Endovascular therapy using mechanical thrombectomy devices for acute ischaemic stroke

Input from manufacturers, external reviewers and Strand B members on V 1.1 of the pilot rapid assessment

Pilot ID: SB-16

Content

The 2nd version of the Pilot Rapid Assessment on "Endovascular therapy using mechanical thrombectomy devices for acute ischaemic stroke" was open to review by Strand B members, manufacturers, external experts and one patient representative between 7th and 28th of October 2015.

Strand B members

Name	Affiliation
Dorottya Dudas, Jacinta Juhasz, Orsolya Lorincz, Veronika Doczy	National Institute of Pharmacy and Nutrition, Department of Health Technology Assessment (OGYÉI), Hungary
Sandra Molnar	Institute for Quality and Efficiency in Health Care (IQWIG), Germany
Anna Zawada, Aleksandra Pelczarska, Ewelina Żabczyńska, Kinga Grzywacz, Ewa Strzelec	Agencja Oceny Technologii Medycznych i Taryfikacji (AOTMiT), Poland
Anna Nachtnebel, Julia Mayer	Ludwig Boltzmann Institute for HTA (LBI HTA), Austria

Comment #	Comment received from	Page	Line/ section number	Comment	Author's reply
General remarks/Other					
1.	LBI HTA	General	-	Congratulations to the authors on this excellent report. It is concise yet summarises the most important information in a very readerfriendly and transparent way. Huge work load!	Nil reqd
2.	LBI HTA	General	-	Please make sure that device and study names are spelled/written consistently throughout the document.	Checked (also for medical writing).
3.	AOTMiT	General	-	Standard of care, in the intervention group as well as in the comparator group, needs to be more precisely characterized in PICO framework (eg. listing groups or types of general procedures most frequently mentioned in guidelines). Otherwise it is not known what specifically has been assessed so the usefulness of REA for national uptake is decreased.	We believe that the statement as is sufficient; "Standard of care (which may include intravenous and/or intra-arterial thrombolysis where appropriate)";
4.	LBI HTA	3	29 - 31	One of the external experts (Dr Dennis) does have a COI, please add that. In addition, it is DOICU – remove the I at the end.	Added a suggestion for the COI declaration and corrected.
5.	LBI HTA	3	-	Update/check affiliations of all experts and the patient, add countries; fill in contributing organisations.	Added.
6.	LBI HTA	4	38	Under the heading summary – Methods should be cursiv	Corrected.
7.	LBI HTA	4	73	Appendix 3: Without any description what is contained therein?	Appendix 3 is now entitled ICD-10-CM Diagnosis Codes
8.	AOTMiT	4	73	No title for this appendix is given.	Appendix 3 is now entitled ICD-10-CM Diagnosis Codes

Comment #	Comment received from	Page	Line/ section number	Comment	Author's reply
9.	LBI HTA	5	78	Remove the reference in the table heading	Corrected.
10.	LBI HTA	5	80 + 96	Text should be cursiv.	Corrected.
11.	IQWIG	general	-	Risk-of-bias assessment of truncated studies: From our point of view the risk of bias of the 4 truncated studies (EXTEND IA, SWIFT PRIME, ESCAPE) should be reconsidered. We assume that the publication of data from the MR CLEAN trial triggered unplanned interim analyses of EXTEND IA, SWIFT PRIME and ESCAPE, which led to early termination of these studies. When calculating the sample size, any planned interim analyses are taken into account to prevent type 1 errors. In contrast, unplanned interim analyses are not adjusted for type 1 errors and therefore the corresponding results might represent over- or underestimations of effects. As stated on p. 42 ll. 1037, trials stopped early because a benefit of the test intervention was shown may overestimate its effects. Hence, it is questionable whether the test intervention actually shows advantages over standard medical therapy for effectiveness endpoints. In addition, and safety endpoints might be underestimated in these studies. (In the REVASCAT and IMS 3 study, the interim analyses that led to termination of the study were planned beforehand.)	In recognition of this, we have changed the risk of bias under 'other' to unclear for the three trials that stopped on foot of unplanned interim analyses.
12.	OGYÉI	7 12 15 18 25 36 48 60 63	111 288 356 385 559 812 1261 1704 1750	Missing tables and figures from the list of tables and figures: The name of the table is missing, and it does not nominate in the list. Summary table of relative effectiveness of Mechanical Thrombectomy The name and the number of the table is missing, and it does not nominate in the list. The table is not numbered, and it does not nominate in the list: Research questions The table is not numbered, and it does not nominate in the list: Research questions The table is not numbered, and it does not nominate in the list: Research questions The table is not numbered, and it does not nominate in the list: Research questions The table is not numbered, and it does not nominate in the list: Search strategy for EMBASE, Date of Search 11th August 2015 The figure is not numbered, and it does not nominate in the list: FLOW CHART OF STUDY SELECTION	Line 385: from some perspective, this is not a table in the text, it is a guide of the research question, all the table like this are not nominated. Line 559: the same as above
13.	OGYÉI	6	List of	IA-tPA means intra-arterial tissue plasminogen activator, instead of	Corrected.

Comment #	Comment received from	Page	Line/ section number	Comment	Author's reply
			abbrevations	intravenosus tissue plasminogen activator, it would be better.	
14.	OGYÉI	6	List of abbrevations	The following abbrevations are missing from the list : RCTs (in the text: line 123; page 8) HTA (in the text: line 152; page 8) PISTE (in the text: line 283; page 11) ECAS (in the text: line 368; page 16) EMS, ED (in the text: line 463; page 20) TIA (in the text: line 484; page 20) ESPro (in the text: line 520; page 21) FDA (in the text: line 543; page 24) FAST (in the text: line 630; page 27) WHO, DALYs (in the text: line 654; page 27) CRP (in the text: line 752; page 34) AHA/ASA (in the text: line 769; page 34) SAE (in the text: line 1350; page 50)	The list has been updated accordingly.
Summary					
15.	LBI HTA	7	Scope	According to the assessment template, please include only a narrative summary of the scope and the link to chapter 1.	The narrative summary has now been included.
16.	LBI HTA	8	114-140	Please, include the according AE numbers	This has been amended.
17.	LBI HTA	8	121	"the" guidelines – please describe which one?	Added
18.	LBI HTA	8, Appendix	151ff.; 1634ff.	Please, also mention the submission files received from manufacturers here - they are not mentioned in the whole document. Also applies to the methods section in the appendix. Or didn't you use the submission files at all for the assessment?	In addition, submissions of effectiveness and safety data from the manufacturers of the products under review were assessed. We now state that "No additional data on clinical effectiveness or safety was obtained from review of manufacturer submissions nor from the Health Products Regulatory Authority of Ireland".
19.	LBI HTA	8	152	Which Core model was used?	Amended
20.	LBI HTA	8	161	RCT has already been introduced as an abb.	Amended
21.	OGYÉI	9	168	Instead of **prosepective, prospective** would be better.	Corrected.
22.	OGYÉI	9	177 178	intra-venous - spelling is not unified intra-arterial - spelling is not unified	Corrected
23.	LBI HTA	9	178	Remove the or after the +/-	Corrected.
24.	LBI HTA	9	181	Does this mean that the population enrolled patients who had been already treated with IV t-PA and those who HAVE NOT?	Yes. Some patients had not been treated with IV tpa.
25.	LBI HTA	9	189	mRS – already introduced?	Included.

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26.	OGYÉI	9	191	There is a missing space: "(...) of '**Safety'.With** the (...)"	Corrected.
27.	OGYÉI	9	211	Instead of **heteogeneity, heterogeneity** would be better.	Corrected.
28.	LBI HTA	9	204	MRS has already been introduced as abb	Corrected.
29.	OGYÉI	10	262	There is an unnecessary dot ("**.**") in the sentence: *" (risk ratio = 1.97; 95% CI: 0.64 to 6.03; 261 p=0.24)**.** (C0008)."*	Corrected.
30.	LBI HTA	10	262	At the end of the risk ratio bracket remove the . before the assessment elements ID	Corrected.
31.	LBI HTA	12	Summary table	Formatting – cursiv estimates of the body of evidence not consistent Why are there several brackets where the references are displayed? Isn't the comparator standard of care according to the PICO?	Corrected - need to be checked again during formatting (EndNote). Yes, the comparator is standard of care – this has been changed.
32.	LBI HTA	13	294	Please replace "draft" assessment with pilot assessment	Done
33.	OGYÉI	13	297	Other safety issues could be written here also – as mentioned in the section line 322-328 (any cerebral hemorrhage) – regarding the original scope outcomes	Done
34.	LBI HTA	13	309	In the scope, you list 15 devices	Changed.
35.	LBI HTA	13	324	Why **draft** analysis	Changed to pilot
36.	LBI HTA	15	Comparison	If possible, please give references for the clinical guidelines used and name the EUnetHTA guidelines	American Heart Association/American Stroke Association (AHA/ASA) 2015 AHA/ASA Focused Update of the 2013 Guidelines for the Early Management of Patients With Acute Ischemic Stroke Regarding Endovascular Treatment: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association; European Stroke Organisation (ESO), the European Society of Minimally Invasive Neurological Therapy (ESMINT) and the European Society of Neuroradiology (ESNR) Consensus statement on mechanical thrombectomy in acute ischaemic stroke – ESO-Karolinska Stroke Update 2014 in collaboration with ESMINT and ESNR

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					EUnetHTA: Methodological guideline for REA of pharmaceuticals: Direct and indirect comparisons Clinical endpoints Criteria for the choice of the most appropriate comparator(s) Process of information retrieval for systematic reviews and health technology assessments on clinical effectiveness EMA (CPMP): Points to consider on clinical investigation of medicinal products for the treatment of acute stroke. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003342.pdf
37.	OGYÉI	16	360	There is an unnecessary space in the end of sentence: "The following deviations from the final version of the project plan were made :"	Corrected.
38.	OGYÉI	16	368	There is an unnecessary/ not closed bracket in the sentence, and the dot (".") is missing from the end of the sentence, and we recommend to define ECAS and to add this term to glossary. "'Cerebral haemorrhage (symptomatic and asymptomatic) consistent with the **ECAS** III trial definition) (symptomatic being an intracranial bleed associated with a clinical deterioration)' was separated out into 'Symptomatic intra-cerebral haemorrhage (SICH) (consistent with the ECAS III trial definition) (symptomatic being an intracranial bleed associated with a clinical deterioration)' and 'Any intracerebral haemorrhage (symptomatic or asymptomatic) (consistent with the ECAS III trial definition)' "	Corrected.
39.	OGYÉI	16	-	outcomes selection- references to this guidelines could be useful somewhere in the document	See answer to comment number 36
40.	OGYÉI	17	373	The dot (".") is missing from the end of the sentence.	Corrected.
Description and technical characteristics of the technology					

Comment #	Comment received from	Page	Line/ section number	Comment	Author's reply
41.	OGYÉI	18	390	We recommend to change the following sentence. Original: "Recent clinical evidence (MRCLEAN, ESCAPE, EXTEND IA,(...)" Modified: "Recent clinical evidence (MR CLEAN, ESCAPE, EXTEND IA,(...)"	Corrected.
42.	AOTMiT	18	390-392	Recent... The sentence has no meaning, it should be corrected.	Already corrected
43.	LBI HTA	18	390ff	Not a complete sentence	Already corrected
44.	AOTMiT	18	402, 403 and Table 1	It is not clearly said what these "similarities" and "differences" are referred to – comparison only between devices from comparator group or comparators vs. the intervention. Suggested linking three lines of "Similarities" in one column.	Corrected
45.	LBI HTA	18	Table1	Please use same order of devices as indicated in the scope – aspiration/stent/clot. What are the coil retrievers? Are these the clot retrievers? If so please consistent terms	Already changed them to the same order as indicated in the scope. And we have already changed "clot retrievers" to "coil retrievers", which can be seen from reference 21, Raychev & Saver, 2012.
46.	LBI HTA	19	436	compare**D** to t-PA	Corrected.
47.	LBI HTA	19	448	Endovascular treatment (remove vis-a-vis thrombectomy) or replace with in addition to	Not changed.
48.	OGYÉI	20	470	In the middle of the sentence one word beginning with capital letter: "According to ESO Recommendations [15], **Intracerebral** vessel occlusion must..."	Corrected.
49.	LBI HTA	20	470	According to ESO Recommendations [15], **I**ntracerebral should be a lower case capital	Corrected.
50.	LBI HTA	20	471	MRA and CTA not yet introduced as abb	Added
51.	LBI HTA	20	478	In terms of delivery of the procedure, does this mean that it is delivered under general anaesthesia as well as under local (?) anaesthesia? Please clarify	The procedure here means the mechanical thrombectomy intervention, general anaesthesia is another topic.
52.	LBI HTA	20	484	TIA not introduced yet	Added
53.	OGYÉI	20	485	Instead of **ischamic, ischemic** would be better.	Corrected.
54.	AOTMiT	20	489 – 495	Suggested stressing the <u>needed</u> eg. common supplies in the first line of the paragraph, as the research question requires. Supplies that "can be used" should be described in further lines.	Changed
55.	OGYÉI	21	511	We recommend to change the following sentence. Original: "(...) in addition to the earlier results from **Mr CLEAN**, seem to inspire (...)"	Changed

