RENAL DENERVATION SYSTEMS FOR TREATMENT-RESISTANT HYPERTENSION

INPUT FROM MANUFACTURER(S), EXTERNAL REVIEWER(S), PATIENT REPRESENTATIVE(S) AND STRAND B MEMBERS ON V 1.1 OF THE PILOT RAPID ASSESSMENT

Assessment

Pilot ID: WP5-SB-12

CONTENT

STRAND B MEMBERS

Comments were received from:

Name	Agency
Hilda Emengo	Healthcare Improvement Scotland (HIS)
Teresa Gasparetto	Regione Veneto, Italy
Carmen Furno	USCS A.Gemelli University Hospital
Neill Booth	National Institute for Health and Welfare (THL)
Patricia Harrington	Health Information and Quality Authority (HIQA)

Comment #	Page	Line number	Comment received from	Comment	Authors' reply
1			THL	In the following, questions are highlighted in yellow. Suggested changes in the text are indicated with arrows (->) – with the original first and then the suggested change, followed by a question mark whenever the suggested change is tentative.	OK
2	2	20	HIS	Please include Hilda Emengo as one of the reviewers under Healthcare Improvement Scotland	Done
3	6	162	HIS	Please provide full meaning of REA – it is not mentioned in the list of abbreviations	Done
4	7	179 – 184	HIS	It will be good to include "increasing/older age" as one of the risk factors in this paragraph. Age is mentioned in a couple of paragraph below but the sentence says "according to the abovementioned risk factors, the prevalence is expected to increase in an older and more obese population". Obesity was	Done

Comment #	Page	Line number	Comment received from	Comment	Authors' reply
				mentioned previously but not age.	
5	7	219-224	USCS	The uncertainty regarding prevalence of the diseases is clear, but it is not clear, from the paragraph, if the increase of the experience with procedure will allow the definition of other relevant candidates to the intervention, for example limiting a subgroup of identified population or extending the identified population. Perhaps it could be appropriate explain the sentences if the authors had elements on topic.	Acknowledged, but this is more of a discussion point about the future perspective after having gained more experience with the procedure: if this is not discussed in any of the articles/literature consulted, would guess this would be more up to experts to comment on – but these have not mentioned this issue, so we did not make any changes
6	8	250	THL	guidelines -> searches of clinical practice guidelines?	Deleted "i.e. guidelines"
7	9	289	THL	overlap in patients with another study within the same analysis -> overlap of patients with another study or within the same analysis?	No alterations done.
8	9	316	Regione Veneto	assessied	Corrected
9	9	323	THL	remove „or" ?	Done
10	10	364	THL	addressed -> reported?	Done
11	11	421	THL	delivery of radiofrequency along -> delivery of radio-frequency energy along ?	Changed according to other comments to "delivery of radiofrequency or ultrasound energy"
12	11	424	THL	does „catheter" refer to the whole invasive device, or just the guiding tube along which the radio-frequency ablation device (head/tip) moves?	Text updated
13	12	434 -435	HIS	I note some changes have been made to this statement, in light of previous comment. However, it is still incorrect to state that the NHS has set a fixed budget to pay for a fixed number of procedures and this can be interpreted wrongly as the entire NHS. I would suggest rewording it to say that "NHS England	The paragraph on reimbursement will be changed on the basis of information of Eucomed and Medtronic.

Comment #	Page	Line number	Comment received from	Comment	Authors' reply
				has set a fixed budget to pay for a fixed number of procedures..", so people are clear about the part of the UK this statements applies to – ie England.	
14	12	436	THL	ay if the hospital sends data required for a health technology assessment -> pay if the hospital provides appropriate information which could be used in a health technology assessment	The paragraph on reimbursement will be changed on the basis of information of Eucomed and Medtronic.
15	12	445-6	THL	mortality. In addition none -> mortality as none	Done.
16	12	450	THL	Although two out of three studies showed -> Although two out of the three studies found showed	Done.
17	13	474	THL	what is the threshold for using the term very low, rather than just low?	Amended- Left it as low.
18	13	492 1421	HIS	I think that the first sentence of the conclusion needs to be qualified by stating that the conclusion comes from evidence that was deemed to be of moderate quality. From our experience, a lot readers go straight to the concluding statement and do not take time to read the bulk of the report and this sentence could be misleading as moderate quality evidence is associated with a degree of uncertainty.	We agree on the principle. However, we did receive other comments showing that the general interpretation/understanding of the reference to quality was not clear and that the classification needed explanation. Hence, we would like to keep the current phrasing and hope that words like "seems to decrease", uncertainty and preliminary trials will give a hint on the level of confidence to results.
19	15	NHS	HIS	Is the National Health Service not Service**s**	Done *(abbrev. Table)*
20	15	NHS	THL	Should this refer to National Health Service (UK), NHS England/NHS Commisioning Board, **or** NICE's jurisdiction (NHS England and Wales)?	The paragraph on reimbursement will be changed on the basis of information of Eucomed and Medtronic.
21	17	514	THL	Although general associations in populations between decreased blood pressure and decreased morbidity and mortality are well known, it would be good to have a reference to **evidence** which shows that	No changes made: There is no evidence available that shows decrease in mortality in individuals with treatment-res. hypertension, but there is evidence

