assessment."
17.	LBI HTA	42	1232-1234	Confusing: you state that 14 HTAs were included but then only 10 were extracted? Do you mean 14 on abstract level and 10 included?	1	Amended.
18.	LBI HTA	42	1237ff	You only included Munkholm-Larson and NOT the HTAs? Please clarify why HTAs were not used to develop AEs for MitraClip? Selection criteria? Please also provide a clearer explanation which search strategy you used for updating the results.	1	See reply to comment #16. We privileged the use of the latest review as the reviews performed within the HTAs published in the past are obviously not updated. Search strategy is presented in Appendix.
19.	LBI HTA	42	1247	Somehow unclear why you suddenly used lower evidence?	1	See also reply to comment #4.
20.	LBI HTA	43	1286	You mention two studies but give 3 references for the sentence?	2	Amended.
21.	LBI HTA	43	1288	Could you explain what is meant with "new" studies? In relation to which secondary study?	2	Amended.
22.	LBI HTA	44	1330f.	Please give the references to the particular studies mentioned here.	2	Amended.
23.	LBI HTA	42-45	Included studies	Overall, maybe you could try to explain/ present more clearly how studies were identified, selected, included, not included but still used for AE development, assessed etc; currently, it is quite confusing and hard to follow..	1	See reply to comment #4.
24.	LBI HTA	46	Table	It would be nice if in the row "population assessed" either FMR or DMR was used consistently.	2	Data extracted from the original document.
25.	LBI HTA	49ff.	Results	In general, is it possible to present the results for the different devices and AEs consistently, i.e. always give numbers and percentages, follow the same order	2	Checked and amended when needed.

				etc? That would increase reader friendliness and comparability.. Also, the p-value is sometimes written as P and sometimes as p.		
26.	LBI HTA	49	1377	Compared to what at baseline?	2	Amended.
27.	LBI HTA	51	1463ff.	It would be interesting to have the score range for the tool used to interpret the results. The same for lines 1471ff.	2	Amended.
28.	LBI HTA	52	1487ff	As mentioned already in the summary: A discussion of the different inclusion criteria used in the study and the scope of the actual assessment would be of interest	1	Amended.
Safety						
29.	LBI HTA	54	1576	Also an update from the Munkholm review?	2	Amended; a clearer description was provided
30.	LBI HTA	54	1581ff	This means no new case-series were available for assessing SAF?	2	No, it doesn't; see section 5.1 sub-heading "Primary studies".
31.	LBI HTA	58	1753ff.	Maybe consider to refer to the safety data provided in the appendix?	2	Amended.
32.	LBI HTA	61	1870	AE is used for assessment element and for adverse event.	3	Amended.
Appendix						
33.	LBI HTA	74	Flow chart	Discrepancies in numbers compared to description in domain.	1	Amended.
34.	LBI HTA	99	Table	Would be nice to have one row with total number of Yes for each study.	2	Amended.
35.	LBI HTA			Apart from the table 4.1 summarising the HTA reports, we did not find an extraction table for the Munkholm-Larsen review; could you please clarify?	2	No table was believed necessary since the study to extract is only one.
General remarks/Other						
36.	LBI HTA	2	11	The date for the 2nd version is missing.	2	We did not edit all the "layout" field.
37.	LBI HTA			How will the summary table be produced? Currently, it is unclear how a summary judgement will be conducted since in the current assessment version only an assessment of risk of bias on study level has been performed (will the studies assessed by IHE checklist be included in the summary table even though they did not meet the inclusion criteria?) According to the guideline on internal validity an assessment of risk of bias on outcome and study level is recommended.	1	As no studies met the inclusion criteria for EFF defined in the scope, summary table could not be produced for this domain.
38.	LBI HTA			It would be nice if DMR and FMR were used consistently throughout the assessment.	2	Thank you.
39.	LBI HTA			Please use the ® and ™ symbols consistently throughout the assessment.	3	Thank you.
40.	LBI HTA			Please provide references in Vancouver Style using EndNote or RefMan.	2	Not all authors have such software.
41.	LBI HTA			Please use the names of the products consistently throughout the assessment; also refers to any abbreviations of the names (e.g., CMCS).	2	Thank you.
42.	LBI HTA			Not all abbreviations are introduced at first use.	2	Thank you.