Comment #	Comment received from	Page	Line/ section number	Comment	Author's reply
				Modified: "(...) in addition to the earlier results from **MR CLEAN**, seem to inspire (...)"	
56.	LBI HTA	21	517	I don't understand that? SITS is a registry? How can this then affect the number of trials?	Just an example to highlight the importance of the registry.
57.	LBI HTA	22	Table 2	How are these tecs sorted? Why not all stent retrievers first? What about the clot retrievers? It is a little bit unclear to which country the name provided applies to and thus the difference in names in other countries? References for the information are missing.	Already changed the only aspiration device at the end. And we deleted the items of "name in other country", because they are the same, it is not necessary to mention that. We take the manufacturers submission files as a reference; we formulated this table based on the information from manufacturers.
58.	LBI HTA	24	526ff	Aren't this still to a large extent the findings of the EFF domains and not really the major findings of the TEC domain?	Efficacy results are no longer referenced in this section.
Health problem and current use of the technology					
59.	LBI HTA	25	565	[..] and **patients** may even die; or do you refer to the brain that may die?	Yes, some how
60.	OGYÉI	25	574	The dot (".") is missing from the end of the sentence.	Corrected.
61.	LBI HTA	26	588	Please rephrase.."The severity of stroke is measured according to ...	Amended
62.	LBI HTA	26	595-597	Reference?	Added
63.	OGYÉI	26	600	Instead of **scocially, socially** would be better.	Corrected.
64.	LBI HTA	26	600	Scocially – spello remove the c	Corrected.
65.	OGYÉI	26	601	The size of the letters are different: "The **consequences** of stroke vary widely depending on size (...)"	Corrected.
66.	LBI HTA	27	664ff	I would rephrase that sentence to " due to reduced mortality associated with"..." stroke has become a huge PH burden in terms of morbidity ...	Changed
67.	LBI HTA	28	684	Why explicitly mention FDA approved devices? Difference to CE marked?	From the comments of reviewers of the internal review.
68.	LBI HTA	28	687	I would suggest to rephrase: Common contradictions are a know hypersensitivity or allergy to (???); or do you mean: Common contraindications are a known hypersensitivity or allegy to XY and...?	Changed
69.	LBI HTA	29	696ff.	It might be helfpul if this table was also organised according to the overarching mode of thrombectomy (i.e. clot/stent/aspiration)	Added

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				Please give a reference for the information included; and maybe state for which devices information is missing.	
70.	LBI HTA	32	Table 4	NIJZ (Slovenia) sent the following information: The Health Insurance Institute of Slovenia do not reimburse medical devices which are built-in to the body. They are included in regular medical services. Avalia-t (Spain) sent the following information: mechanical thrombectomy devices are included in common services porfolio of National Health Care System and publicly funded.	Added
71.	AOTMiT	32	Table 4	Reimbursement status in Poland – Yes. Mechanical thrombectomy devices are available in Polish specialistic hospital units. Hospitals buy devices from their own funds, but National Health Fund refunds the procedure on the basis of positive list of procedures guaranteed in health care system (thrombectomy (inter alia in acute ischaemic stroke) – procedure without specifying the device type to be used).	Added
72.	LBI HTA	33	739	Immediate – use lower case capitals	Corrected.
73.	LBI HTA	34	774	rtPA – suddenly rtPA...not introduced yet, not consistent yet	Changed
74.	LBI HTA	35	784	Could you replace Campbell with why this reference is actually important? A large registry...??	Replaced
Clinical effectiveness					
75.	IQWIG	general reporting of effectiveness endpoints		We strongly recommend distinguishing between patient-relevant endpoints and surrogate endpoints. Therefore, we suggest classifying reperfusion and revascularization at final angiography as surrogate endpoints and reporting them separately. Patient-relevant endpoints such as stroke and haemorrhages cannot be compared to surrogate endpoints such as reperfusion (at 24 hours or later). As stated on p. 47 ll. 1234 onwards, studies reporting reperfusion at 24 hours tend to favour the intervention, whereas studies reporting reperfusion at 7 days suggest no difference. In addition, asymptomatic haemorrhages should be reported, if the data allow for it.	While revascularization and reperfusion were originally planned to be analysed separately, as noted in the responses to the last round of reviews of this pilot assessment, there was overlap and a lack of distinction across trials in relation to these terms and hence they have been grouped together under one heading. As is noted in section 4.2, "It is noted that the description of the outcome which the mTICI score is taken to represent varies across the included studies. It is variably described as being a measure of reperfusion (i.e. ESCAPE, MR CLEAN) or revasularization (i.e. MR RESCUE, REVASCAT) or recanalization (i.e EXTEND-IA), and the terms are often used interchangeably".

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					We believe that we have been as clear as is feasible outlining the differences between results for reperfusion and revascularization and believe that the reader should be able to come to their own conclusions from the description and data provided. Similarly, in terms of patient-relevant vs surrogate endpoints, we believe that the results have been laid out in a manner which allows the reader to examine and weigh the evidence and decide upon the weight which they wish to give to particular endpoints. The data do not allow for reporting of asymptomatic haemorrhages.
76.	LBI HTA	36	808	Replace *draft* with *pilot* assessment	Done
77.	LBI HTA	38	812	Still D0001 and D003 separate questions – shouldn't this be one according to new model?	In the preliminary working version that was used for this assessment, these questions were still separate.
78.	LBI HTA	37	821	Remove the "	Corrected.
79.	LBI HTA	37	827	If patients satisfaction was not considered at all, I would suggest to delete it here and also in the overview table on assessment elements included.	It was considered but not included because there was no data upon which to base an assessment. However, it was included as part of the project plan, under the question 'was the use of the technology worthwhile?" and hence it has been left in.
80.	LBI HTA	38	871	Why are two different abbreviations mentioned in brackets?	Because imaging may have been done with either CT or MRI.
81.	OGYÉI	38	888	It is not clear what the star shows.	Changed.
82.	LBI HTA	38	888	*It is noted that the description of the outcome which the mTICI score is taken to represent varies 888 across the included studies. " Is this a complete sentence ? A bit hard to understand? Add this whole paragraph as footnote?	Changed.
83.	OGYÉI	38	890	Instead of **revasularization, revascularization** would be better.	Corrected.
84.	LBI HTA	38	899	Sometimes mTICI is used and then TICI only- difference? Or	Corrected. All now mTICI

Comment #	Comment received from	Page	Line/ section number	Comment	Author's reply
				consistent use of either of the terms	
85.	LBI HTA	39	911	Table 5 first row describing tecs remove the ' at the end of the study duration.	This is a star referring to the footnote.
86.	LBI HTA	39	928	mechanical thrombectomy +/or intra-arterial t... remove the or and replace with -	Corrected.
87.	OGYÉI	40	952-955	The using of brackets is not clear here, we recommend using different type of brackets.	Amended.
88.	OGYÉI	41	1023	There is a missing bracket. Original: "(...)EXTEND IA (43 minutes (IQR 24-53**),** REVASCAT (75 minutes (IQR 50-114))" Modified: "(...)EXTEND IA (43 minutes (IQR 24-53**)),** REVASCAT **(75 minutes (IQR 50-114))**" We recommend to use different type of brackets: "(...)EXTEND IA **[43 minutes (IQR 24-53)]** (...)"	Corrected.
89.	LBI HTA	43	1084	Ad a blank between 90days	Corrected.
90.	OGYÉI	43	1084	There is a missing space: "(...)on mRS at **90days** across(...)**"**	Corrected.
91.	OGYÉI	45	1132	In the middle of the sentence one word beginning with capital letter: "(...) in the control and **Intervention** groups (...)"	Corrected.
92.	OGYÉI	45	1161	The size of the letters are different: "The scales 1160 used were either from 0 to 100 (ESCAPE) or from **-0.33 to 1 (REVASCAT, MR CLEAN).**"	Corrected.
93.	LBI HTA	46	1183	I don't understand this paragraph...mechanical thrombectomy is subject of this assessment...why are then the frequencies so low of pts who had undergone mechanical thrombectomy. Don't you mean here the intra-arterial thrombolysis instead...? then also the first sentence would fit.	No, it reads correctly; unfortunately it is true that two of the trials did indeed have very low proportions of their patients undergoing mechanical thrombectomy (IMS3, 16.1%, SYNTHESIS Expansion, 30.9%); this is discussed in the text (discussion) – "There were a number of reasons for the different rates across the trials, including the use or non-use of imaging in patient selection, clinical deterioration or improvement, and system or process issues (ie the availability of an interventionist)."
94.	OGYÉI	46	1189	Instead of **availalility, availability** would be better.	Corrected.

Comment #	Comment received from	Page	Line/ section number	Comment	Author's reply
95.	LBI HTA	46	1215	Replace "draft" assessment with pilot assessment or remove completely.	Done
Safety					
96.	LBI HTA	48	1257	Replace "draft" assessment with pilot assessment	Done
97.	AOTMiT	49	1278-1281	The methodology of prospective non randomized trials selection for safety analysis should be justified more detailed. According to the description it was not based on systematic literature review performed for clinical effectiveness analysis, so it should be described on what basis Punal-Riobo 2015 publication was chosen as appropriate, and why publications were not searched by authors within systematic literature search based on provided strategy. Any assessment of Punal-Riobo 2015 quality should be provided. This situation implies disagreements in number of selected and found studies in the flow chart of study selection on page 63.	The justification for use of the search results of Punal Riboo et al has now been added. The systematic review was used to supplement the search results from the review of clinical effectiveness. The Punal-Rioboo study used the main bibliographic databases and was up to March 2015. It highlighted a small number of prospective studies that would only have been detected by a bespoke systematic review for safety. A foot-note has been added to the flow chart to provide additional clarity, and the flow chart numbers have been updated.
98.	LBI HTA	49	1279	Reference is missing	Corrected
99.	LBI HTA	49	1312ff	References are missing	Corrected
100.	LBI HTA	50	1325	Replace "draft" assessment with pilot assessment or remove completely.	Corrected
101.	LBI HTA	50	1325	Why has the quality not been assessed formally? Reasoning? Aren't these studies included in the summary table in the summary section because they don't compare against standard medical care? Replace "draft" assessment with pilot assessment.	This has now been assessed.
102.	LBI HTA	52	1390	The porportion OF patients	Corrected.
103.	OGYÉI	52	1395	Instead of **elimated, eliminated** would be better.	Corrected.
104.	OGYÉI	53	1400	Figure 5 could be placed in the line 1387, before the „Recurrent stroke within 90 days section"	This has been changed.
105.	OGYÉI	54	1459	Instead of **subseqent, subsequent** would be better.	Corrected.
Appendix					
106.	LBI HTA	59	1636f.	This description does not accord with methods described on page	Amended the methods on page 8.

Comment #	Comment received from	Page	Line/ section number	Comment	Author's reply
				8.	
107.	LBI HTA	59	1643	Please delete *domains*	Corrected.
108.	LBI HTA	59		Please, also describe methods used for assessing risk of bias on study level.	Done
109.	LBI HTA	64	1756	Table title? Incations?	The spelling has been corrected.
110.	AOTMiT	64	Table	Not clear which device the first table refers to	The REVIVE SE device, as stated above the table.
111.	LBI HTA	85	1820	The table should be referenced somewhere in the SAF domain. Is there more information available what these AEs were in detail?	The table is already referred to in the text in page 52. The details of the device related adverse events, where available, have now been included in the footnote of the relevant table.
112.	LBI HTA	87	Table	It should read authors' not author's judgement	Corrected.
113.	LBI HTA	93	Table	For consistency between the assessments, could you please use the layout suggested in the assessment template.	As noted, while the format has changed slightly, the information is essentially the same. As discussed by email, we will therefore leave this table unchanged.

Manufacturers

Name	Company
Maria Velleca	Johnson & Johnson Medical
Anne-Laure BOCQUET	Stryker Neurovascular
Marcel Kyri	phenox GmbH
Matthieu Cuche	Medtronic
Mairsil Claffey	Neuravi Ltd.