Comment #	Page	Line number	Comment received from	Comment	Authors' reply
				decreases in the SBP or DBP of **individuals with treatment-resistant hypertension** have the same effect.	available for blood pressure, and this is presented.
22	17	524	HIQA	It is noted that the Rheos system/barocepter stimulation was removed as a comparison in accordance with a suggestion from the public consultation. In the interest of transparency, it would be preferable to state why this recommendation was considered plausible and was thus acted upon, i.e., state the reason why it was not considered a legitimate comparator	This change in project plan is now explained in the deviations from the project plan section.
23	18	535	THL	The last questions of the table (A0020 e A0021) seem not appropriate in this section, in fact at page 23 the authors invite to cross refer to other sections, could the questions be considered directly in the appropriate section?	Thank you for a very constructive comment. There is currently ongoing a revision of the template for pilot rapid REAs by WP5.The information will be directed to that process.
24	21	683, 760	HIQA	In the interest of clarity, it would be helpful if this sentence „One should be awared about differences in blood pressure across countries" was more precise – ie specifically stating that noticeable differences in average BP levels across countries have been noted which may impact the transferability of prevalence estimates.	Now is written: One should be aware about differences in blood pressure across countries which should be a point of attention when addressing the prevalence of resistant hypertension (Mancia 2013).
25	21	684	HIS	No literature has been found on the specific costs of resistant hypertension.....in terms of what? The sentence will be more useful if it was specific	Changes have been made
26	21	686	Regione Veneto	Might be useful do add information on ambulatory and in office pressure measurement in A0024?	Changes have been made
27	22	699	Regione Veneto	May reference to ESC Guidelines (Mancia 2013) be appropriate to answer at A0001?	Mancia 2013 is an important reference and is mentioned earlier. The references mentioned in A0001 relates more specifically to renal

Comment #	Page	Line number	Comment received from	Comment	Authors' reply
					denervation.
28	22	739	THL	accident -> event?	Yes event may be a better expression, but accident is the expression used in the reference
29	23	746-7	THL	Data potentially indicate many candidates for renal denervation - > Data potentially indicate there will be many candidates for renal denervation, given the "Indications and contra-indications for renal denervation (A0001)" ?	No changes done. This is based on the figures of prevalence of resistant hypertension that has been reported to range from 5-30 % of the overall hypertensive population, and the prevalence of hypertension (all cases) which is estimated to be approximately 30-45 %.
30	23	750-751	USCS	See the above comment	See reply above
31	26	869	HIQA	See comment pg17 line 524. The assessment identifies that carotid barorecepetor stimulation is another alternative to drug treatment. and is indicated for patients with resistant hypertension. In light of this, it is particularly important to be transparent as to why this was excluded as a comparator.	OK. See answer to comment #22
32	27	896-930	USCS	The consideration of the phase of development and implementation (B0003) maybe are disconnected from the issues related description and technical characteristic of the procedure.	That is a question relating to the Core model more than to this assessment. There is currently ongoing a revision of the template for pilot rapid REAs by WP5.The information will be directed to that process.
33	28	932-962	USCS	The entire paragraph refers to organizational issues that are disconnected from the issues related description and technical characteristic of the procedure, as in the above comment. Probably it could be useful separate the sentences and define another section. In the current use as paragraph?	See answer to comment 32.
34	29	972-4	THL	It is an add-on therapy, thus leading to additional health care resources in terms of the cost of the system, the training of specialist staff, and the use of	The current text and reference to CADTH will be maintained as we feel it is clear as it is, and we refer to an existing text in the assessment of

Comment #	Page	Line number	Comment received from	Comment	Authors' reply
				hospital radiology services during the procedure (CADTH 2013). -> It is an add-on therapy, thus creating a need for additional health care resources due to the financial costs of the system ()due to the radio-frequency generator or the single-use catheter devices), the training of specialist staff, and the use of hospital radiology services during the procedure (CADTH 2013).	CADTH.
35	31	1016	HIS	C007 should be **C0007**	Corrected
36	34	Table SAF1	HIQA	Final row –all data are reported as column totals, not means as identified by the row label.	This column was deleted because it was felt to be misleading as studies do not systematically report all adverse events (see risk bias table). All references to overall frequencies have been omitted.
37	35	Table SAF2	HIQA	Final row – with the exception of the number of follow-up months, all data are reported as column totals, not means as identified by the row label.	This column was deleted because it was felt to be misleading as studies do not systematically report all adverse events (see risk bias table). All references to overall frequencies have been omitted.
38	36	1136	THL	seems to be -> is usually ?	Corrected
39	36	1140	THL	The reporting of adverse events -> The reported frequency of adverse events ?	Corrected
40	36	1170	HIS	What does "..... these were not **flow limiting**" mean? Are you referring to blood flow or something else? This is not clear	Corrected. It now reads not limited to blood flow.
41	37	1191	THL	Since these systems can present differences with regards to the ablation mechanisms -> Since these systems do not use exactly the same ablation mechanisms	Corrected