Manufacturers

Name	Company
Sophie Cros on behalf of Abbott Vascular	Abbott Vascular International
Omari V. Bouknight	Cardiac Dimensions, Inc.

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Summary						
1.	Abbott Vascular			„Abbott" is misspelled throughout the document as „Abbot".	3	Thank you, changed accordingly.
2.	Abbott Vascular	8	123	Please replace clip par device as durability is a matter relevant for all devices.	2	Amended.
3.	Cardiac Dimensions	8	123	It's not clear why durability of the clip is being used as a safety outcome, which when as written it would only apply to MitraClip.	2	Amended.
4.	Abbott Vascular	8	135	Please correct statement to read "device is delivered to the heart through the femoral vein after transseptal puncture is performed"	2	Thank you, changed accordingly.
5.	Abbott Vascular	9	185-189	Please correct the statements to read "enlarged because of the additional workload required to maintain normal blood flow. Therefore mitral regurgitation results in suboptimal blood delivery to the rest of the body, clinically known as decreased cardiac output. Mitral regurgitation is due to primary abnormalities that affect the valve leaflets, the annulus, the chordae tendineae or papillary muscles, or can be due to secondary abnormalities that result from dysfunction of the left ventricle [A0002]. The presentation of MR can be acute or chronic depending on the underlying pathology."	2	Thank you, changed accordingly.
6.	Cardiac Dimensions	9	187	The sentence is incomplete.	3	Please see changes written in this paragraph.
7.	Cardiac Dimensions	10	214	Should this be written as: 40% of patients with significant CHF have "*more than mild"* MR	2	Thank you, changed accordingly.
8.	Abbott Vascular	11	248	It should be stressed that actually no direct comparator is available as MitraClip is a first of its kind for patients non-eligible for surgery.	1	Thank you for your comment, we slightly revise the text (…no comparative studies were available for inclusion...) and we think that from all the text written in this assessment it is obvious that for DMR with contraindication for surgery (standard of care) there is

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						no appropriate comparator and definitely there is no direct (for head to head studies) comparator currently available on the market.
9.	Cardiac Dimensions	11	257	It is incorrect to say that the surgical risk was not assessed: All patients were deemed to be poor surgical candidates, and almost all were considered to be non-surgical candidates.	1	*De facto*, surgical risk was not formally assessed in the mentioned study.
10.	Abbott Vascular	11	260-265	Comparative evidence on the use of MitraClip in high surgical risk patients with moderate-to-severe and severe primary MR versus standard care is available based on the results from EVEREST II. Additionally positive results from small comparative series, case series, and national registries support the claims made in EVEREST II. Therefore some institutions and scientific societies have recommended the procedure, and the FDA has recommended use of the device in a specific subset of the potential population (patients with severe DMR which are symptomatic despite optimal medical treatment, not eligible for surgery with a life expectancy greater than 1 year). For FMR there is also evidence using data from EVEREST II, ACCESS EU, national registries and small comparative series that the device is safe and effective. References: 1. Mauri L, Foster E, Glower DD, Apruzzese P, Massaro JM, Herrmann HC, Hermiller J, Gray W, Wang A, Pedersen WR, Bajwa T, Lasala J, Low R, Grayburn P, Feldman T. 4-Year Results of a Randomized Controlled Trial of Percutaneous Repair Versus Surgery for Mitral Regurgitation. Journal of the American College of Cardiology. 2013;62:317-328. Maisano F, Franzen O, Baldus S, Schäfer U, Hausleiter J, Butter C, Ussia GP, Sievert H, Richardt G, Widder JD, Moccetti T, Schillinger W. Percutaneous Mitral Valve Interventions in the Real World: Early and 1-Year Results from the ACCESS-EU, a Prospective, Multicenter, Nonrandomized Post-Approval Study of the MitraClip Therapy in Europe. Journal of the American College of Cardiology. 2013;62:1052-1061.	1	Partially amended. Most of the sentences refer to the claimed comparator (standard of care). The whole paragraph refers to comparative evidence in the context of the Scope of the present assessment. Since "standard care" for those patients is not surgery, we do not believe correct to state that "comparative evidence on the use of MitraClip versus standard care is available based on the results from EVEREST II" – as suggested by Abbott Vascular.
11.	Cardiac Dimensions	11	270	Given the low complication rates in the Carillon studies, which were done in centers just learning the procedure (since these were initial studies), it is difficult to see how learning curve could	2	Unclear comment.