Comm. #	Comment received from	Page	Line/ section number	Comment	Author's reply
General remarks/Other					
1.	Johnson & Johnson Medical	General		We are concerned that the review of the 8 reported studies does not provide an adequate reflection of outcomes in current clinical practice. By including the three studies that do not represent current thinking, technologies, and best practice, this review is underestimating the real outcomes achievable from mechanical thrombectomy. To be specific, 3 out of the 8 RCTs (MR RESCUE, IMS3, SYNTHESIS expansion) analyzed are incomparable with the other 5 due to the fact that: • They have different patient inclusion criteria: they didn't select patients with large vessel occlusion, now considered clinically appropirate for the procedure • They used the old generation of mechanical thrombectomy devices • They used differents endovascular techniques recognised to now be obsolete This has an impact on the results in terms of effectiveness and heterogeneity, as noted in section 1079-1085 and thus affect the conclusion. Our recommendation is to make an additional review of the 5 RCTs published in 2015 (MR CLEAN, EXTEND IA, ESCAPE, SWIFT PRIME and REVASCT) to make this analysis more clinically relevant and consistent with the current clinical practice and evidence available for the mechanical thrombectomy.	Subgroup analysis has now been performed as suggested.
2.	Johnson & Johnson Medical	General		We understood your intent was to evaluate the devices at class level, as agreed in the first scoping meeting. To align with this approach and to be consistent with the different clinical approaches, we recommend presentation of the results appropriate for each individual category of medical device (Aspiration/Suction Devices; Stent Retrievers; Clot retrievers). This approach should be consistent	While we had committed to evaluating the devices at class level if feasible, this did not prove to be the case. However, subgroup analysis has now been performed which focuses on those trials commenced in 2010 or

Comm. #	Comment received from	Page	Line/ section number	Comment	Author's reply
				through the document. We also recommend clearly showing the differentiation of the clinical results for the first generation and second generation of mechanical thrombectomy devices, to align with current clinical practice. Whilst it is appropriate to judge products at the class level (for any particular approach), it is inappropriate to asume that the outcomes from different surgical techniques are equivalent.	later and this should address the concerns regarding first versus later generation devices.
3.	Stryker	General		We suggest to always mention "Mechanical Thrombectomy with Stent Retrievers" when referring to the new proven benefits of mechanical thrombectomy. It is well established in the new published guidelines (from ESO and AHA) that mechanical thrombectomy by stent retrievers is recommended: ESO – Karolinska Stroke Update, ESMINT and ESNR : • For mechanical thrombectomy, stent retrievers approved by local health authorities should be considered (Grade A, Level 1a, KSU Grade A). 2015 AHA/ASA Focused Update of the 2013 Guidelines for the Early Management of Patients With Acute Ischemic Stroke Regarding Endovascular Treatment • Patients should receive endovascular therapy with a stent retriever if they meet all the following criteria (Class I; Level of Evidence A)…..	The potential benefits of 'stent retriever' technology have now been highlighted in the discussion.
4.	Medtronic	2	19	Please communicate names of the external reviewers. It should be disclosed at this stage for transparency purpose.	The names will be added in the next version of the assessment.
5.	Johnson & Johnson Medical	6	List of abbreviation	The correct name for IA-tPA is "Intra**Arterial** Tissue Plasminogen Activator" instead of "Intravenous tissue plasminogen activator".	Corrected.
6.	Johnson & Johnson Medical	6	List of abbreviation	The correct name for NIHSS "National **Institute** for Health Stroke Scale" instead of "National Institutes of Health Stroke Scale".	Corrected.
Summary					
7.	Neuravi	8	123-125	Five recent RCTs (MR CLEAN, ESCAPE, Extend IA, SWIFT PRIME and REVASCAT) demonstrated that mechanical thrombectomy administered within 6 to12 hours after stroke onset is effective and safe and delivered **statistically significant improvements** in clinical outcomes in patients with large vessel occlusions as compared to IV t-PA alone. **Intra-arterial therapy was consistently favored vs. the control arm with a number needed to treat for one additional good outcome of ~4.**	In the text, we changed to a neutral saying: *"Endovascular treatment with mechanical thrombectomy administered within six to 12 hours of stroke onset has been suggested as an effective and safe adjunct to usual care such as t-PA alone."*

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				(Grotta & Hacke, Stroke 2015; 46: 1447-1452 – "despite differences in the timing and amount of recanalization achieved, there was a consistent difference across all studies in good outcome between the interventional and control arms favoring IAT of 14% to 31% (number needed to treat for one additional good outcome, ≈4;Figure). Variability in benefit between studies probably reflects differences in the patients selected irrespective of IAT treatment…. **The consistency and logic of the results can make neurologists confident that they should refer similar acute stroke patients as evaluated in these IAT trials…..")** (Campbell et al, Endovascular stent thrombectomy: the new standard of care for large vessel ischaemic stroke.Lancet Neurology 2015 Aug;14(8):846-54. Despite differences in the details of eligibility requirements, all these trials required proof of major vessel occlusion on non-invasive imaging and most used some imaging technique to exclude patients with a large area of irreversibly injured brain tissue. The results indicate that **modern thrombectomy devices achieve faster and more complete reperfusion than do older devices**, leading to improved clinical outcomes compared with intravenous alteplase alone. The **number needed to treat to achieve one additional patient with independent functional outcome was in the range of 3·2–7·1** and, in most patients, was in addition to the substantial efficacy of intravenous alteplase. No major safety concerns were noted, with low rates of procedural complications and no increase in symptomatic intracerebral haemorrhage**….** On the basis of available trial data, intravenous alteplase remains the initial treatment for all eligible patients within 4·5 h of stroke symptom onset. Those patients with major vessel occlusion should, in parallel, proceed to endovascular thrombectomy immediately rather than waiting for an assessment of response to alteplase, because minimising time to reperfusion is the ultimate aim of treatment" (Pierot & Derdeyn, Stroke 2015; 46: 1440-1446 - "These data confirm the benefit of early mechanical reperfusion for selected patients with large vessel occlusion and recent ischemic stroke. The strongest evidence is for patients treated with intravenous tPA" " In the most recent trials (MR CLEAN, ESCAPE, EXTEND-IA, and SWIFT PRIME), clinical outcome at 3 months was better in EVT group. .. The 2 main differences between the positive and negative trials were (1) the mandatory use of CTA or MRA for the demonstration of a large vessel occlusion by CTA or MRA…and) and (2) the use of latest generation devices (stent-retrievers) mandatory in EXTEND-IA, SWIFT PRIME, recommended (ESCAPE) and widely used in MR CLEAN. In ESCAPE and MR CLEAN EVT stent-retrievers	

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				were used in 86.1% and 97.4% cases, respectively.)	
8.	Medtronic	8	124	Include mechanical thrombectomy "mainly with stent retrievers". It is critical to note that the recently published clinical evidence (i.e., MR CLEAN, ESCAPE, EXTEND-IA, SWIFT PRIME, and REVASCAT) are primarily based on the use of new generation of stent retrievers. Here below some three references for consideration: 1) Publication of Hacke W. The results of the recent thrombectomy trials may influence stroke care delivery: are you ready? Vol 10, July 2015, 646–650. 2015 World Stroke Organization DOI: 10.1111/ijs.12541 According to this editorial by Werner Hacke: - "The results published apply for IAT using stent-retrievers. There is no convincing evidence that these results would also apply to other devices such as the Penumbra suction device (THERAPY, which did not show significant superiority) (reference: 11 of the paper: Mocco J. THERAPY. Preliminary results. Oral presentation ESOC 2015 Glasgow. (11)" Note: The reference 11 in this publication is not publically available but was presented to large audience of attendees at the ESOC conference) - "How much more extrapolation regarding variations of IAT is permissible? Can we assume that the results will also apply for other types of endovascular instruments or maneuvers? While some talk about a class effect for stent-retrievers (although in the far majority, a single stent-retriever brand was used), the results of the trials are not transferrable to suction devices, rotation ablation, or simple mechanical manipulation of thrombus. The results of THERAPY, so far known, indicate a much smaller treatment effect of just 8%, which failed to show superiority in an underpowered early terminated trial." 2) publication of James C. Grotta: Stroke Neurologist's Perspective on the New Endovascular Trials, MD Stroke. 2015;46:00-00. DOI: 10.1161/STROKEAHA.115.008384 "THERAPY (ClinicalTrials.gov Identifier: NCT01429350) was a company-sponsored trial evaluating the Penumbra aspiration system in an 8-hour time window on top of r-tPA against standard treatment. It required evidence of anterior circulation large vessel occlusion by a thrombus with a length of at least 8 mm. This trial was also stopped prematurely and did not reach the estimated enrollment of 692 patients. The results have not been published, but reportedly failed to show significant benefit with IAT."	About the new statement, we added in the following text. About the five RCTs, we changed to a neutral saying: *"Endovascular treatment with mechanical thrombectomy administered within six to 12 hours of stroke onset has been suggested as an effective and safe adjunct to usual care such as t-PA alone."*

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				3) Finally, also for consideration, here below are the two key points from the Consensus statement on mechanical thrombectomy in acute ischemic stroke – ESO/Karolinska Stroke Update February 2015 in collaboration with ESMINT and ESNR. The Consensus reports: - "For mechanical thrombectomy, stent retrievers approved by local health authorities should be considered (Grade A, Level 1a, KSU Grade A). – new - Other thrombectomy or aspiration devices approved by local health authorities may be used upon the neurointerventionists discretion if rapid, complete and safe revascularisation of the target vessel can be achieved (Grade C, Level 2a, KSU Grade C) – new"	
9.	Johnson & Johnson Medical	8	127 – 128	We suggest "**within 4.5 hours**" instead of "within 3 – 4.5": this could be interpreted to mean between 3 and 4.5 hours.	Yes, changed to "within 4.5 hours"
10.	Neuravi	8	128	…in order for the administration of t-PA to be effective and most beneficial, it must be administered within 3-4.5 hours after the onset of symptoms. In the setting of Large Vessel Occlusions (or Proximal Artery Occlusions), it is limited in its ability to revascularize the occlusion.	Added "In the setting of Large Vessel Occlusions (or Proximal Artery Occlusions), it is limited in its ability to revascularize the occlusion."
11.	Medtronic	8	128	"it must be administered within 3 – 4.5 hours after the onset of stroke symptoms". This need to be corrected to "administered within 4.5 hours" and please reference to the marketing authorization from European Medicine Agency for the use of the drug Alteplase (IV tPA)	Yes, changed to "within 4.5 hours".
12.	Neuravi	8	138	Delays in recanalization have been demonstrated to reduce the odds of a good outcome, and so the speed with which reperfusion is achieved makes a difference …	Added accordingly.
13.	Neuravi	8	138-140	The target population of mechanical thrombectomy in this assessment is patients experiencing an acute ischemic stroke due to a proximal or large neurovascular vessel occlusion. Patients with an occlusion of a major intracranial artery, such as the internal carotid artery (ICA), middle cerebral artery (MCA), or basilar artery (BA) have a very poor prognosis if the occlusion is not opened. (Jayaraman MV, Hussain MS, Abruzzo T, *et al.* Embolectomy for stroke with Emergent Large Vessel Occlusion (ELVO): Report of the Standards and Guidelines committee of the Society of NeuroInterventional Surgery. *J NeuroIntervent Surg* 2015;7:316-21: "The natural history of patients with acute ischemic stroke and occlusion of a major intracranial vessel such as the internal carotid artery (ICA), middle cerebral artery (MCA), or basilar artery is dismal, with high rates of mortality and low rates of disability-free survival…	Changed accordingly.

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				Among acute ischemic stroke, ELVO accounts for the greatest proportion of patients with long-term disability.")	
14.	Neuravi	9	189	Five of the eight trials were stopped early due to loss of equipoise after overwhelmingly positive trial results.	Only Revascat was stopped because of loss of equipoise. IMS 3 stopped because of futility The release of data from MR CLEAN led to interim analyses being performed in SWIFT PRIME, ESCAPE and EXTEND IA, and all were stopped early following this analysis Action: No change made
15.	Neuravi	9	general	The 8 trials referenced can be (and have been) divided into two groups. The first 3 trials (IMS III, Synthesis & MR RESCUE) did not consistently confirm the presence of a large vessel occlusion on imaging, nor did they use 2nd generation technology. The subsequent 5 trials did require imaging confirmation of a large vessel occlusion and they used primarily 2nd generation stent-retriever technology to revascularize the vessels. These trials demonstrated a clear benefit to endovascular therapy in patients with large proximal artery occlusions. The data from these 5 trials, even though some were halted early due to loss of equipoise, has been categorized as compelling by numerous experts, including leading neurologists*. The American Heart Association / American Stroke Association revised its stroke treatment recommendations citing Class 1, Level A evidence in support of endovascular therapy with a stent-retriever in specific patients. "AHA/ASA revised recommendations state there is Class I, Level of Evidence A that patients should receive endovascular therapy with a stent retriever if they: have prestroke mRS 0-1, have AIS and received IV r-tPA within 4.5 hours of onset, the causative occlusion is in the ICA or proximal MCA, are age 18 or oler, have an NIHSS score of 6 or greater, have an ASPECTS score of 6 or greater, and treatment can be initiated (groin puncture) within 6 hours of symptom onset. ….Use of stent-retrievers is indicated in preference to the MERCI device (Class I; Level of Evidence A)" *Grotta & Hacke, Stroke 2015; 46: 1447-1452 -	Subgroup analysis has now been performed.

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				"The main take home points for neurologists from the body of evidence contained in the 5 trials are (1) IAT is a potently effective treatment and should be offered to patients who have documented occlusion in the distal ICA or M1 arteries, have a relatively normal NCCT, significant neurological deficit, and can have recanalization within 6 hours of LSN; (2) benefits refer to patients receiving r-tPA before IAT; r-tPA should not be withheld if the patient meets criteria, and benefit in patients who do not receive r-tPA or have r-tPA exclusions requires further study; (3) favorable results occur when IAT is performed at an endovascular stroke center by a coordinated multidisciplinary team that extends from the prehospital stage to the endovascular suite, minimizes time to recanalization, uses stent-retriever devices, and avoids general anesthesia (GA)." (Grotta & Hacke) (Pierot & Derdeyn, Stroke 2015; 46: 1440-1446 – "EVT with stent-retrievers is now proven effective and is dramatically so, for a well-defined subset of patients with acute ischemic stroke. Current practice needs to incorporate the lessons from the recent trials: careful patient selection and optimizing time to reperfusion and reperfusion rate are critical to providing any benefit to our patients.")	
16.	Phenox	General	-	We have finalized the ARTESp Study for pREset.	We appreciate that this has been brought to our attention. This does not warrant any amendments to the document at this point.
17.	Phenox	General	-	pREset and pREset LITE will be included in the SITS-Open Study	We appreciate that this has been brought to our attention. This does not warrant any amendments to the document at this point.
18.	Stryker	7,15, 22	111, 356, 523	Please add in Aspiration/Suction Devices: "AXS Catalyst™ Distal Access Catheter" from Stryker	This was not included in the original study plan and thus cannot be included at this stage in the assessment
19.	Medtronic	10	225	"While six trials reported on NIHSS in different ways and at different time points, all appeared to demonstrate relatively better outcomes in the intervention groups – the significance of this is difficult to assess, however, given the aforementioned heterogeneity in reporting." Suggest further clarification regarding the phrase "the significance of this is difficult to assess..." The below table presents detailed reporting of NIHSS	We have already been clear that the intervention appears to be favoured, despite the heterogeneity in results. We now provide an example of this heterogeneity in the narrative.