Comment #	Page	Line number	Comment received from	Comment	Authors' reply
42	37	1208	THL	occurrence of adverse effects. -> occurrence of possible, long-term adverse effects. ?	Corrected
43	38	1230	HIS	I do not think the questions (D0017 and D0018) under the "patient satisfaction" topic fits nicely in the clinical effectiveness section. One question in particular is focused on assessing if patients are willing to undergo RDN and does not relate, in any way, to how clinically effective the procedure is. Although these questions are very relevant to the review, it seems out of place in the clinical effectiveness section.	Thank you for a constructive comment. We will look into how all questions should be best allocated to domain in coming pilots. See comment 23
44	38	1230	HIS	I think question D0023 is too wide and vague. It will be more beneficial if it was as specific as questions D0001, 2, 6 or 11. It can be reworded to ask "What is the impact/effect of RDN on the number of antihypertensive medication a patient is taking"?	We see your point, but the questions is re-phrased based on the generic question in the HTA core model. D0023"How does the technology modify the need for other technologies and use of resources?"
45	41	1304	HIS	See two comments above relating to questions D0017, 0018 and 0023.	See comment 44 and 43
46	43	General	HIS	The findings for question D0018 has not been reported anywhere in the body of the report. It is only mentioned in Appendix 2 in pages 138 and 139 (line 3975 - "None of the identified studies in this rapid review have addressed patients' willingness to undergo renal denervation"). I think this is an important finding and should be a part of the report (not Appendix)	It is part of Table 5 under results No SR or RCT or non-RCT found. It is now added in the section Quality of life (QoL) and patient satisfaction, as we have classified this in table 5 to in the theme of patient satisfaction There was no documentation available on issues related to QoL or patient satisfaction. (D0012, D0013, D0017, D0018) No changes done in summary section.

Comment #	Page	Line number	Comment received from	Comment	Authors' reply
47	54	1738	Regione Veneto	Flow chart: incorrect: 4807-4776≠33	Amended
48	p. 60		THL	The declaration of funding source and competing interests seems to have been well researched, with judicious use of the term "Not declared". Might "Absence of conflict of interest" be usefully be softened to "Probable absence of conflict of interest", though?	There are now evidence tables and risk of bias tables for safety, which should "solve" this
49	84	1979	Regione Veneto	Verify character of "resistant"	No alterations done. We feel the sentence is clear.
50	100	2545	Regione Veneto	Eliminate space between alter and natives "alter natives?"	Done
51	General		HIS	There are a lot of abbreviations in the text that are not part of the list of abbreviations (eg SAG, CT, REA.....)	Added: CT, SAG, REA
52	General		HIS	Well done is preparing this rapid review and making all the necessary changes in a very short time.	Thank you

MANUFACTURES

Comments were received from:

Organisation
Medtronic
St. Jude Medical
EUCOMED Hypertension Working Group
Covidien
Johnson & Johnson (J&J) Medical BV/Biosense Webster
Boston Scientific
ReCor Medical

Comment #	Page	Line no.	Comment received from	Comment	Authors' reply
1	1	8	EUCOMED	Suggestion to delete the word: "other"	No alteration done. This is the title of WP5 Strand B.
2	1	8	J&J/Biosense Webster	Suggestion to delete the word "other"	As comment 1
3	2	20	EUCOMED	This document would strongly benefit from the inclusion of expert advisors in hypertension and Renal Denervation, the author list of the ESC expert consensus on renal denervation is a good place to start.	We agree that input from clinical experts is important. External clinical experts comment on the draft assessment in parallel with the manufacturer (second draft= version 1.1). For future pilots, we will consider the suggestion of involving more clinical experts in the pilot

Comment #	Page	Line no.	Comment received from	Comment	Authors' reply
					process.
4	2 Table	20	Boston Scientific	External Reviewers We suggest that it is important to include in the revision of the document expert physicians, clinical users. And also the patient associations are important stakeholder.	Clinical experts and patient representatives comments are sought and included. See comment 3.
5	3	72	EUCOMED	Lisa Da Deppo part of the SAG	Comments from Lisa Da Deppo were received in her capacity as manufacturer. No changes made.
6	6	162	EUCOMED	Comparator to the interventional therapy should be clearly defined. "Standard of care" is not specific. The comparator is currently pharmacological treatment only. Baro-receptor stimulation could perhaps be considered but there are currently no direct comparisons published or planned (that we are aware of). Specify what is the device-based therapy of hypertension. Renal nerve ablation/denervation system are device-based therapy of hypertension.	Based on other comments the new text is: Standard of care (which includes here: *no treatment, additional* pharmacological treatment, device-based therapy of hypertension and sham treatment). *It should be noted that all patients continue their treatment of at least three hypertensive drugs. Additional intervention or comparator is as add-on therapy.*
7	6	162	Medtronic	The intervention involves destruction of efferent sympathetic nerves and afferent nerves within the wall of the renal arteries to reduce sympathetic nerve traffic, thereby causing a reduction in blood pressure.	Done
8	6	162	EUCOMED	Intervention Suggest to write:	Done

Comment #	Page	Line no.	Comment received from	Comment	Authors' reply
				Renal Nerve ablation and denervation Systems	
9	6	162	EUCOMED	"Kidney catheter ablation" is not a MeSH term. Suggestions are: "Catheter Ablation", "Hypertension", "Renal Artery", "Kidney"	Done (now as in search strategy)
10	7	171	EUCOMED	Mention what is meant by "traditional / conventional" treatment here. Meaning pharmacological. Authors should consider listing the pharmacological therapies currently available. This should be referenced and a good reference would be the ESC guidelines for the management of arterial hypertension: Mancia, G. *et al.* 2013 ESH/ESC Guidelines for the management of arterial hypertension The Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Eur Heart J* **34,** 2159–2219 (2013).	Addition is made
11	7	174	EUCOMED	Here the definition of resistant hypertension should be introduced and described. Authors can describe one definition that they intend to use throughout (and reference it) but also acknowledge that there are alternative definitions (and provide references).	Addition have been made
12	7	192	EUCOMED	Exact prevalance is often difficult to define but there are certainly publications availble which provide ranges and enough publications to make a good assumption (I would suggest around 12% of patients with existing hypertension as a conservative estimate) Kumbhani, D. J. *et al.* Resistant hypertension: a frequent and ominous finding among hypertensive patients with atherothrombosis. *Eur Heart J* **34,** 1204–1214 (2013). Roberie, D. R. & Elliott, W. J. What is the prevalence of resistant hypertension in the United States?: *Current Opinion in Cardiology* **27,** 386–391 (2012). Kandzari, D. E. *et al.* Catheter-Based Renal Denervation for Resistant Hypertension: Rationale and Design of the SYMPLICITY HTN-3 Trial.	Calhoun 2008, Persell 2011 describes that the exact prevalence of resistant hypertension is unknown. It is in the literature mentioned that prevalence of resistant hypertension has been reported to range from 5–30 % of the overall hypertensive population. These figures show that the prevalence is significant