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				be considered an issue (with regards to safety).		
12.	Abbott Vascular	12	280-286	Several studies are ongoing on MitraClip and will be crucial to define clear indications of MitraClip and criteria for patients with moderate-to-severe and severe functional mitral regurgitation. For the present assessment, four studies are particularly relevant as they use guideline-directed medical therapy as the comparator: the RESHAPE-HF1-FU (NCT02444286) that will present results in January 283 2017, the MITRA-FR trial (NCT01920698) that will present results within October 2017, another 284 single-centre randomised trial (NCT02444338) that expects to be completed by September 2019, 285 and the COAPT study (NCT01626079) that will be completed in 2020.	1 For moderate-to-severe and severe functional MR, there is no definitive evidence that surgery is superior to guideline-directed medical therapy. Therefore these 4 trials are important to prove the safety and efficacy of the device in this patient population.	Partly amended. In the present assessment, surgery has not been considered an option for the high surgical risk or non-surgical candidates.
13.	Cardiac Dimensions	12	283	The RESHAPE HF study has ceased due to poor enrollment.	2	The mentioned study is the RESHAPE-HF1-FU (NCT02444286) and not the RESHAPE HF (NCT01772108).
14.	Cardiac Dimensions	12	304	This is not all loss-to-follow-up (I.e., exited or non-compliant), the bulk of these numbers is sue to mortality in this sick patient population.	1	Acknowledged and amended accordingly also in paragraph 4.2 Results and 4.3 Discussion. Deaths are all reported within the study and judged to be not device-related.
15.	Cardiac Dimensions	12	307	The document is completely incorrect in stating that the REDUCE FMR is not addressing patients at high surgical risk – all patients in REDUCE FMR (and prior Carillon studies) are at high surgical risk, based upon the poor EF, and most have been formally excluded from surgery. In addition, the lack of convincing data regarding the role of surgery in treating FMR	1	Acknowledged and amended accordingly also in paragraph 4.3 Discussion.

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				makes many reluctant to operate on such patients. It is noted that the document later reports the high incidence of surgeon turn-down based upon EF, with >60% of patients with EF < 40%, and 86% turn-down with EF < 30%. The mean EF in TITAN was < 30%, and the current REDUCE FMR criteria includes an EF < 40%.		
16.	Abbott Vascular	12	316	Please add after "….subgroup of patients. This is due to the current clinical dilemma as these patients should be managed surgically but are too high risk and therefore do not receive definitive treatment."	2	Not amended. This sentence would not add anything to what already mentioned.
17.	Cardiac Dimensions	13	325	The number of implanted patients with MitraClip is closer to 25,000. 200,000 is not correct.	2	Amended.
18.	Abbott Vascular	13	325-327	In contrast, MitraClip was implanted in almost 20,000 patients worldwide before studies comparing MitraClip therapy to its claimed comparator (i.e., optimal medical therapy, surgery) were published. Actually, the current number of implanted patients on a worldwide basis is 23,000.	2	Partially amended: surgery is not claimed as a comparator for MitraClip.
Scope						
19.	Cardiac Dimensions	16	345	Not sure why it does not also read "standard medical care with pharmacological treatment for HR" for Carillon.	2	In this assessment, comparators were chosen based on CE mark, specific indications, information in published clinical guidelines for treatment of MR [12, 13] and EUnetHTA guidelines, and were amended following comments from dedicated reviewers and external experts: In patients with DMR who are surgical candidates, the use of the NeoChord DS1000 device was compared to surgery. In patients without HF, with DMR who are at high surgical risk or are non-surgical candidates, the MitraClip® System was compared to no pharmacological treatment. In patients with HF, with DMR who are at high surgical risk or are non-surgical candidates, the MitraClip® System was compared to pharmacological treatment.