<table>
<tr><th>Comm. #</th><th>Comment received from</th><th>Page</th><th>Line/ section number</th><th>Comment</th><th>Author's reply</th></tr>
<tr><td></td><td></td><td></td><td></td><td>results. With the exception of the SYNTHESIS Expansion trial which utilized early generation thrombectomy devices (i.e. Merci Retriever and Penumbra Aspiration System), the recent trials demonstrate both early and long-term improved neurological outcomes favoring intervention primarily with stent retrievers despite the heterogeneity in reporting results.

<table>
<tr><th>STUDY</th><th>TIMEPOINT</th><th>ENDPOINT RELATED TO NIHSS SCORE</th><th>RESULT (I-intervention; C-control)</th></tr>
<tr><td>SYNTHESIS Expansion</td><td>7 days</td><td>2°: NIHSS ≤6 (mild neurologic deficit or none)</td><td>I: 54%, C: 55%, p=0.89</td></tr>
<tr><td>MR CLEAN</td><td>24 hours
5-7 days or d/c</td><td>2°: Median score
2°: Median score</td><td>I: 13, C: 16, beta 2.6 unadj, 2.3 adj
I: 8, C: 14, beta 3.2 unadj, 2.9 adj</td></tr>
<tr><td>EXTEND IA</td><td>3 days</td><td>Co-1°: ≥8-pt reduction or score of 0 or 1 (early neurologic improvement)</td><td>I: 80%, C: 37%, p<0.001</td></tr>
<tr><td>REVASCAT</td><td>24 hours</td><td>2°: ≥8-pt reduction or 0-2 (early dramatic response to treatment)</td><td>I: 59%, C: 20%, OR 5.5 unadj,</td></tr>
<tr><td>SWIFT PRIME</td><td>27 hours</td><td>2°: Change in NIHSS score</td><td>I: mean change -3.9±6.2, C: -8.5±7.1, p<0.001</td></tr>
<tr><td>ESCAPE</td><td>90 days</td><td>2°: NIHSS 0-2 (neurological disability)</td><td>I: 51.6%, C: 23.1%,
Diff 28.4, rate ratio 2.2 unadjusted, 2.1 adjusted</td></tr>
</table></td><td>More information on NIHSS reporting is provided in the appendices (currently table 12).</td></tr>
<tr><td>20.</td><td>Medtronic</td><td>10</td><td>232</td><td>"Restoration of cerebral blood flow on final angiography, as assessed using the mTICI score, was only reported in the intervention groups."
Suggest to include additional context as to the reason flow restoration was assessed and reported in the intervention groups. At the end of the sentence suggest to add "...as the catheter angiography procedure is not standard of care for patients administered IV t-PA alone."</td><td>Change made.</td></tr>
<tr><td>21.</td><td>Medtronic</td><td>10</td><td>242</td><td>A total of 8 RCTs both old and recent studies were included in the assessment. While all studies were RCTs comparing endovascular treatment with standard medical treatment, major methodological differences remain between the three early RCTs (MR RESCUE, IMS3, and SYNTHESIS Expansion) and the recent trials (MR CLEAN, ESCAPE, EXTEND-IA, SWIFT PRIME, and REVASCAT) that cautions against pooling all data. It is strongly recommended that the three early RCTs not be included in the assessment for the following reasons:

• Previous studies using mechanical thrombectomy devices in the treatment of acute ischaemic stroke failed to demonstrate clinical benefit which can be attributed to multiple methodological pitfalls and use of first generation technology (1)(2)(3).
• Firstly, the 'older' studies were characterised by a lack of advanced imaging for</td><td>Subgroup analysis has now been performed
The issues of imaging, timing and changing technology are all referred to in the substance of the document; it is not feasible to go into these issues in depth in the report summary.

In addition, we now make clear that we believe the evidence of benefit applies to those procedures in which stent retrievers (as opposed to older technology) is used.</td></tr>
</table>

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				patient selection which is required to ensure the presence of vessel occlusion and salvageable brain tissue. Indeed, confirmation of largevessel occlusion by imaging was not performed in some of the older studies prior to randomisation, allowing patients without proximal vessel occlusion to enter the studies. The importance of neuroimaging criteria for the selection of patients has been a key part of newer trials. • A heightened awareness of the importance of time has improved. A significant delay of more than two hours between initiation of intra-venous tPA and endovascular intervention which occurred in earlier studies could have diminished the effects of the intra-arterial endovascular intervention. An emergency department door–to–groin puncture time of 90 minutes was achieved in the some of the newer studies. • Also, it is vital to highlight that endovascular technology has changed and the older studies reflect first generation devices. New generation stent-retriever technology, such as Solitaire FR has been shown in recent RCTs to result in faster, more complete recanalization as defined by significantly higher rates of Thrombolysis in Cerebral Infarction angiographic scores of 2b (indicating successful reperfusion of _50%) or 3 (complete reperfusion), as compared with intravenous t-PA alone or earlier- generation thrombectomy devices. All of the older studies utilised very few stent retrievers in their intervention arm, in fact the MR RESCUE study used no new generation stent retrievers (0/70 patients) in their embolectomy arm (Merci Retriever or Penumbra System . While in the IMS3 study only 5/434 or 1% of patients received stent retrievers. In the SYNTHESIS EXPANSION expansion study,thrombectomy using stent retrievers was used in 23/181 or 23% of patients, which is in direct comparison to the new studies, whereby 77%-100% of patients in the intervention arm were treated with stent retrievers. • Finally, in the editorial of Pierot L. et al. (4) in which the authors discuss the following limitations/weaknesses of the IMS III, Synthesis Expansion, and MR RESCUE trials: o All studies: Long period of inclusion/recruitment, small number of patients per center per year, and heterogeneity of endovascular techniques used (IA tPA and/or mostly 1st gen devices) o IMS III and Synthesis: Inappropriate preoperative imaging including absence of CTA or MRA to detect an occlusion and no evaluation of salvageable brain with perfusion CT or MR o Synthesis and MR RESCUE: Comparison of IV tPA to Endovascular treatment alone (instead of comparing IV tPA to a combined approach of endovascular treatment + IV tPA) References indicated above: 1. Broderick JP, Palesch YY, Demchuk AM, Yeatts SD, Khatri P, Hill MD, et al.	

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				Endovascular therapy after intravenous t-PA versus t-PA alone for stroke. N Engl J Med [Internet]. 2013 Mar 7 [cited 2014 Jul 11];368(10):893–903. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3651875&tool=pmcentrez&rendertype=abstract 2. Kidwell CS, Jahan R, Gornbein J, Alger JR, Nenov V, Ajani Z, et al. A trial of imaging selection and endovascular treatment for ischemic stroke. N Engl J Med [Internet]. 2013 Mar 7 [cited 2015 Apr 14];368(10):914–23. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3690785&tool=pmcentrez&rendertype=abstract 3. Ciccone A, Valvassori L, Nichelatti M, Sgoifo A, Ponzio M, Sterzi R, et al. Endovascular Treatment for Acute Ischemic Stroke. N Engl J Med [Internet]. 2013 Mar 7 [cited 2015 Apr 14];368(10):904–13. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3708480&tool=pmcentrez&rendertype=abstract 4. Pierot L. et al AJNR Am J Neuroradiol. 2013 Jun 6. Mechanical Thrombectomy after IMS III, Synthesis, and MR-RESCUE.	
22.	Medtronic	10 and overall	242	It is recommended to have an introduction for each chapter. For example here, communicating how each parameter of safety is considered and why. For a health care decision maker or generally anyone interested in this report, it is difficult to understand the relevance of content because of the way it is presented (i.e. presenting directly the outcomes for each endpoint without explaning the relevance of the endpoints)	An introduction would be of benefit but this is not part of EUnetHTAs assessment template. In addition, information (albeit limited given the nature and timeframe for this rapid report) has been provided on the outcomes used to determine effectiveness.
23.	Medtronic	overall		It is critical to note that the recently published clinical evidence (i.e., MR CLEAN, ESCAPE, EXTEND-IA, SWIFT PRIME, and REVASCAT) are primarily based on the use of stent retrievers. According to the editorial by Werner Hacke, MD in the International Journal of Stroke (2015), there is no convincing evidence that these positive results for endovascular treatment would also apply to other devices such as the Penumbra suction device (THERAPY, which did not show significant superiority). The results of THERAPY, so far known, indicate a much smaller treatment effect of just 8% (absolute difference), which failed to show superiority in an underpowered early terminated trial. Reference: Hacke W. The results of the recent thrombectomy trials may influence stroke care delivery: are you ready? Vol 10, July 2015, 646–650. 2015 World Stroke Organization DOI: 10.1111/ijs.12541	Subgroup analysis has now been performed In addition, we now make clear that we believe the evidence of benefit applies to those procedures in which stent retrievers (as opposed to older or other technology) is used.
24.	Stryker	11	278	The THERPAY Trial has stopped also following the MR CLEAN publication. The results were presented by Dr. Mocco at the European Stroke Organization	For estimating efficacy we have restricted our analysis to published

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				Conference in Glasgow, Scotland on April 17, 2015. They did not reach the primary or secondary pre-specified endpoints in either the intent to treat or per protocol analysis.	RCTs.
25.	Medtronic	12	288	Pooled data from 8 RCTs (3 early and 5 recent trials) were included. Please refer to previous comment for page 10, line 242. The pooling of data from the early and recent trials is strongly not recommended.	Subgroup analysis has now been performed In addition, we now make clear that we believe the evidence of benefit applies to those procedures in which stent retrievers (as opposed to older or other technology) is used.
26.	Medtronic	13	296	"The intervention is not associated with an increase in symptomatic intracerebral haemorrhage at 90 days." This is only valid if the comparator is IV t PA, otherwise, it does not make sense. It is not clear in the report what is the comparator. For additional clarity on the comparator, suggest to add "when compared to IV t-PA alone" at the end of the sentence.	It has been amended to read "when compared with standard medical therapy alone".
27.	Stryker	13	309	Please correct number of devices it is now 15 with AXS Catalyst™ Distal Access Catheter.	This was not included in the original study plan and thus cannot be included at this stage in the assessment
28.	Neuravi	13	310-316	The device categories covered by the clinical trials include stent-retrievers (Trevo, Solitaire, others); retrievers (Merci); and aspiration (Penumbra). The most recent trials that demonstrated statistically significant benefit to endovascular therapy as compared to IV t-PA alone were conducted using more advanced technology – stent-retrievers. The evidence shows that use of stent-retrievers led to high rates of rapid recanalization and the associated good clinical outcomes. The recanalization rates were higher not only than the IV t-PA only arm, but also in comparison to the earlier trials where first-generation retrievers like the Merci, and first-generation aspiration devices like Penumbra, were utilized. Thus, the data strongly supports the use of the stent-retriever category of devices. (Pierot & Derdeyn, Stroke 2015; 46: 1440-1446 – " The data from these trials demonstrate the dramatic technological improvement using Stentrievers") (ESO/ESMINT/ESNR Consensus – "there is very good evidence for early thrombectomy with stentretrievers. There is good evidence to favour stentretrievers over the MERCI™ device. At this moment only limited data on	Subgroup analysis of the five most recent trials has now been performed In addition, we now make clear that we believe the evidence of benefit applies to those procedures in which stent retrievers (as opposed to older or other technology) is used.