Comment #	Page	Line no.	Comment received from	Comment	Authors' reply
				Clinical Cardiology **35,** 528–535 (2012). Persell, S. D. Prevalence of Resistant Hypertension in the United States, 2003–2008. *Hypertension* **57,** 1076–1080 (2011). Sierra, A. de la *et al.* Clinical Features of 8295 Patients With Resistant Hypertension Classified on the Basis of Ambulatory Blood Pressure Monitoring. *Hypertension* **57,** 898–902 (2011). Sarafidis, P. A. & Bakris, G. L. Resistant Hypertension: An Overview of Evaluation and Treatment. *Journal of the American College of Cardiology* **52,** 1749–1757 (2008). Pimenta, E. & Calhoun, D. A. Resistant Hypertension: Incidence, Prevalence, and Prognosis. *Circulation* **125,** 1594–1596 (2012). Daugherty, S. L. *et al.* Incidence and Prognosis of Resistant Hypertension in Hypertensive Patients. *Circulation* **125,** 1635–1642 (2012).	
13	7	210	EUCOMED	Please reference from which sources the set of criteria for defining the eligibility of the patients to receive Renal Denervation were taken from.	It is mentioned in section 2.2 under "Indications and contra-indications for renal denervation" - Mahfoud 2013
14	7	211	ReCor Medical	For consistency with prior statements, change to OSBP>140mm Hg or >130mm Hg if diabetic)/ General comment – the recommended baseline BP for RDN is inconsistent. Both OSBP >160 and OSBP >140 are provided as recommended baseline values.	140 relates to diagnostic criteria and 160 to the criteria for operation. This might change coming expert consensus documents. For now I we refer only to the expert consensus document from 2013
15	7	214	EUCOMED	This paragraph should describe the currently accepted indications for renal denervation as stated in the ESC expert consensus. Doing so would greatly increase clarity. The ESC indications are widely accepted by renal denervation practiotioners.	Addition is made

Comment #	Page	Line no.	Comment received from	Comment	Authors' reply
				Mahfoud, F. *et al.* Expert consensus document from the European Society of Cardiology on catheter-based renal denervation. *Eur Heart J* **34,** 2149–2157 (2013).	
16	7	217	Medtronic	Clinical studies have allowed RDN with accessory renal arteries as long as the main artery supplies >70% of total renal blood flow.	This might change coming expert consensus documents. For now we refer only to the expert consensus document from 2013
17	7	217	ReCor Medical	Polar or accessory arteries should be eligible if ≥4mm diameter	See comment 16
18	7	218	ReCor Medical	Change to clinically significant renal artery stenosis Prior revascularization should not be an exclusion	See comment 16
19	7	218	EUCOMED	Renal Denervation can address accessory arteries (Ref: Bertoldi L. - Blood Press. 2013)	See comment 16
20	7	219	EUCOMED	See previous comment RE: Prevalence	See comment 12
21	7	222	EUCOMED	What data "potentially indicating many candidates" is being referred to here? As mentioned regarding prevalence of resistant hypertension, data certainly does exist which would allow the authors to make assumptions regarding the potential population which could benefit from this therapy. The authors should research this paragraph more thoroughly and try to provide more detail here, this information is important in an HTA and is one of the points that readers of this document will be looking for. Any assumptions made here must be backed with references.	This is based on the figures that prevalence of resistant hypertension has been reported to range from 5–30 % of the overall hypertensive population, and that prevalence of hypertension (all cases) is estimated to be approximately 30–45 %, which makes the reader aware of the significant magnitude of the disease.
22	8	227	ReCor Medical	Delete "low-level"	Text will be left unchanged
23	8	229	ReCor Medical	Add „pressure" after „blood"...	The word 'flow' was missing and has been added.