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						In patients with FMR who are at high surgical risk or are non-surgical candidates, the MitraClip® System or the CARILLON® Mitral Contour System® was compared to pharmacological treatment (with or without CRT).
20.	Cardiac Dimensions	16	345	Shouldn't MR reduction be a primary effectiveness endpoint.	1	Outcomes were selected based on the recommendations from the clinical guidelines for treatment of MR [and the EUnetHTA Guidelines on Clinical and Surrogate Endpoints and Safety and amended following comments from dedicated reviewers and external experts.
Description and technical characteristics						
21.	Abbott Vascular	19	378	Please correct statement to read "device is delivered to the heart through the femoral vein after transseptal puncture is performed"	2	Thank you, changed accordingly.
22.	Abbott Vascular	19	381	Correct the statement with the following: "The MitraClip System is contraindicated in patients"	2 The four contraindications stated in the IFU apply to any patient treated with MitraClip not just those with DMR	Contraindications are listed according the IFU: "The MitraClip Clip Delivery System is contraindicated in DMR patients with the following conditions: • Patients who cannot tolerate procedural anticoagulation or post procedural anti-platelet regimen • Active endocarditis of the mitral valve • Rheumatic mitral valve disease • Evidence of intracardiac, inferior vena cava (IVC) or femoral venous thrombus"
23.	Cardiac Dimensions	21	475	The group may wish to review the recent publication by Acker et al. which is a randomized trial comparing mitral valve repair to replacement, in which replacement performs better than anticipated.	2	Thank you for your suggestion.
24.	Abbott Vascular	22	508	Correct "too high risk for mitral valve surgery and would not benefit from the intervention"	2 VAD implantation and transplantation are also surgical procedures but the point here	Partially adapted according suggestion.

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					is these patients are too sick to even benefit from MV surgery so need something more extreme	
25.	Abbott Vascular	23	578	Please add "inoperable symptomatic patients with functional or degenerative mitral regurgitation."	2	Unclear.
26.	Abbott Vascular	24	623	The sentence starting by "Use of the device.." applies to all devices therefore it should be a distinct paragraph.	3	Thank you.
Health problem and current use of the technology						
27.	Abbott Vascular	29	782-783	Correct" FMR occurs due to ischemic heart disease or non-ischemic dilated cardiomyopathy, resulting in heart failure."	2	Thank you, modified accordingly.
28.	Abbott Vascular	33	883	Correct "resulting in mitral annular calcification",	2	Thank you.
29.	Abbott Vascular	35	977	We understand the reference to the most recent guideline however given the scope of this report, European guidelines from ESC should be mentioned.	1	Please see Appendix 1 where a European guideline is mentioned.
Clinical effectiveness						
30.	Abbott Vascular	42	1227	It is stated that 15 secondary studies were identified. However, afterwards 14 HTA reports and 11 systematic reviews are mentioned. So, in total 25?	1	The sentence about the HTA reports has been amended following comments from dedicated reviewers (the right figures and flow-chart have been added).
31.	Abbott Vascular	42	1237	Can you provide some explanations with regards to the choice of the Munkholm-Larsen meta-analysis only?	1	The review by Munkholm-Larsen et al. was selected according to the following criteria (already stated at paragraph 4.1): "Systematic reviews were assessed according to time range, scope, and inclusion criteria to identify the most recent review that overlapped with the present assessment."
32.	Abbott Vascular	44	1307	Comment on the list of institutions: FDA is not an HTA agency per se as its remit is about regulatory approval and as such does not include economics in their reviews therefore we question its inclusion into that table given the different perspective.	1	FDA was not listed as a HTA agency: the term "institutions" was used in the text to refer to the agencies. However, the heading of Table 4.1 has been amended. Since economic analyses were not relevant for the present assessment, limited to only four of the HTA