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				other types of recanalization devices such as the Penumbra™ system are available")	
29.	Medtronic	13	311-312	"it can be surmised that the bulk of the evidence presented here relates to just four devices (Merci Retriever; Penumbra System®; Solitaire FR; Trevo®)" Suggest to add "Solitaire 2" in the devices specified as the majority (83.2%) of devices used in the SWIFT PRIME trial was the Solitaire 2 device.	This has been amended
30.	Medtronic	13	317	"Five of the eight trials included in this analysis were stopped early. While the reasons for this are explained in each instance, it does affect the overall interpretation of the data presented, and it is possible that the estimated effects of mechanical thrombectomy are at risk of bias as a result." For additional context, consider the following key points regarding RCTs: • Five of the pivotal randomised controlled trials (RCTs) were stopped early for clinical benefit (SWIFT, SWIFT PRIME, EXTEND-IA, ESCAPE, REVASCAT). An RCT that stops earlier than initially planned is called a truncated RCT (tRCT) • All five studies had rigorously designed study protocols that met International ethical standards and were publicly registered and transparent in their methodological approach and deviations. Most importantly all 5 studies employed the use of validated sequential monitoring rules for early stopping that appropriately controls for type I errors. These included O'Brien-Fleming, Haybittle-Peto and Pocock rules(11)(12). • The appropriate implementation of the early stopping rules by an independent Data and Safety Monitoring Board (DSMB) not only reduces potential biases but assists interpretation of results. In the case of the Solitaire FR studies, the overwhelming clinical significance of revascularisation and functional benefit of Solitaire over IVtpA is not diminished as methodological quality of the studies is high. • Early stopping rules are integral in RCT design to prevent loss of equipoise in a study, prevent harm and unacceptable adverse events (non-maleficence). Indeed, maintaining the integrity of the trials and obtaining precise final results must be balanced against the risks for patients who are randomly assigned to an apparently inferior treatment and the need to rapidly disseminate evidence supporting a treatment benefit to the broader community. There is an ongoing debate in the medical literature concerning possible bias in studies stopped early for benefit. However, recent evidence suggests that excluding truncated studies leads to underestimation of treatment effects and overestimation of statistical information (in meta-analyses)(13). References: 11. Whitehead J. The Design and Analysis of Sequential Clinical Trials, (2nd edn). Chichester, UK: Wiley-Blackwell; 1997.	While taking the comments of the manufacturer into account, we believe it is still reasonable to summarise that „and it is possible that the estimated effects of mechanical thrombectomy are at risk of bias as a result." Despite this risk we are still concluding that the technology is of benefit. In section 4.3 we lay out the reasons why each of the truncated trials stopped early; as alluded to by the manufacturer, there is ongoing debate concerning possible bias in studies stopped early – hence our approach has been to provide the reader with information on which studies stopped early and why, and to acknowledge the potential for risk of bias – but ultimately it will be up to the reader to come to their own conclusions in relation to the ongoing debate

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				12. Jennison C TB. Group Sequential Methods with Applications to Clinical Trials. Boca Raton, FL,: Chapman & Hall/CRC; 2000. 13. Schou IM, Marschner IC. Meta-analysis of clinical trials with early stopping: an investigation of potential bias. Stat Med [Internet]. 2013 Dec 10 [cited 2015 May 15];32(28):4859–74. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23824994	
31.	Stryker	13	324	Higher rate of symptomatic cerebral haemorrhage not shown in the RCTs using Stent Retrievers.	This has been made more explicit
32.	Neuravi	13	333-354	The evidence presented in this draft assessment supports the benefit of mechanical thrombectomy in the setting of acute ischemic stroke due to proximal artery occlusion up to 6 hours as recommended by leading neurologists* and numerous experts, including the leading professional stroke bodies including the European Stroke Organisation (ESO) The American Heart Association / American Stroke Association, etc. The evidence is strong in terms of morbidity and function and, perhaps, generic quality of life, in selected patients with anterior circulation acute ischaemic stroke, treated with new generation thrombectomy devices after having first received IV t-PA. Additionally, initial evidence suggests that patients, who don't receive IV t-PA due to ineligibility or other reasons, may benefit from mechanical thrombectomy[1-3]. Without treatment, this patient population's prognosis is dismal [4-5]. While both the MR CLEAN and the ESCAPE trials included broad heterogeneous patient populations, it will be helpful to continue to monitor how the applicability of the trial evidence applies to the real-world setting. Additional studies would be useful in determining the best treatment strategy for patients arriving at extended time points (i.e. outside the 12 hour time window)	We cannot conclude from the evidence presented that 6 hours is the appropriate timeframe – although it may well be. We have been explicit in detailing the time to intervention in each of the trials This pilot assessment aims to assess the evidence on its own merits and we cannot extrapolate from the conclusion of experts/professional bodies. We believe that the current wording in relation to the strength of the evidence is appropriate. Therefore we have kept "the evidence suggests that…" and not changed to the manufacturers suggestion which is to say that "the evidence is strong.." Again, while we agree with the manufacturers wording re initial evidence for patients not eligible or iv t-pa, this has not been examined in this current assessment and hence it would be inappropriate to make a concluding statement about it As noted in a recent editorial by Wardlaw and Dennis, the cohorts included in the trials were relatively specific and their applicatation of the results to the

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				The evidence suggests that mechanical thrombectomy is safe – with regard to all-cause mortality at 90 days, SICH and recurrent stroke - when compared with standard medical care alone, in selected patients. There remains insufficient evidence, however, to determine the significance or otherwise of device- and/or procedure-related complications which may be associated with this intervention. It appears that the results of the five trials published most recently have acted as a 'watershed' for mechanical thrombectomy, with a number of other trials having halted and an apparent sea- change in attitude when compared with that which followed publication of the first three trials in 2013. As a result, numerous professional societies have come together to advocate for the immediate practice of rapid assessment and addition of mechanical thrombectomy as a treatment for patients with large proximal vessel occlusions due to the compelling evidence of clinical benefit, with minimal additional risk, as compared to treatment with IV t-PA alone [6-8]. Additional studies will be helpful in further delineating subpopulations and techniques that will further enhance the delivery of optimal care for this devastating disease. Finally, the maximum follow-up presented in this draft assessment has been 90 days. Outcome data with longer-term follow-up for second generation devices would provide useful additional evidence as to whether the benefits of mechanical thrombectomy persist. [1] ESO/ESMINT/ESNR Consensus Statement: If intravenous thrombolysis is contraindicated (e.g. Warfarin-treated with therapeutic INR) mechanical thrombectomy is recommended as first-line treatment in large vessel occlusions (Grade A, Level 1a, KSU Grade A) – changed and updated level of evidence. [2] Pierot & Derdeyn, Stroke 2015; 46: 1440-1446: "in both MR CLEAN and ESCAPE, the OR in favor of mechanical thrombectomy was similar in the subgroups of patients receiving or not receiving intravenous r-tPA. Most of these patients were within the intravenous tPA time window but met medical exclusions for systemic fibrinolysis..... There is also good evidence, from MR CLEAN and ESCAPE, for patients who present within the tPA window of 4.5 hours and are ineligible for intravenous tPA for exclusions related to bleeding complications with systemic fibrinolysis. These include recent surgery or anticoagulation within a reasonable range (international	real world setting remains to be seen. We don't believe it is appropriate to highlight Mr Clean or Escape Again, the scope of this assessment is to assess the published evidence and it is inappropriate to strengthen our conclusions from the evidence based on others conclusions. Additional studies will be helpful in further delineating subpopulations and techniques that will further enhance the delivery of optimal care for this devastating disease. – this has been included

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				normalized ratio <3.0). [3] The AHA/ASA guidelines (updated) concluded that "In carefully selected patients with anteiror circulation occlusion who have contraindications to intravenous r-tPA, endovascular therapy with stent retrievers completed within 6 hours of stroke onset is reasonable (Class IIa; Level of Evidence C). [4] Preliminary Results from the FIRST Trial: Natural History of Acute Stroke from Large Vessel Occlusion Janardhan et al, Stroke 2013; 44: A194. [5] Intra-arterial Prourokinase for Acute Ischemic Stroke The PROACT II Study: A Randomized Controlled Trial Furlan et al, *JAMA.* 1999;282(21):2003-2011 (natural history arm) [6]ESO/ESMINT/ESNR Consensus Statement [7]AHA/ASA Recommendations, Stroke 2015; 46: 3020-3035. [8]SNIS Recommendations, Jayaraman et al., *J NeuroIntervent Surg* 2015; 7 (5): 316.	
33.	Johnson & Johnson Medical	13	334-341	We note that the conclusion of this assessment differs from the largest study (MR CLEAN) included in this assessment. As this was a real-world study that reflects true clinical practice, we recommend further review of the conclusion. This variation in outcome is likely driven by including the 3 clinical studies mentioned previously which do not represent the outcomes achievable in current clinical practice.	We disagree. Similarly to Mr Clean, our conclusion states clearly that "mechanical thrombectomy is of benefit, in terms of morbidity and function and, perhaps, generic quality of life, in selected patients with anterior circulation acute ischaemic stroke, treated with new generation (stent retriever) thrombectomy devices after having first received IV t-PA" We have performed subgroup analysis on the five most recent studies and this is also reflected in the discussion and conclusion.

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34.	Stryker	13	334	Add: mechanical thrombectomy with stent retrievers	The issue of stent retrievers has now been addressed within the conclusion
35.	Medtronic	13	336	In the conclusion: "new generation thrombectomy devices": please be specific and mention "new generation of stent retrievers" Please refer to comment for page 8 line 124.	Done
36.	Medtronic	13	337	"There is currently insufficient evidence, however, to determine the applicability of this evidence to the much larger, heterogeneous cohort of patients with ischaemic stroke who are treated in the real-world setting and who may be ineligible for IV- tPA, who arrive outside the time window for treatment and/or who are managed in non-specialised institutions or units." The comment that there is "insufficient evidence" to determine applicability is inappropriate in this type of systematic review where only RCT evidence has been examined. If a comment is to be made on how mechanical thrombectomy works in a 'real world' setting the HTA should have included non-randomised and observational evidence as part of the PICO criteria. It is important to note that there are a number of published observational studies that examine the real world effectiveness of mechanical thrombectomy in acute ischemic stroke patients.	The comment does not say that mechanical thrombectomy will not work in the real world setting. We are simply pointing out that – because we only examined RCTs – we cannot say for sure that it will work in the real world setting.
37.	Neuravi	14	347-354	AHA/ASA revised recommendations (Oct 2015) state there is Class I, Level of Evidence A that patients should receive endovascular therapy with a stent retriever if they: have prestroke mRS 0-1, have AIS and received IV r-tPA within 4.5 hours of onset, the causative occlusion is in the ICA or proximal MCA, are age 18 or oler, have an NIHSS score of 6 or greater, have an ASPECTS score of 6 or greater, and treatment can be initiated (groin puncture) within 6 hours of symptom onset. Observing patients after IV r-tPA to assess for clinical response before pursuing endovascular therapy is not required to achieve beneficial outcomes and is not recommended (Class III, Level of Evidence B-R) Use of stent-retrievers is indicated in preference to the MERCI device (Class I; Level of Evidence A) *Grotta & Hacke, Stroke 2015; 46: 1447-1452 - "The main take home points for neurologists from the body of evidence contained in the 5 trials are (1) IAT is a potently effective treatment and should be offered to patients who have documented occlusion in the distal ICA or M1 arteries, have a relatively normal NCCT, significant neurological deficit, and can have	We have added that "In the interim, careful patient selection, optimisation of time to intervention and the use of stent retriever technologies should help to ensure maximum benefit is derived for these patients."

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				recanalization within 6 hours of LSN; (2) benefits refer to patients receiving r-tPA before IAT; r-tPA should not be withheld if the patient meets criteria, and benefit in patients who do not receive r-tPA or have r-tPA exclusions requires further study; (3) favorable results occur when IAT is performed at an endovascular stroke center by a coordinated multidisciplinary team that extends from the prehospital stage to the endovascular suite, minimizes time to recanalization, uses stent-retriever devices, and avoids general anesthesia (GA)." (Grotta & Hacke) (Pierot & Derdeyn, Stroke 2015; 46: 1440-1446 – "EVT with stent-retrievers is now proven effective and is dramatically so, for a well-defined subset of patients with acute ischemic stroke. Current practice needs to incorporate the lessons from the recent trials: careful patient selection and optimizing time to reperfusion and reperfusion rate are critical to providing any benefit to our patients.")	
38.	Medtronic	14	348	Include mechanical thrombectomy "mainly with stent retrievers" Please refer to comment for page 8 line 124.	This issue has been addressed
39.	Medtronic	14	353	"Outcome data with longer-term follow-up for second generation devices would provide useful additional evidence as to whether the benefits of mechanical thrombectomy persist." It is standard for studies evaluating safety and effectiveness of acute treatment (e.g. IV fibrinolysis, mechanical thrombectomy, etc) for ischemic stroke patients to assess outcomes at 90 days (i.e. 3 months) as significant clinical improvement as a result of primary acute treatment is not expected beyond 3 months.	The comment is accepted and this point has been removed from the text
Description and technical characteristics of the technology					
40.	Medtronic	18	390	"Recent clinical evidence (MRCLEAN, ESCAPE, EXTEND IA, SWIFT PRIME and REVASCAT) suggests that, administered within 6 to12 hours after stroke 391 onset [3-7]. " This sentence is incomplete or not completely understandable. Please also add "mainly applicable for stent retrievers" after mentioning the studies. Please refer to comment for page 8 line 124.	Changed to: *"Endovascular treatment with mechanical thrombectomy administered within six to 12 hours of stroke onset has been suggested as an effective and safe adjunct to usual care such as t-PA alone."*
41.	Medtronic	18	399	Suggest to clarify that "new generation of stent-retrievers are the only ones that have demonstrated efficacy." Please refer to comment for page 8 line 124.	There are no conflicts between the original contents in the text and your comment. We also highlight the stent retrievers.
42.	Stryker	19	409	The wording is not the same as in the consensus Statement Please include all the LEVEL 1 evidences stated in the ESO Consensus Statement	Completed them all.