Comment #	Page	Line no.	Comment received from	Comment	Authors' reply
24	8	231	ReCor Medical	Add femoral or „radial" artery	Text has been left unchanged
25	8	237	ReCor Medical	Re-Write this paragraph so it's clearer. State „of all the renal denervation systems, there are 5 CE marked systems that use RF and one CE Marked system that uses ultrasound: Paradise® system	Text has been changed.
26	8	238	Boston Scientific	Please replace V2 with Vessix TM V2. V2 is not correct	Changed.
27	8	247 and 254	EUCOMED	Specifically this should be "The HTA core model for rapid relative effectiveness assessment *for pharmaceuticals*" As previously mentioned by the Eucomed HTA Working Group, medical devices and related interventions are different from drugs and therefore assessment should be adapted for devices.	The comments regarding different adaption for pharmaceuticals and medical devices will be included in future discussion and/or revision of the template.
28	8	262	Boston Scientific	As this document was developed using only published literature, please specify "*literature data published in peer review journal were extracted….*"	No alteration done. We did use only published material (public available), but the suggested formulation may not be correct for HTA reports. They use peer-review or other quality procedures, but may be published in other formats than journals.
29	8	268	Boston Scientific	As above, please specify "*only from literature published in peer review journals"*	See comment 28
30	9	279	EUCOMED	State the version of RevMan software used and that RevMan is software provided by the Cochrane information management system intended for researchers developing Cochrane reviews.	Added 5.2 in summary and in results: version 5.2, available to download from http://ims.cochrane.org/revman.
31	9	283	Covidien	The outcomes of the RAPID study and part of RHAS study are missing. The outcomes were communicated on August 5 to EUnetHTA as	The indicated studies does not include a control group, hence it is outside the

Comment #	Page	Line no.	Comment received from	Comment	Authors' reply
		309		"publically available" for consideration by the producers of the present HTA report and therefore Covidien agreed to have those data communicated in the HTA report. This is aligned with the "EUnetHTA Joint Action WP4 – Policy for the HTA Core Model ® and core HTA information FINAL VERSION – 12 Dec 2012" Also since August, the six month follow-up outcomes of RAPID study were communicated at the International Congress Transcatheter Cardiovascular Therapeutics 2013 (TCT). Could you please include those clinical outcomes in this summary section according to the following information presented in the comments below for the clinical effectiveness and safety sections (in pages 30 to 43 of the report). In addition, for further information, please find attached the presentation of the RAPID study at the congress by Dr S. Verheye.	inclusion criteria/scope for evaluation of clinical effectiveness in this rapid assessment. The study protocol for the safety domain only contemplates the inclusion of information retrieved from the bibliographic literature search. Congress abstracts or unpublished data are not considered in the review. For this reason, these studies cannot be incorporated.
32	9	284	EUCOMED	Besides the comments below there are some comments applicable to the whole "Available Evidence" section. All studies in this section must be properly referenced. This HTA should focus on the therapy, not the trade names. It is misleading to the reader when so many unfamiliar model names of catheters are mentioned. For instance both the MarinR and the Thermocool catheters are designed for cardiac ablation but it is only mentioned that MarinR is a cardiac ablation catheter. Outcomes of the therapy are similar regardless of the catheter employed and it will be easier for readers to follow if they are presented with the evidence as it pertains to the therapy of renal denervation as opposed to the different tools used in delivering that therapy.	The referenced page is part of the summary. Studies are referenced in later chapters. However, how and where we use referencing will be discussed upon revision of the template (see comment 1). We feel that it is appropriate to show the actual data for each of the devices. But as commented we also include an overall analysis where available. We do not think it is confusing for the reader to have all type names. If in one specific European country one type is not available, the reader might still recognize the other types. And the studies are carried out with different

Comment #	Page	Line no.	Comment received from	Comment	Authors' reply
					types, which might have different catheter sizes, etc., so information would get lost for the reader if they were not mentioned.
33	9	295	Medtronic	Both arms in randomized trials involved maximally tolerated doses of at least 3 anti-hypertensive drugs, not „no therapy"	Clarified in scope. See comment 6 Note that is also apparent from the sentence following: "all included patients with resistant hypertension, and renal denervation were compared to no treatment or a sham procedure. Moreover, all patients continued with their usual pharmaceutical treatment for hypertension)
34	9	304 330	EUCOMED	The ThermoCool irrigated tip catheter is a catheter designed for cardiac ablation. It is mentioned that the MarinR catheter is designed for cardiac ablation but not the ThermoCool.	Now indicated also for Thermocool
35	9	306-311	Medtronic	This entire paragraph is written in an unclear manner and should be more clearly written to indicate which products were used in the randomized studies, which in the non-randomized studies, and which in the registries (case series).	See comment 32 Done- The paragraph has been changed to incorporate the suggestion.
36	9	313	St Jude Medical	St Jude Medical has publically committed to conducting the EnligHTNment clinical investigation. The EnligHTNment investigation is a randomised controlled trial designed to evaluate the effect of renal denervation on cardiovascular mortality and morbidity. http://investors.sjm.com/phoenix.zhtml?c=73836&p=irol-newsArticle&ID=1822742	Added under upcoming evidence in summary: Feedback from manufactuers include information that the The EnligHTNment study will evaluate the EnligHTN System and its ability to reduce the risk of major cardiovascular events such as heart attack, stroke, heart failure and cardiovascular death. They also state