#	Comment received from	Page	Line no.	Comment	Character	Author's reply
						dimensions, we do not believe pertinent the request of exclusion of the FDA document from the table.
33.	Abbott Vascular	44	1338	Correct "data on long-term outcomes and durability of device are limited but there are 4 year results published from the clinical study EVEREST II". Reference: Mauri L, Foster E, Glower DD, Apruzzese P, Massaro JM, Herrmann HC, Hermiller J, Gray W, Wang A, Pedersen WR, Bajwa T, Lasala J, Low R, Grayburn P, Feldman T. 4-Year Results of a Randomized Controlled Trial of Percutaneous Repair Versus Surgery for Mitral Regurgitation. Journal of the American College of Cardiology. 2013;62:317-328.	1	Partially amended (that was what Munkholm-Larsen et al. reported; pag. 477).
34.	Cardiac Dimensions	49	1367	Mortality was reported in Siminiak et al.: Table 3: 30 day mortality 1.9%. In addition, 1 year mortality was provided as well: 22.2% in the implanted group and 23.5% in the non-implanted group.	1	Amended.
35.	Cardiac Dimensions	52	1526	Again, they are mistaken in stating that patients in REDUCE FMR are surgical candidates. As the protocol currently stands, patients in the study will all be high-surgical risk or non-surgical candidates.	1	Acknowledged and amended accordingly.
36.	Abbott Vascular	53	1552	Please correct all references to Mitra-FR as it is a multi-center study, not single center study as stated in the report	2 There are currently 18 centers for Mitra-FR	Amended.
37.	Abbott Vascular	53	1555-1558	Please correct all references to RESHAPE-HF-a "Another multi-centre randomised trial (NCT02444338) is expected to be completed by September 2019; 380 patients with chronic HF and clinically significant FMR (NYHA II to NYHA IV) will be randomised to MitraClip plus optimal standard of care therapy or standard of care therapy alone.	2 There are 40 proposed centers for this study	Amended as multi-centre. No acronym appears on the clinicaltrial.gov database for the study number NCT02444338. RESHAPE-HF is registered as NCT01772108 and has been terminated.
38.	Abbott Vascular	53	1562-1564	Please correct all references to COAPT: "Percutaneous mitral valve repair using MitraClip will be compared to optimal medical therapy, as per the current guidelines for this patient population.	2	Unclear comment. The sentence reported in the document comes from clinicaltrial.gov database (https://clinicaltrials.gov/ct2/show/record/NCT01626079?term=coapt&rank=1) that was updated and verified (by Evalve) on June 2015. No amendments are believed necessary.

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39.	Abbott Vascular		1565-1569	Please correct all references to MATTERHORN: "Another ongoing study that deserves to be mentioned given its use of a surgical comparator for a select group of high risk patients with FMR is the MATTERHORN trial (NCT02371512), aimed to assess mitral valve repair with the MitraClip system in the context of a multi-centre randomised study enrolling 210 high surgical risk patients with clinically significant MR of primarily functional pathology. Results are expected within December 2017.	2 This study has 15 centers	Partially amended. The sentence in the document intends to differentiate the MATTERHORN study from the previous ones given the difference in the choice of comparators (as stated in the Scope, the present document does not consider surgery as a comparator of MitraClip).
Safety						
40.	Cardiac Dimensions	56	1639	Not sure what this means.	2	Amended.
41.	Cardiac Dimensions	58	1764	The numbers of complications are simply too low to draw any statistical conclusions, or even to attempt – 1 complication in 30 days in both groups together is obviously low.	1	Amended. Your explanation was included in the sentence.
42.	Abbott Vascular	59	1801	Correct "Device-related complications were reported and were rare: partial detachment of the Clip from one of the leaflets was seen in 2% of patients."	2	Amended.
43.	Cardiac Dimensions	60	1822	The perforations were during coronary sinus access and therefore had no impact on where and how to place a Carillon device (The complications occurred prior to introduction of the Carillon device).	1	Amended.
44.	Abbott Vascular	60	1831	Learning curve: we suggest including as well Ledwoch (reporting on learning curve with regard to MACCE). Reference of the paper: Impact of the learning curve on outcome after transcatheter mitral valve repair: results from the German Mitral Valve. Jakob Ledwoch, Jennifer Franke, Stephan Baldus, Wolfgang Schillinger, Raffi Bekeredjian, Peter Boekstegers, Ulrich Hink, Karl-Heinz Kuck, Taoufik Ouarrak, Helge Mo¨llmann, Georg Nickenig, Jochen Senges, Olaf Franzen, Horst Sievert. RegistryClin Res Cardiol. DOI 10.1007/s00392-014-0734-y	1	Amended.
Appendix						
45.	Abbott Vascular	70	2213-2215	Can the authors explain the choice of the quality rating tools as it is not substantiated in the report.	1	Quality assessment tools have been chosen according to their scope (e.g., *"to assess the methodological quality of systematic reviews of public health interventions"*, in the case of R-AMSTAR). They are

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						validated tools, used from other groups, and have been used in previous EUnetHTA WP5 pilots.
46.	Abbott Vascular	79	2257 table A	See comment above related to the FDA which is not a HTA agency/body.	1	See reply to comment #32.
47.	Abbott Vascular	95	Table A4	NCT02444338 is a multi-center study such as MATTERHORN, MITRA-FR	2	Amended.