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				Including "For mechanical thrombectomy, stent retrievers approved by local health authorities should be considered (Grade A, Level 1a, KSU Grade A)" - new	
43.	Medtronic	19	419	Here, the important points of the ESO guidelines (March 2015) are not completely reported here. This may therefore mislead the scientific community as it is stated despite the chapter of the guideline reported in table 7 of the report. For convenience, here are some of the key points that stakeholders would expect as a minimum: "Mechanical thrombectomy, in addition to intravenous thrombolysis within 4.5 hours when eligible, is recommended to treat acute stroke patients with large artery occlusions in the anterior circulation up to 6 hours after symptom onset (Grade A, Level 1a, KSU Grade A). - new Mechanical thrombectomy should not prevent the initiation of intravenous thrombolysis where this is indicated, and intravenous thrombolysis should not delay mechanical thrombectomy (Grade A, Level 1a, KSU Grade A). - new Mechanical thrombectomy should be performed as soon as possible after its indication (Grade A, Level 1a, KSU Grade A). **For mechanical thrombectomy, stent retrievers approved by local health authorities should be considered (Grade A, Level 1a, KSU Grade A). – new** **Other thrombectomy or aspiration devices approved by local health authorities may be used upon the neurointerventionists discretion if rapid, complete and safe revascularisation of the target vessel can be achieved (Grade C, Level 2a, KSU Grade C)** If intravenous thrombolysis is contraindicated (e.g. Warfarin-treated with therapeutic INR) mechanical thrombectomy is recommended as first-line treatment in large vessel occlusions (Grade A, Level 1a, KSU Grade A) – changed and updated level of evidence. Patients with acute basilar artery occlusion should be evaluated in centres with multimodal imaging and treated with mechanical thrombectomy in addition to intravenous thrombolysis when indicated (Grade B, Level 2a, KSU Grade C); alternatively they may be treated within a randomized controlled trial for thrombectomy approved by the local ethical committee – new"	Completed them all.
44.	Neuravi	19	438-444	Compared to IV t-PA, mechanical thrombectomy has the following benefits: • Endovascular treatment has been demonstrated in RCT's to deliver a higher rate of reperfusion (mTICI 2b-3) and a higher rate of good clinical outcomes (mRS 0-2 at 90d) as compared to IV t-PA in the setting of Large Vessel Occlusions. (ICA and proximal MCA in particular) • Based on the trials, patients may be treated with both IV t-PA and with	The safety and effectiveness of thrombectomy is illustrated in the following parts in detail.

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				endovascular therapy without an increase in the risk of symptomatic hemorrhage. • (in addition to the 2 bullets listed)	
45.	Stryker	20	468	Please indicate the LEVEL of evidence	Added
46.	Medtronic	20	497	"There is no specific supply for the comparators such as intravenous t-PA." To clarify, administration of IV t-PA does require medical supplies, in particular, syringes and infusion lines.	Thank you for reminding. Changed accordingly.
47.	Medtronic	21	511	"SWIFT" to be replaced by "SWIFT PRIME"	Changed accordingly.
48.	Stryker	22	523	For TREVO, Name in other countries should be changed to "Same" Add here as well the AXS Catalyst™	Changed accordingly about TREVO. For AXS Catalyst™: This was not included in the original study plan and thus cannot be included at this stage in the assessment.
49.	Medtronic	22	523	Please add additional reference of Solitaire: "Solitaire 40": it is planned to be CE marked in the coming weeks before the publication of this report. We can communicate CE Mark certificate to EUnetHTA as soon as received.	This was not included in the original study plan and thus cannot be included at this stage in the assessment.
50.	Medtronic	22	523	The name for MindFrame Capture LP is listed as "Aspiration Device". It should be "Stent Retriever".	Changed
51.	Medtronic	22	523	In table 2: Change the "Class/GMDN Code" for Solitaire 2 which has the exact same wording as MindFrame Capture LP: "58'173, Embolectomy" Pease delete in table 2 "Solitaire FR Revascularization Device received CE mark approval to restore blood flow in patients with AIS including a different IFU with different bench testing and validation to differentiate from the previous approved Solitaire AB Remodeling Device which was indicated to provide support for aneurysm coiling procedures" This information is not relevant.	Already deleted and corrected
52.	Phenox	22	-	Include PRE-4-20 and PRE-6-30 as pREset reference codes. Include PRE-LT-3-20 and PRE-LT-4-20 as pREset LITE reference codes.	Added
53.	Medtronic	24	528	Include mechanical thrombectomy "with stent retrievers" Please refer to comment for page 8 line 124.	See the above reply, we changed to a neutral saying in the text.
54.	Medtronic	24	530	"Three RCTs focused on thrombectomy with a specific device, the Solitaire FR stent retriever." Suggest to add "...the Solitaire FR and Solitaire 2 stent retriever" to the sentence as a majority (83.2%) of Solitaire devices used in the SWIFT PRIME study were Solitaire 2.	We rewrite this part in the text.
55.	Medtronic	24	535	"The earlier techniques and the first generation of mechanical thrombectomy devices failed to show significant	Yes, deleting this sentence makes it much clearer. But changed after the

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				efficacy. The clinical impact was illustrated in several trials comparing first-generation and second-generation devices and showing a higher efficacy in the latter, in terms of both recanalization and clinical outcome. However this has been attributed to study limitations including the heterogeneity of techniques used, inappropriate selection of the patients, important process delays and small patient numbers [1]." For further clarity, suggest moving the third sentence, "However this has been atributed..." after the first sentence.	second sentence.
56.	Johnson & Johnson Medical	24	542-545	We fail to understand the relevance of the reference to FDA approval in this Rapid REA as this maybe dependent on the individual company's commercial strategy and we therefore recommend removal of this reference.	That is a comment we changed according to internal review. This is just a description of the current status, no judgement.
57.	Medtronic	24	547	"The results of five recent RCTs focusing on thrombectomy are highly promising but methodological heterogeneity of these studies affects the comparability of efficacy and safety results." Please be specific about the identified "heterogeneity". Consider modifying sentence to include a few examples of the methodological heterogeneity such as patient populations, imaging-selection strategies, and treatment alacrity. Please also include thrombectomy "mainly with stent retrievers" Please refer to comment for page 8 line 124.	Changed accordingly in the text
58.	Medtronic	24	550	"Population-based registries (stroke registry) to monitor thrombectomy in an unbiased way generate real-life, longterm data on clinical outcomes as well as costs." Registries are needed but we cannot say that they are "unbiaised". The quality and relevance of the registry depends on what the "data collection". For example, if the data collection is not completely relevant, can we say that it is unbiaised. There is no perfect study… each study aims to answer research questions but cannot answer all questions.	Added "for selecting participants and reporting data"
Health problem and current use of the technology					
59.	Medtronic	28	681	Can you replace the word "devices" by mechanical thrombectomy devices	Yes, replaced
60.	Neuravi	28	682-684	Recent trials demonstrated, however, that patients treated rapidly with both IV t-PA and mechanical thrombectomy did better than those treated with IV t-PA alone; and this led the AHA/ASA to revise their guidelines to recommend that waiting for IV t-PA to fail before pursuing endovascular therapy is not recommended, and is not required to achieve beneficial outcomes.	But the text has no conflict with the guideline form AHA, the group people we mean is who did not catch the time for IV t-PA, who may have chance to receive thrombectomy.
61.	Medtronic	28	684	Can you replace the word "devices" by mechanical thrombectomy devices	Changed
62.	Medtronic	28	685	Can you remove the sentence "EmboTrap is designed…..". it is not part of this chapter.	Removed
63.	Stryker	28	685	Why this focus on EmboTrap device instruction for use?	Removed

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64.	Medtronic	28	690	Can you replace the word "devices" by mechanical thrombectomy devices	Changed
65.	Medtronic	29	Table 3	Can you remove the sentence in the table 3 "The same as above: The Solitaire 2 FR ……."	Removed
66.	Stryker	29	697	Sort the devices by alphabetic order Add AXS Catalyst™ Add Trevo ProVue & Trevo XP Provue just add the same indication and Contraindications than for Trevo") Trevo &Trevo Provue & Trevo XP), is also approved by FDA	Table has been sorted. Additional devices have not been incorporated (see above).
67.	Medtronic	29	697	please write "Solitaire 2 Revascularization" instead of "Solitaire 2 FR Revascularization" because it is the name in Europe (the other one is other regions)	Changed
68.	Medtronic	30	699	"What is the reimbursement status of mechanical thrombectomy devices?" As mentioned in the project scope comments, this question should be out of scope for a European relative effectiveness assessment review, as it would require answers at a country level. Whether the technology or procedure is reimbursed in different European countries or not is irrelevant to its measure of effectiveness. Countries can certainly use the final "European" report to review their reimbursement status, but that is a local consideration not European.	That is a local consideration, we just put the current information from each region, there is no comparison.
69.	Stryker	32	704	Germany: Since 2015 there are 2 differents "Zusatzentgelte (ZE)" for Mechanical Thrombectomy using MicroCatether (ZE133) (Aspiration) or Stent Retrievers (ZE152)	Added accordingly.
70.	Stryker	32	704	Comment: Why No data from France & UK?	That is not an investigation from each country; we collect information, and write down what we have. There is no information provided from France or UK.
71.	Neuravi	35	786	In large referral centers, ≈5% to 10% of all acute ischemic strokes and 20% to 30% of r-tPA eligible patients may be candidates for IAT (Grotta & Hacke, Stroke Neurologist's Perspective on the New Endovascular Trials, Stroke.2015; 46: 1447-1452)	Added accordingly.
Clinical effectiveness					
72.	Medtronic	38	904	CLINICAL EFFECTIVENESS chapter - Pooled data from 8 RCTs (3 early and 5 recent trials) were included. Please refer to previous comment for page 10, line 242. The pooling of data from the early and recent trials is strongly not recommended..-	Subgroup analysis of the latter 5 has now been performed
73.	Neuravi	39	general	Stroke.2015; 46: 1440-1446: in Interventional Management of Stroke III (IMS III), no imaging screen for large vessel occlusion was used in nearly half of the enrolled patients, leading to the inclusion of many patients who were not	Subgroup analysis of the latter 5 has now been performed

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				candidates for intervention.14 The more recent trials have benefited from wide availability of computed tomographic angiography (CTA). Second, revascularization rates were extremely poor in the failed trials. The past 5 years has seen dramatic improvement in technology, with stentrievers and distal access/suction catheters, often in combination, that have provided extremely high revascularization rates.15–17 Finally, the failed trials had long times to revascularization.18 This was largely because of the relative ineffectiveness of early generation endovascular devices and intra-arterial lytic infusion. A strong inverse relationship with outcome and time to reperfusion was found.19	
74.	Stryker	39	911	Comment: It could be interesting to underline the differences in the inclusion criteria in those studies.	The inclusion criteria are dealt with in detail under the subheading 'patient characteristics'
75.	Medtronic	39	911	For ESCAPE. Please specify 80% of Solitaire (the percentage is important and it is mentioned in the publication)	86.1% . Change made
76.	Medtronic	39	918-926	It is strongly recommended that data from MR RESCUE, SYNTHESIS Expansion, and IMS3 not be included. Please refer to previous comment for page 10, line 242. Consider the implications of including trials in which confirmation of large-vessel occlusion by imaging was not performed prior to randomisation, allowing patients without proximal vessel occlusion to enter the study (MR RESCUE & SYNTHESIS and the first 284 patients randomized in IMS3). This is not in-line with current clinical practice guidelines for the management of Ischaemic stroke (outlined in Table 7 of this report) – which state that endovascular therapy with a stent retriever should be used when patients meet certain criteria whereby 'causative occlusion of the ICA or proximal MCA' has been established (AHA/ASA 2015). We propose that the PICO criteria on page 15 be amended – such that the Population in this review includes: Adults aged 18yrs or older with **confirmed large vessel ischaemic stroke in the anterior /or posterior region**.	Subgroup analysis which does not include MR RESCUE, Synthesis or IMS3 has now been performed
77.	Medtronic	39	918	Delete "MR RESCUE." MR RESCUE did use image-guided patient selection as it was the premise of the trial and further described in lines 921-926.	We have changed 'image guided patient selection' to 'non-invasive arterial imaging'
78.	Medtronic	42	1037-1040	The author provides a reference that suggests trials that stop early for benefit may overestimate the treatment effect [reference 52, Bassler, D., et al.,2010]. It must also be acknowledged that early stopping rules are integral in RCT design to prevent loss of equipoise in a study, prevent harm and unacceptable adverse events (non-maleficence). Indeed, maintaining the integrity of the trials and obtaining precise final results must be balanced against the risks for patients who	The importance of early stopping rules has now been emphasised in the subsection ‚Quality'. That said, it is still necessary to highlight that early stopping can potentially lead to bias. A more in-depth analysis of this topic,

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				are randomly assigned to an apparently inferior treatment and the need to rapidly disseminate evidence supporting a treatment benefit to the broader community. While we concede that abandoning early stopping certainly leads to a more unbiased estimation, it is currently not feasible given the range of ethical and practical imperatives involved in clinical trial research. Furthermore, on the basis of recent evidence by Shou and Marschner 2013, such an approach is inefficient and unnecessary. They found that the exclusion of truncated studies from systematic reviews and meta-analyses leads to an underestimation of treatment effects and overestimation of statistical information (in meta-analyses). Schou IM, Marschner IC. Meta-analysis of clinical trials with early stopping: an investigation of potential bias. Stat Med 2013 Dec 10 32(28):4859–74. Same argumentation as above Other argumentation (also coming from Liesl drafted few months ago, there is also a more detailed version) • Five of the Solitaire FR pivotal randomised controlled trials (RCTs) were stopped early for clinical benefit (SWIFT, SWIFT PRIME, EXTEND-IA, ESCAPE, REVASCAT). An RCT that stops earlier than initially planned is called a truncated RCT (tRCT) • All five studies had rigorously designed study protocols that met International ethical standards and were publicly registered and transparent in their methodological approach and deviations. Most importantly all 5 studies employed the use of validated sequential monitoring rules for early stopping that appropriately controls for type I errors. These included O'Brien-Fleming, Haybittle-Peto and Pocock rules(11)(12). • The appropriate implementation of the early stopping rules by an independent Data and Safety Monitoring Board (DSMB) not only reduces potential biases but assists interpretation of results. In the case of the Solitaire FR studies, the overwhelming clinical significance of revascularisation and functional benefit of Solitaire over IVtpA is not diminished as methodological quality of the studies is high. • Early stopping rules are integral in RCT design to prevent loss of equipoise in a study, prevent harm and unacceptable adverse events (non-maleficence). Indeed, maintaining the integrity of the trials and obtaining precise final results must be balanced against the risks for patients who are randomly assigned to an apparently inferior treatment and the need to rapidly disseminate evidence supporting a treatment benefit to the broader community. There is an ongoing debate in the medical literature concerning possible bias in studies stopped early for benefit. However, recent evidence suggests that excluding truncated studies leads to	while interesting, is beyond the scope of this review. As noted earlier in this document, while we acknowledge the potential for bias which may have been introduced by early stopping, we nevertheless conclude that the evidence suggests that mechanical thrombectomy is of benefit.