Comment #	Page	Line no.	Comment received from	Comment	Authors' reply
					that mortality data is routinely collected during clinical trial.
37	9	313	EUCOMED	There are more than 26 studies shown on the ICTRP portal as "Recruiting" Indeed none list mortality or CV mortality as a Primary endpoint. It is important to note that all studies collect and publish mortality and morbidity data and although there are no studies conducted to date with mortality and morbidity reduction as a fully powered primary endpoint that evidence exists to show that the therapy certainly does not increase mortality and morbidity.	See comment 36
38	9	318-320	Medtronic	Medtronic has completed enrollment in two randomized trials (Symplicity HTN-2 and HTN-3 – HTN-3 will be reported in early 2014) and has started enrollment in a third randomized trial (Symplicity HTN-4). This information is not portrayed correctly in thsi section.	Added under upcoming evidence in summary: indicates that these companies plan their first, additional or reporting from randomized controlled trial in the next year or two
39	9	318	EUCOMED	All the on-going and planned studies investigate mortality. Mortality and cardiovascular mortality are always captured in the studies in the Adverse Events session.	See comment 36
40	10	325	EUCOMED	The diffuse visceral abdominal pain referred to here is experienced during the procedure. This should be noted as currently the sentence suggests that the pain may persist after the procedure requiring long term management.	Done.
41	10	334	Medtronic	Not sure what „poas" is	Corrected- It should read "psoas".
42	10	339	EUCOMED	It is not necessary to highlight that the two Symplicity trials are included in this group of seven. If those two trials are reffered to by name, all seven trials must be referred to by name. There is no benefit	The reason for highlighting the simplicity trial is that authors refer to themselves as the "Symplicity HTN-2

Comment #	Page	Line no.	Comment received from	Comment	Authors' reply
				to the reader by highlighting the Symplicity trials here.	investigators" and thus it must be referenced as such. However, we have introduced the name of other trials in the description section.
43	10	347-357	Medtronic	The information from the 210 Lancet Symplicity HTN-2 publication is not correct. First, the count mixes minor procedural and major adverse events so the first sentence stating adverse events should read: "Major and minor adverse events included 21/52 (40%) in the RDN group and 6/54 (11%) in the control group." The next sentence is correct: "Serious adverse events appeared during the 6 months follow-up in 8 RDN patients (i.e. 15.4 %) and 5 control patients (i.e. 9.3 %), respectively." The next sentence needs correction: "One patient 350 from each group underwent PCI with stenting for myocardial ischemia; 1 RDN patient and 2 control patients suffered a transient ischemic attack." The next sentence is incorrect and should read: "Among the patients who underwent RDN, one experienced nausea and oedema and one experienced a hypotensive episode, and 2 required hospitalization due to hypertension (versus 2 in the control group)." The next sentence needs to be corrected to: "In the Symplicity HTN-2 trial, control patients could cross over to RDN treatment; at 6 months after cross over, 4/35 (11%) cross-over patients experienced a serious adverse event which included included two hypertensive and hypotensive episodes and one case of renal artery dissection on placement of RDN catheter. None or the original randomized RDN patients experienced any additional adverse events between 6 months and 1 year."	Partly amended - First suggestion has been incorporated because it clarifies the test. - The second sentence has not been corrected because the article only makes reference to 3 hospital admissions due to a hypertensive emergency and 2 ischemic attacks in the control group (5/54). We have been unable to find the other adverse event. - Third sentence corrected - Forth sentence changed
44	10	357-359	Medtronic	This sentence needs to be rewritten to present what is and what is not presented in the manuscript: „In the RCT with 27 patients that assessed the impact of RDN using the ThermoCool® catheter added to pulmonary vein isolation (PVI) compared to PVI alone, no acute procedural adverse events or renal artery stenosis at 6 months were reported in either group; the manuscript does not comment on other post-procedural adverse events."	Done.

Comment #	Page	Line no.	Comment received from	Comment	Authors' reply
45	10	361	EUCOMED	This section "clinical effectiveness" needs to be properly referenced. Again, focus should be on the therapy and not the individual tool. A brief description of the methods utilized to decide upon the quality of evidence should be included here. The authors often make statements such as "the evidence is very low" or "the evidence is low" without qualifying the meaning. Does this imply that the study was of poor quality, the design did not serve to evaluate that particular endpoint very well, the study was not powered to detect the particular outcome described and so on. The criteria to describe quality of evidence needs to be clear for these statements to have value to the reader.	On references: see comment 32 Text updated with explanation of GRADE categories (Summary) The resulting classification and definitions of the quality of the evidence include: high (We are very confident that the true effect lies close to that of the estimate of effect), moderate (We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different), low (Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect) and very low (We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect).
46	10	363	EUCOMED	It would be useful to the reader to know the range of follow up periods being described here.	No alteration done. Detailed in the next sections.
47	11	379	EUCOMED	Again, the Navistar ThermoCool is an irrigated catheter designed for cardiac ablation and is not a "system" as described here. The description of the device as a system is misleading and could cause the reader to infer that it is designed specifically for performing renal denervation procedures. However, the earlier point that the review should avoid the use of brand names and focus on the therapy is relevant here and would solve this issue.	Removed the word system We will keep brand names. See comment 32