External expert

Name	Affiliation
Prof Giuseppe Boriani MD PhD	Professor of Cardiology, Cardiology Division, DIMES Department. University of Bologna, Bologna Italy.

#	Page	Line	Comments	Character	Author's reply
Description and technical characteristics					
1.	General		In the HTA 3 invasive treatments are discussed (NeoChord DS1000 (NeoChord), annulus repair with CARILLON (Cardiac 115 Dimensions), and leaflet repair with MitraClip (Abbott Vascular) . Especially for Carillon and Mitral Clip key issues are the learning curve, the need for training and tutorship or proctorship (assistance for a N. number of procedures). These issues have major implications for the access to these treatments, for the organization of the institutions where they are planned and also for the costs. These issues should be discussed together with some indication on the minimum number of cases required for achieving satisfactory results, and for maintaining them (ie, case load for training, case load for maintenance of skillness)	1	The observation is absolutely pertinent. Further considerations on the effects of a learning curve have been added to the answer to [C0007] "Are the technologies and comparators associated with user-dependent harms?". The manufacturer Abbott Vascular highlighted a more recent analysis from the German Mitral Valve Registry (496 patients in 10 centres) that investigates the impact of the learning curve on procedural success and complications [Ledwoch, 2014]. The analysis, which however is limited to centres performing at least 50 procedures per year, showed that a learning curve does not appear to significantly affect acute MR reduction, hospital and 30-day mortality. Issues like "patients flow" (i.e., number of procedures required to ensure reasonable outcomes) or "education and training of the staff" (i.e., case load for training, case load for maintenance of skill) have been only mentioned in Chapter 6. POTENTIAL ETHICAL, ORGANISATIONAL, SOCIAL AND LEGAL ASPECTS. A deep analysis of this very important aspects is beyond the scope of the present assessment (it's not a "full HTA" but only a rapid assessment, limited to four dimensions of HTA).
2.	19	373-389	Mitral Clip . The indication is severe DMR or functional FMR but the presence of a low LV ejection fraction could be a contraindication for any treatment aimed to correct MR (low response or even worsening of the clinical status). As a matter of fact the ESC guideline son Valvular HD put a very low level of recommendation for surgical correction of MR when LVEF is equal to or lower than 30% (level of recommendation IIb- class C)(as reported at page 36). Is this valid also for Mitral Clip ? (Personally I think this is valid for any	1	Thank you for your comments. Further text was added according IFU: "According the precautions data evaluable data regarding safety or effectiveness is not available for prohibitive risk DMR patients with an LVEF <20% or an LVESD >60 mm. MitraClip should be used only when criteria for clip suitability for DMR have been met."

			correction of severe MR when the LVEF is very low). This aspect is not included in the text but should be included, by reporting available data on MitalClip for pts with LVEF <=30% (if available) or by indicating that no data are available and therefore , within this uncertainty, the very low degree of recommendation of ESC guidelines (class IIb) should be followed also for Mitral Clip.		
3.	19	373-389	As compared with the description of the Carillon system (410-439) there is substantial heterogeneity in the body of information provided. . Similarly to Carillon the description of Mitral Clip should include: time required, need for anesthesia / sedation, need for an expert in echocardiography with availability of TEE echo in the lab.	1	Thank you; some data such as time required is considered confidential by Manufacturer, and some data are provided in more details now.
4.	20	434	Text "There are approximately 30 different device sizes (lengths and anchor diameters) that allow for the placement of the device in a variety of different patient anatomies. " How is the appropriate length slected? Before the procedure by means of echo? During the procedure) How often it is necessary to use a second device during the procedure because the first selected is not appropriate? These are important issues to add, in view of the organizational and financial implications?	1	Thank you for that; we added some further data, but tried to find balance. More details needed for organizational or economic domain which are not part of Rapid REA should be done at national/regional level when producing local report.
5.	20	429	It is very hard from the clinical point of view to accept the indication to Carillon for a MR 2+; all the guidelines on correction of MR deals with severe MR or mod to severe (al least grade 3). In view of the paucity of data I think it is not possible to report this indication (grade 2). At present is more judicious to report that "The clinical focus of the treatment modality is patients with advanced systolic heart failure due to dilated ischemic or non-ischemic cardiomyopathy and functional mitral regurgitation of grades 3+ or 4+.". Extension to grade 2 is at present not justified by data, would result in an enormous number of candidates, creating a lot of confusion in the referral. This is a very important point requiring correction.	1	Thank you for that; data were presented in Manufacturers submission file and according the EU CE Mark the Carillon® Mitral Contour System® is indicated for use in patients with functional mitral regurgitation. We decided to delete this sentence.
6.	21	473	***TEXT: "Mitral valve surgery***: According to guidelines, mitral valve surgery is the recommended standard of care for patients with symptomatic DMR or asymptomatic DMR with an evidence of LV dysfunction or dilation, with mitral valve repair…" TO BE CORRECTED INTO "***Mitral valve surgery***: According to guidelines, mitral valve surgery is the recommended standard of care for patients with symptomatic **severe** DMR or asymptomatic **severe** DMR with an evidence of LV dysfunction or dilation, with mitral valve repair.. " (adding severe is necessary, according to guidelines)	1	Thank you, word "severe" is added accordingly, and also clearly visible in domain Health Problem and Current Use of Technology.
7.	21	491	The text reports "Late survival is reduced in patients with congestive heart failure, reduced LV ejection fraction, 491 pulmonary hypertension, or atrial fibrillation [Braunberger 2001; David 2013; DiBardino 2010; 492 Salvador 2008; Heikkinen 2005; Lung 2003; Anyanwu 2010; Montant 2009]." According to what reported in ESC guidelines (see page 36) the term reduced LV	2	Thank you, LVEF <=30% is added accordingly.