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				underestimation of treatment effects and overestimation of statistical information (in meta-analyses)(13). References: 11. Whitehead J. The Design and Analysis of Sequential Clinical Trials, (2nd edn). Chichester, UK: Wiley-Blackwell; 1997. 12. Jennison C TB. Group Sequential Methods with Applications to Clinical Trials. Boca Raton, FL,: Chapman & Hall/CRC; 2000. 13. Schou IM, Marschner IC. Meta-analysis of clinical trials with early stopping: an investigation of potential bias. Stat Med [Internet]. 2013 Dec 10 [cited 2015 May 15];32(28):4859–74. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23824994	
79.	Neuravi	42	1038-1040	Trials stopped early may also underestimate the treatment effect of the intervention (which is the argument presented by the THERAPY trial which did not reach statistical significance, and was stopped early due to loss of equipoise.	See previous point. We now note that trials stopped early may under- OR over-estimate treatment effect
80.	Medtronic	42-44	1042-1104	There are clear methodological differences between the 5 RCTs which began enrolling from 2010 onwards (Mr CLEAN, REVASCAT, EXTEND-IA, ESCAPE and SWIFT PRIME) compared to the older studies (MR RESCUE & SYNTHESIS Expansion and IMS3) Most importantly the newer studies include: the use of patient-imaging to select patients; higher porportion of patients treated with new generation stent-retriever technology and a heightened awareness of the importance of time as a vital factor in patient treatment success. Given these major differences in methods a separate meta-analysis that includes only the 5 newer studies is warranted. Indeed, the confirmation of large vessel occlusion prior to the use of mechanical thrombectomy in ischemic stroke patients is an essential part of current clinical practice and as such the three older studies do not reflect this. Please also refer to previous comment for page 10, line 242.	Subgroup analysis which does not include MR RESCUE, Synthesis or IMS3 has now been performed
81.	Stryker	-	-	MR CLEAN: When IAT was performed, it was with 97% of Stent Retrievers (with 66% of TREVO)	It is unclear what needs to be done with this information.
82.	Medtronic	43	1079-1085	It is clear a sensitivity analysis was performed on the 5 newer RCTs that included patient-imaging selection critria (i.e. Mr CLEAN, REVASCAT, EXTEND-IA, ESCAPE and SWIFT PRIME). It would be useful to present the forest plots and relative risks from this analysis and exclude the three old studies for the reasons mentioned above. Please refer to previous comment for page 10, line 242.	This has been done
83.	Stryker	43	1080	In these five studies the Endovascular treatment was performed in a large majority with newer devices "Stent Retrievers"	The issue of stent retrievers is now dealt with in detail elsewhere i.e. under the 'synthesis' subheading

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84.	Medtronic	43	1088	Please mention that the studies are mainly stent retrievers. Please refer to comment for page 8 line 124.	See last point
85.	Medtronic	44	1105	NIHSS Section: Should mention that the studies use mainly stent retrievers Please refer to comment for page 8 line 124.	See last point
86.	Medtronic	45	1145	Add clarification to the exact TICI grading scale used and by type of imaging used to perform assessment. • MR RESCUE – used the TICI grading scale as assessed on CTA/MRA imaging at day 7. In addition per primary publication, TICI 2a-3, as determined on postprocedural angiography, was achieved in 67% of the patients.	It has been clarified that escape and mr rescue were based on tici and the others on mtici and the description of tici scores has also been inserted Re MR Rescue….our outcome measure was TICI score at final angiography and therefore the % recorded is that at 7 days rather than the one at 24hrs.
87.	Medtronic	45	1146	In ESCAPE reperfusion was assessed using the TICI grading scale, not modified TICI scale.	This has been amended
88.	Medtronic	45	1157	Please add the following note: "Health-related quality of life (EQ-5D) in SWIFT PRIME was not reported in primary results publication as it was neither a primary nor secondary endpoint."	If we add this note, then similar notes will need to be added for the other trials which did not report on this endpoint, and for the other endpoints for which not all trials have reported. As a compromise, we have noted that "not all trials included health related quality of life (EQ-5D) as a primary or secondary endpoint"
89.	Medtronic	46	1177	"the quality of the pooled data for the outcomes under review was rated as low or moderate" . This conclusion would probably change if only the 5 relevant RCTs are considered in the meta-analysis. Please refer to previous comment for page 10, line 242.	The chapters on clinical effectiveness and safety now include a subgroup analysis based on the most recent five trials. However, it should be noted that four of the five trials stopped early, three on the basis of unplanned interim analyses. This introduces a risk of bias that cannot be ignored and is reflected in the judgement on quality of evidence.
90.	Medtronic	46	1183-1186	"Two of the studies in particular had markedly lower proportions of their intervention groups undergoing mechanical thrombectomy (IMS3, 16.1%, SYNTHESIS Expansion, 30.9%); this compared with the other six trials where the proportion of the intervention group undergoing mechanical thrombectomy	Again, we believe this point has been adequately dealt with by including a subgroup meta-analysis of the 5 latest trials

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				ranged between 77.1% and 100%." This point is very important as the meta-analysis undertaken in this HTA seeks to estimate efficacy and safety of mechanical thrombectomy vs. Standard of care in acute ischemic stroke patients, but includes 2 studies (IMS3 & SYNTHESIS expansion) in which very few patients (16% and 31%) actally received any form of mechanical thrombectomy. The authors justify including both the IMS3 and SYNTHESIS expansion studies by stating "all of the trials randomized patients on the basis that they were eligible for mechanical thrombectomy", while this might be true, the fact that the majority of patients in these 2 older studies failed to receive mechanical thrombectomy is an issue, especially with their inclusion in a formal meta-analysis. It is evident that we are not comparing similar studies in this case and we therefore request that they be removed from the main meta-analysis.	
91.	Medtronic	46	1193	The use of older devices is not recommended in the most recent clinical guidance on mechanical thrombectomy and as such does not reflect current clinical practice. Reconsider including studies which employ mostly first generation devices into a sub-analysis. For example the following studies used either intraarterial thrombolysis or older generation mechanical thrombectomy devices in their intervention arms: In the IMS3 study 266/434 or 61% of patients had intraarterial thrombolysis vs. 5/434 or 1% receiving new generation stent retrievers; In MR RESCUE, no patients received stent retrievers & 64/70 or 91% of patients in the intervention arm received first generation mechanical thrombrombectomy devices that are no longer receommended by the AHA/ASA. Finally, in the SYNTHESIS Expansion trial, the majority of patients in the intervention arm received intraarterial thrombolysis, while only 56/181 or 31% actually underwent mechanical thrombectomy. Of those patients that had a mechanical thrombectomy procedure, only 23 patients (13% - (5 Trevo and 18 Solitaire)) received treatment with a new generation stent retriever. Please change text accordingly.	Again, we believe this point has been adequately dealt with by including a subgroup meta-analysis of the 5 latest trials
92.	Stryker	46	1199	MR CLEAN: 97% of Stent Retrievers when IAT performed / ESCAPE 86% of Stent Retrievers	It is unclear what needs to be done with this information.
93.	Medtronic	46	1208-1213	It should be highlighted that confirmation of large vessel occlusion with imaging prior to the use of mechanical thrombectomy procedures is recommended in the most recent clinical guidelines. Not only did the older studies not require confirmation of vessel occlusion with imaging before trial enrolment, it is important to note that imaging techniques have evolved significantly over time. IMS3 and SYNTHESIS Expansion only required an initial non-contrast CT (NCCT) to rule out ICH. In recent trials, enrolment additionally required measurement of the extent of early ischaemic changes with multimodal CT or magnetic resonance imaging (MRI).	The issue of imaging has now been dealt with in more detail through out the document and we make it clear in our conclusion that the benefits derived form thrombectomy were in trials in which advanced imaging was employed

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				ESCAPE, EXTEND-IA, and SWIFT PRIME trials also required proof of either adequate collaterals (using CTA) or salvageable brain (using CT perfusion or CTP/MRI). Again this highlights the evolution of technology over time and that the older studies are not reflective of current clinical practice.	
94.	Medtronic	47	1224	"the last five of the eight trials... " add "that mainly evaluate stent retrievers" Please refer to comment for page 8 line 124.	This has been altered
95.	Medtronic	47	1231	Newer generation "stent retriever" devices Please refer to comment for page 8 line 124.	See above
96.	Stryker	47	1250	Replace "particular devices" by "Stents Retrievers" as stated in the new guidelines (ESO and AHA – level 1of evidence)	Altered
97.	Medtronic	47	1250	Delete "particular" and suggest edit to "...when using stent retriever devices"	See above
Safety					
98.	Medtronic	48	1255	SAFETY same comment as efficacy. Consider old studies for the meta analysis... not relevant to mix new RCTs with old Please refer to previous comment for page 10, line 242.	We believe this point has been adequately dealt with by including a subgroup metaanalysis of the 5 latest trials
99.	Medtronic	general	-	Given the large differences in the methodology and interventions used between the older studies (IMS3, SYNTHESIS EXPANSION & MR RESCUE) compared to the more recently published RCTs a formal meta-analysis that compares results only from the new studies is justified. The most notable differences when comparing old vs new RCTs are: a) the lack of advanced imaging in the old studies to detect ischemic stroke (NCCT used primarily – to rule out ICH) b) enrolment of patients into the older studies that did not have confirmation of vessel occlusions – this is not inline with current clinical practice c) use of first generation devices in the older studies – also not in-line with current clinical practice. A recent systematic review and meta-analysis by Sardar et al. 2015 also examined the clinical outcomes in RCTs comparing endovascular therapy + IvtPA with IvtPA alone. The investigators also noted the differences in the older and newer RCTs and as such conducted a seperate meta-analysis of the newer studies only. This analysis included the 5 RCTs - MR CLEAN, EXTEND IA, ESCAPE, SWIFT PRIME, and REVASCAT. The investigators noted that these 5 trials selected patients meticulously with the use of computed tomographic angiography (CTA) or perfusion imaging and used modern stent-retriever procedures for reperfusion. **For convenience, here below some key chapter of the Sardar et al. paper:** "**Analysis limited to newer trials** Five trials including 1287 patients were published between the end of 2014 and	We believe this point has been adequately dealt with by including a subgroup metaanalysis of the 5 latest trials

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				early 2015 (MR CLEAN, EXTEND IA, ESCAPE, SWIFT PRIME, and REVASCAT).8 – 12 These trials selected patients meticulously with the use of computed tomographic angiography (CTA) or perfusion imaging and used modern stent-retriever procedures for reperfusion. Notably, there was a marked improvement in functional independence (90-day mRS of 0–2) with EVT (46.1 vs. 26.2% in the control group; OR 2.42, 95% CI 1.91–3.08; P , 0.001, NNT ¼ 5.0) (Figure 2A). There was no significant heterogeneity between the five studies (I2 statistic ¼ 0%) noted with analysis of this outcome. We observed a non-significant lower mortality with EVT when limiting the analysis to the newer trials (14.5 vs. 17.3% in the control group; OR 0.80, 95% CI 0.54–1.18); the rate of sICH was also not increased with EVT (4.1 vs. 4.3% in the control group; OR 1.08, 95% CI 0.62–1.88) (Figure 2B and C)." "**Discussion** Our meta-analysis of meticulously performed RCTs that compared EVT with or without IV tPA with conventional IV thrombolytics alone in patients with anterior-circulation, large-artery acute ischaemic stroke showed significant benefit of 90-day functional independence with EVT. The risk of all-cause mortality was also lower with EVT (statistically non-significant), without any increase in rates of intracerebral haemorrhage. Initial large RCTs evaluating EVT showed negative or inconclusive results.5 – 7 These trials were criticized for their use of older recanalization devices that were associated with lower recanalization rates (in contrast to newer devices such as retrievable stents), for the long interval between the onset of stroke and timing of intervention, and a disappointingly low recruitment rate, which suggested that many eligible patients were not included in the trials. Subgroup analyses suggested that there were benefits for patients treated in shorter time windows.23,24 Moreover, two of these trials5,6 did not require evidence of an occluded vessel prior to randomization, thereby making EVT futile from the very beginning. Key lessons learnt from these previous trials were that studies involving EVT ought to enroll patients with severe strokes, have confirmation of proximal vessel occlusion, have rapid and effective imaging methods, be able to initiate treatment as early as possible, and incorporate the usage of modern thrombectomy devices.25 The five new trials8 – 12 published thereafter (2014–15) followed modified strategies. Despite inclusion and procedural strategies varying across the trials, our pooled sensitivity analysis with only these five trials showed consistent and profound benefits in the functional outcomes of patients with EVT (NNT was only 5.0 vs. 9.3 with all eight trials), without an increased risk of sICH."	
Appendix					
100.	Stryker	64	1756	Sort the devices by alphabetic order	This has been done.
101.	Stryker	74	1774	Indicate the Level of Evidence	This level of detail is not required and