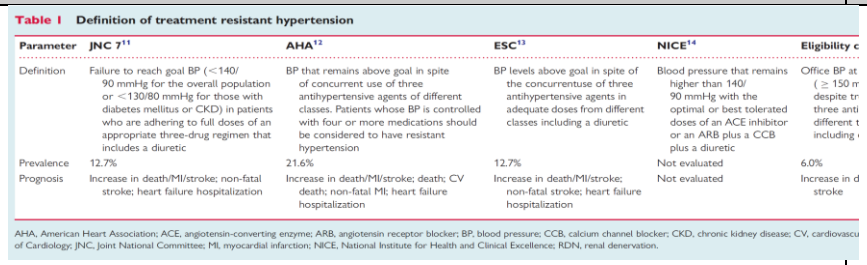
Comment #	Page	Line no.	Comment received from	Comment	Authors' reply
48	11	382	EUCOMED	Please specify what is meant for evidence very low. Clarify how it has been evaluated	See comment 45 Details on evaluation in result chapter and appendix
49	11	393	EUCOMED	Please specify what is meant for evidence very low. Clarify how it has been evaluated	As comment 48
50	11	401	EUCOMED	Please specify what is meant for evidence very low. Clarify how it has been evaluated	As comment 48
51	11	411	EUCOMED	Please specify what is meant for evidence very low. Clarify how it has been evaluated	As comment 48
52	11	417	EUCOMED	The authors should explain what is meant by "our" inclusion criteria, again it is recommended to use the ESC expert consensus criteria for patient selection and to properly reference.	No alteration done. Refers to the inclusion criteria/scope in this rapid assessment
53	11	418-419	EUCOMED	Although there is a possibility that physicians may use the technique outside of recommended indications and guidelines it is not clear how that speculative usage is relevant to the HTA. The fact is that the population in which the technique is expected to be most beneficial is already well described and widely accepted. Specify what is the level of "*higher blood pressure*". The number or the range is needed.	No alteration done. Refers to that our scope was BP >140, but some of the studies had higher inclusion criteria.
54	11	421	ReCor Medical	Add „or ultrasound energy"	Done
55	11	429-431	Medtronic	This is not correct. A quality of life manuscript is available: Stephanie K. Tanamas, Jonathan Shaw, Henry Krum, John B. Dixon, David A. Barton and Gavin W. Lambert, Dagmara Hering, Murray D. Esler, Petra Marusic, Elisabeth A. Lambert, Markus P. Schlaich. Treatment-Resistant Hypertension Health-Related Quality of Life After Renal Denervation in Patients With Treatment-Resistant Hypertension. Hypertension. 2012; 60: 1479-1484.	This study examines HQoL before and 3 mo after RDN. It does not include a comparison for the post-intervention measurement. It only includes baseline matched comparison to data from the population based Australian Diabetes, Obesity, and

Comment #	Page	Line no.	Comment received from	Comment	Authors' reply
					Lifestyle database. New: At this stage, no **controlled** studies
56	11	430	EUCOMED	Patient satisfaction for medical device therapy is difficult to assess. Certainly more work needs to be done regarding the impact on health and disease related quality of life measures.	Agreed. No alteration done.
57	11	431	EUCOMED	The clinical benefit is known as there is a consistent and statistically significant reduction in blood pressure. Suggested wording here is "At this point in time there is promising evidence that renal denervation reduces blood pressure and based on previous research relating to blood pressure reduction via pharmacologic therapies it is reasonable to assume that renal denervation will have similar beneficial outcomes in this specific and difficult to treat population of hypertensive patients providing long term studies demonstrate that the blood pressure reduction is sustained and that there are no hitherto unseen long term complications."However, the benefit in the reduction of blood pressure by 20 mm/hg gives, on average, a decrease of the cardiovascular risk by 50%.	No alterations done. There is more to the phrase "full clinical benefit" than a statistically significant reduction in BP.
58	12	435	EUCOMED	This section is misleading. It should be clarified that renal denervation is available for use in every European country, no country has denied market access. The information provided is inaccurate, there is no formal reimbursement for the therapy in the UK, however individual hospital can decide to purchase the devices until a formal reimbursement is established, NICE will evaluate the technology prior to the therapy being available through the NHS. Why is the "reimbursement" status mentioned for three specific countries, and not for all countries covered by EUnetHTA? If the information is to be provided then it must be complete. A tabular and accurate representation for all countries would be the best way to	The paragraph on reimbursement will be changed on the basis of information of Eucomed and Medtronic.

Comment #	Page	Line no.	Comment received from	Comment	Authors' reply
				achieve this.	
59	12	440	EUCOMED	This table needs to be properly referenced and referred to in the text. The purpose of the table is not clear.	The table is now referred to in the text. References to publications/trials are not included in the summary (but will be in coming assessments in the work package).
60	12	444	EUCOMED	General comment for the discussion is that similarly to previous comments the focus should be on the therapy and note the brand names.	See comment 32
61	12	445	EUCOMED	This is misleading, it can be concluded that renal denervation does not increase mortality compared to pharmacological therapy but there is no evidence yet to show that it has a beneficial effect on mortality and morbidity although as mentioned before it is reasonable to assume that a significant and sustained blood pressure reduction will be of benefit to these patients. Although a large scale RCT is needed to definitively show this effect it should be noted that a new BP lowering drug would merely need to demonstrate its efficacy in lowering blood pressure.	No alterations done We feel that "No conclusion could be drawn from the evidence available regarding overall mortality" is representative.
62	12	449	EUCOMED	The effect on left ventricular hypertrophy, although relevant should appear later in the discussion. Currently the strongest evidence concerns blood pressure reduction and this should be presented first.	No alterations done. The order we present data is based on the scope.
63	12	454	EUCOMED	The definition of "poor quality evidence" needs to be clarified here or previously in the text.	Se comment 45
64	13	475	EUCOMED	The collection of safety data and adverse events is mandatory in all studies. Do the authors mean to say that safety outcomes were not reported in all published articles that were reviewed? This does not necessarily mean that this data was not collected merely that the authors omitted it from that article, most commonly because it was not relevant to the focus of their report although their reasons are not	The following report only makes reference to published information. Like the reviewer comments practically none of the studies have been aimed at presenting safety data. This has been highlighted in the text and bias risk