			function should be better characterized by including in brackets (LVEF <=30%)		
8.	22	510	TEXT" For patients with heart failure and prolonged QRS duration, cardiac resynchronization therapy (CRT) has been shown to improve mortality, heart failure hospitalization, quality of life,.. " I suggest t change as follows "" For patients with heart failure and prolonged QRS duration**, especially if associated with left bundle branch block,** cardiac resynchronization therapy (CRT) has been shown to improve mortality, heart failure hospitalization, quality of life,.. "	2	Thank you, we added as suggested.
Health problem and current use					
9.	30	793	In the text (Angiographic grade) and in the ESC guidelines there is mention of the grading 2/3/4. In would be the case to discuss the criteria for defining a MR as 4, rather than 3 degree.	2	Thank you, further text is added: MR severity classification used in US and a large of the clinical and epidemiological literature (4 grades: mild, moderate, moderate to severe and severe) is different from the classification used most frequently in Europe in 3 grades (mild, moderate and severe).
10.	38	1122	TEXT "The clinical focus of the treatment modality is patients with advanced systolic heart failure due to dilated ischemic or non-ischemic cardiomyopathy and **secondary (functional) mitral regurgitation** of grades 2+, 3+ or 4+." Again, for Carillon the same critical point raised above . It is very hard from the clinical point of view to accept the indication to Carillon for a MR 2+; all the guidelines on correction of MR deals with severe MR or mod to severe (al least grade 3). In view of the paucity of data I think it is not possible to report this indication (grade 2). At present is more judicious to report that "The clinical focus of the treatment modality is patients with advanced systolic heart failure due to dilated ischemic or non-ischemic cardiomyopathy and functional mitral regurgitation of grades 3+ or 4+.". Extension to grade 2 is at present not justified by data, would result in an enormous number of candidates, creating a lot of confusion in the referral. This is a very important point requiring correction. This is even more justfified if we consider the available studies (line 1271, page 43) which were focused on MR 3+ or 4+.	1	We added the explanation text that this is according the manufacturer's data; according the CE mark indication, severity is not mentioned at all.
Clinical effectiveness					
11.	49	1376	Assessment of NYHA has an important "placebo effect" The type of study should be described (eg. Open non randomized study, if this is the case)	2	Description of study design is provided at the sub-heading "Included studies", paragraph 4.2 Results. Colli, 2015 is a case-series.
12.	49	1380	Assessment of NYHA has an important "placebo effect" The type of study should be described (eg. Open non randomized study, if this is the case)		Description of study design is provided at the sub-heading "Included studies", paragraph 4.2 Results.

					Siminiak, 2012 is a prospective, non-randomised, non-blinded, multicentre study.
13.	51	1463	Assessment of QoL has an important "placebo effect" The type of study should be described (eg. Open non randomized study, if this is the case)		Please, see reply to comment #49.