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					can be obtained from the source material if necessary.
102.	Medtronic	79	1784	For MR CLEAN – Comparator: Per publication, usual care alone (including IV alteplase). Delete Urokinase.	Done
103.	Medtronic	79	1784	For MR CLEAN – Location of stroke: Delete "on CTA, MRA or DSA" for consistency as imaging is not noted for the other trials listed.	Done
104.	Neuravi	94	1848	Intervention: The majority of the evidence presented here relates to three device categories, stent-retrievers, aspiration catheters, and retrievers. The data demonstrating positive clinical outcomes is based on the stent-retriever category. Applicability of the results to devices in other categories of thrombectomy is uncertain.	This has now been reiterated within the narrative of the preceding chapters
105.	Neuravi	general		Powers WJ, Derdeyn CP, Biller J , et al. 2015 American Heart Association/American Stroke Association Focused Update of the 2013 Guidelines for the Early Management of Patients with Acute Ischemic Stroke Regarding Endovascular Treatment, Stroke 2015: 46:3020-3035. • 5 RCT's of endovascular treatment of AIS with primarily stent-retrievers were carried out from 2010 – 2015 demonstrated improved results for both recanalization rates and outcome o (Earlier 3 studies with primarily IA Lytics and first-generation thrombectomy devices did not) • TICI 2b-3 recanalization was achieved in 59% to 88% of the endovascularly treated patients in the 5 stent-retriever trials o (whereas in the previous 3 studies the rate had been 25-41%) Nearly every patient in the 5 stent-retriever studies received IV t-PA	See previous point. Subgroup analysis of the latter five trials has now been performed
106.	Medtronic	General		Ensure cross references to Tables or Figures are correct.	Will also be checked during medical editing.
107.	Medtronic	General		In order to help to better understand the different techniques, here below is a figure from the following paper: Laurent P. et al. Techniques for Endovascular Treatment of Acute Ischemic Stroke: From Intra-Arterial Fibrinolytics to Stent-Retrievers. - Stroke - February 5, 2015. doi:10.1161/STROKEAHA.114.007935 The authors describe the different endovascular techniques in treating acute ischemic stroke. Topics include: Intraarterial thrombolytics First generation clot retrievers: Merci retriever and Penumbra aspiration system Second generation of mechanical thrombectomy devices/techniques: Stent retrievers (e.g. Solitaire revascularization device, Trevo), ADAPT	We appreciate that this graphic has been brought to our attention.

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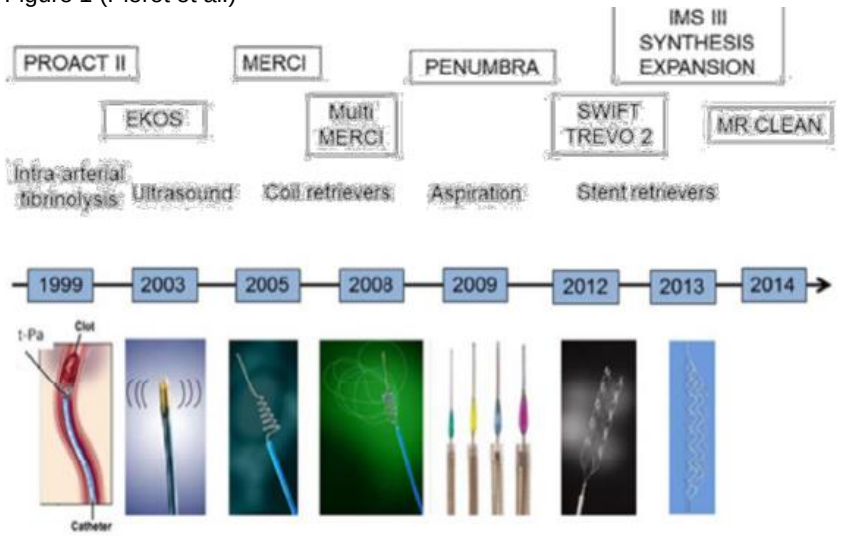
				Figure 1 (Pierot et al.)  	

External experts

Name	Affiliation
Martin Scott Dennis	Prof. of stroke medicine, University of Edinburgh, UK
Colin Cantwell	FFR, FRCR, FSIR, EBIR/Interventional Radiologist at St. Vincents University Hospital, Ireland; member of the British Society of Interventional Radiology

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General remarks/Other					
1.	Martin Scott Dennis	3	28	I presume my declared conflicts of interest will be inserted here	Will be included for the next draft.
2.	Colin Cantwell	-	-	It would be appropriate to have at some stage a neuro interventionalist or neurologist review.	Thank you for the suggestion.
Summary					
3.	Martin Scott Dennis	8	138-140	Odd term –neurovascular occlusion. I would have though one might better refer to "ischaemic stroke due to occlusion of a proximal cerebral artery.	Agree. This has been changed.
4.	Martin Scott Dennis	9	168-169	It is unclear why no quality assessment was carried out because the studies were of devices – this needs clarification	Quality assessment has now been carried out to determine the risk of bias in these studies. Detailed results are provided in Appendix 1.
5.	Martin Scott Dennis	9	177	I suggest "including tPA WHERE APPROPRIATE, since the current wording is slightly ambiguous.	Agree. This has been changed.
6.	Martin Scott Dennis	9	199	I find it odd to start this section with the statement that "Data on mortality from ischaemic stroke was not reported by the studies **(D0001)**.". Such data would likely be meaningless because of the impossibility of teasing out the exact root cause of death in patient who are having complications of the stroke and its treatments. In short term follow up all causes death is far more meaningful.	Agree. This line has been removed.
7.	Martin Scott Dennis	9	206	I think it would be useful to insert "good outcome" or independent survival before mRs0-2 since readers may not be familiar with the scale	Agree. We have inserted (indicative of independent daily function) in brackets.
8.	Martin Scott Dennis	11	281	This makes it sound as if SITS is a randomised trial – it is a registry of procedures/patients and should be distinguished from the randomised trials because only the letter will add to the evidence on effectiveness	This has been done.

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9.	Martin Scott Dennis	12	320	What is the difference between trials which have commenced recruitment and others which are ongoing?	Agree, changed to "A number of other trials are ongoing…"
10.	Martin Scott Dennis	17	375	Strictly a recurrent stroke could include a haemorrhage (i.e. SICH) – I would therefore suggest referring to "recurrent ischaemic stroke" whereever this outcome is referred to	Done
Description and technical characteristics of the technology					
11.	Martin Scott Dennis	18	392	This sentence is unfinished	Changed like this: "Recent clinical evidence (MRCLEAN, ESCAPE, EXTEND IA, SWIFT PRIME and REVASCAT) suggests that, it can be administered within 6 to12 hours after onset of stroke symptom."
12.	Martin Scott Dennis	21	516-17	I don't find the description of SITS Open clear – how does this non randomised study allow for more patients to be enrolled in trials without ethical concerns. Clearly since it is non randomised the level of evidence it can provide is inferior to RCTs.	This sentence we cited from SITS Open is to illustrate more and more centers join to stroke registry, in addition to highlight the importance of the registry.
13.	Martin Scott Dennis	24	552	Perhaps it should be emphasised that such registries need to ensure complete reporting of all cases, and that they have mechanisms in place to prevent selective reporting of successful cases	Added "for selecting participants and reporting data".
Health problem and current use of the technology					
14.	Martin Scott Dennis	25	575-576	There is increasing evidence that some lacunar infarcts are not due to occlusion of small vessels, but rather a breakdown of the blood brain barrier. I would leave this section on lacunar stroke out since it is of very limited relevance to this report and is contentious	To be rigorous, the sentence "this latter type of stroke is also called a lacunar stroke" has been deleted.
15.	Martin Scott Dennis	25	568-569	This sentence suggests that the root cause of all ischaemic stroke is atheroma. That is misleading, and is particularly so when dealing with large vessel occlusion which as stated later are often the consequence of cardiac embolism associated with AF and other pathologies	I think for this point, we have already made it clear, there are two types of obstructions, one is cerebral thrombosis, one paragraph to illustrate cerebral embolism, and also mentioned AF.
16.	Martin Scott Dennis	26	605-609	This paragraph is a mess, mixing up impairments, disabilities and other consequences of stroke	This paragraph is to explain the physical disabilities.
17.	Martin Scott Dennis	26	610-614	No mention of depression which is probably the most common emotional problem after stroke	Added "depression" in the text.
18.	Martin Scott	27	-	The FAST test is simply a very simple screening test	Take the "occasionally" away in the text

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	Dennis			for symptoms and signs for stroke. It is inaccurate to say that strokes "occasionally cause other problems – they very often cause other symptoms such as weakness down one side, visual loss etc.	
19.	Martin Scott Dennis	28	687	This sentence does not make sense – contradictions?? contraindications	This paragraph is a summary or overview from Table 3. We added in the text, "as table 3 shows" and "described by the manufacturers are including:" to make it clear. And yes, that is "contraindications"
20.	Martin Scott Dennis	32	-	It is inaccurate to state that thrombectomy is not available at all in Scotland. A small number of procedures are done each year – mainly in Edinburgh. Perhaps 5-10/year but this is increasing on an ad hoc basis since the trials were published	We will update this information accordingly. But we did not mean that there is no thrombectomy in Scotland, but the reimbursement for thrombectomy.
21.	Martin Scott Dennis	35	780-786	This paragraph is a bit of a muddle – moving from mortality (which thrombectomy does not influence on to reperfusion rates and then onto proportion of patients who might be eligible for thrombectomy. This needs re writing with some logical order.	I think here is in a logical order, we want to say, although the amount of stroke patients is very big, but the percentage can admit to t-PA and thrombectomy is not that high.
Clinical effectiveness					
22.	Martin Scott Dennis	36	787-797	This paragraph includes some very important issues which impact on how easility and quickly the treatment could be rolled out across European countries. Not only are there too few interventional neuro radiologists but there will be a tricky balance between having enough to provide 24/7 services but also not too many to 1ensure that each individual carries out enough procedures to maintain expertise. In places with sparce populations which cannot support a team of INRs systems of rapid transfer over large distances, or perhaps in the future remote support via robotics will need to be considered to deliver thrombectomy to people living in rural and sparcely populated areas.	Thank you for the very important comments from the reviewers, we will revise the text accordingly.
23.	Martin Scott Dennis	40	977-979	I don't think this paragraph is accurate. Table 7 just describes guidelines and is not relevant. I presume this should be Table 9. However the comparator in Table 9 is not described correctly for Mr Rescue, and Mr Clean. MrCLEAN, ESCAPE, REVASCAT and Mr	Yes, it should be Table 9; this has been changed. The comparator has been corrected in the relevant trials.

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				Rescue did not require patients to be treated with iv tPA or be eligible for treatment. The other trials did	
Safety					
24.	Martin Scott Dennis	52	1387	This title and subsequent section should refer to recurrent ischaemic stroke	Done

Patient representative

Name	Organisation
Gary Randall	European Research Manager at Stroke Association & manager of activity in EU funded research at Stroke Association for Europe (SAFE), UK

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1.	-	-	It is mostly a factual account of the trials and there is little content that is subjective or purely opinion, except for issues about the quality or comparability of some of the evidence. The important caveats about applicability and generalisability of the data are given.	No changes reqd.
2.	-	-	From the patient viewpoint the issues are: 1. If I am offered treatment will it help me? The answer is clearly yes for the small target subgroup who are suitable. 2. Can I get access to the treatment? The answer is probably no at the moment.	No changes reqd.
3.	-	-	It may be beyond the scope of EUnetHTA methodology but some assessment of the feasibility of implementing a thrombectomy service in the real world is of critical importance to stroke support organisations like us. The two main factors; who will do the intervention; and how will the service be structured are very briefly mentioned and so my main general comment would be that a larger section about these factors would be useful in the report. We don't expect answers yet, it is still early days, but some explanation of the problems and possibilities would be welcome.	Unfortunately, while we agree that these are crucial questions which will need to be answered in the context of the real-world applicability of this technology, they are questions which are outside the scope of this 'rapid' HTA.