Comment #	Page	Line no.	Comment received from	Comment	Authors' reply
				always apparent.	tables introduced to clarify this point.
65	13	476	EUCOMED	Safety issues are always captured and assessed in the clinical studies in the Adverse Events session.	The majority of studies do not provide an adverse event section. Please see risk bias tables.
66	13	484	EUCOMED	Follow up time needs to be qualified the statement that it was "too short" is not meaningful to the reader.	Rephrased as inadequate.
67	13	491	EUCOMED	This conclusion focuses strongly on "Symplicity" it does not provide the reader with a clear and concise overview of the important points from the previous sections. A reworked suggestion for the conclusion is provided with these comments. Comments are included below on the original conclusion text.	No alterations done. We think that the conclusion represents the current level of evidence
68	13	493	EUCOMED	It should be noted that the blood pressure reduction is an outcome of successful destruction of the afferent and efferent sympahtic nerves in the renal artery, the specific tool used to accomplish this is less important, all available systems have demonstrated safety and similar blood pressure reduction capabilities.	No alterations done.
69	13	498	EUCOMED	The comment regarding differences regarding the ablation mechanism is subjective and unnecessary. The mechanism of ablation is the same for all systems, localized tissue heating by the application of radiofrequency energy through an electrode, catheter shapes vary, electrode shapes vary, radiofrequency generators and connectors vary but the actual mechanism which destroys the nerves is the same. Excepting of course the ultrasound system. All the devices have demonstrated good procedural and periprocedural safety and comparable levels of blood pressure reduction in similar populations.	There is both radiofrequency and ultrasound, it is what we meant by different mechanisms.
70	14	504	EUCOMED	Some abbreviations in the text are not reported in the list of abbreviations	Abbreviations updated
71	16	505	EUCOMED	It is wrong to state that there is no "gold standard" comparator it is more accurate to say that in patients with resistant hypertension there	The scope has been clarified based on

Comment #	Page	Line no.	Comment received from	Comment	Authors' reply
				is no alternative treatment available beyond pharmacological therapy.	other comments. See comment 6
72	17	527	EUCOMED	What is the objective of this rapid HTA? The objective of the HTA should trigger the different HTA aspects/domains to consider. It seems that the decision of choice of the domain and the research for each of them is random.	The project rationale is presented in the project plan. The rationale for this pilot rapid assessment is to test the capacity of national HTA bodies to collaboratively produce structured rapid core HTA information on other medical technologies, such as medical devices, surgical interventions or diagnostics. In addition, the application (translation) of those collaboratively produced HTAs in the national contexts will be tested Included domains follow the Core Model of rapid REA.
73	20	608	EUCOMED	The definition listed here is that accepted by NICE, there are at least 4 definitions plus the eligibility criteria for RDN (see table taken from Messerli, F. H. & Bangalore, S. Treatment-resistant hypertension: another Cinderella story. *Eur Heart J* **34,** 1175–1177 (2013).) Also, helpfully, here are the prevelance estimations that each of those organisations published.	Many thanks for the suggestion; however, we think the definition provided is sufficient for the purpose of this assessment.

Comment #	Page	Line no.	Comment received from	Comment	Authors' reply
				 **Table 1 Definition of treatment resistant hypertension** Parameter | JNC 7[11] | AHA[12] | ESC[13] | NICE[14] | Eligibility c Definition | Failure to reach goal BP (<140/90 mmHg for the overall population or <130/80 mmHg for those with diabetes mellitus or CKD) in patients who are adhering to full doses of an appropriate three-drug regimen that includes a diuretic | BP that remains above goal in spite of concurrent use of three antihypertensive agents of different classes. Patients whose BP is controlled with four or more medications should be considered to have resistant hypertension | BP levels above goal in spite of the concurrentuse of three antihypertensive agents in adequate doses from different classes including a diuretic | Blood pressure that remains higher than 140/90 mmHg with the optimal or best tolerated doses of an ACE inhibitor or an ARB plus a CCB plus a diuretic | Office BP at (≥ 150 m despite tr three anti different t including Prevalence | 12.7% | 21.6% | 12.7% | Not evaluated | 6.0% Prognosis | Increase in death/MI/stroke; non-fatal stroke; heart failure hospitalization | Increase in death/MI/stroke; death; CV death; non-fatal MI; heart failure hospitalization | Increase in death/MI/stroke; non-fatal stroke; heart failure hospitalization | Not evaluated | Increase in d stroke AHA, American Heart Association; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BP, blood pressure; CCB, calcium channel blocker; CKD, chronic kidney disease; CV, cardiovascu of Cardiology; JNC, Joint National Committee; MI, myocardial infarction; NICE, National Institute for Health and Clinical Excellence; RDN, renal denervation.	
74	21	491	EUCOMED	The conclusion would be better to report that Renal denervation as a therapy shows promising results in reducing BP in pharmacologically resistant hypertensive patients. There are certainly more publications from the Medtronic system currently available but the early published results from other systems are certainly comparable to those of medtronic. The opening sentence sounds promotional of Symplicity over other systems. The body of evidence from other systems may not be as large as that for symplicity but the results that have been published are certainly comparable and should not be described as "uncertain".	We do not mean to be promotional, but as commented at the current time there is more documentation available for Simplicity. And as we present data for specific devices in addition to collectively at group-level (D 0006) this will be apparent
75	21	498	EUCOMED	Trials for systems other than Medtronic's are on-going. They are not "preliminary" in all cases. Preliminary suggests that no other systems other than Medtronic's are currently available for use and that their research is pre-market, this is not the case for all manufacturers at all, many are CE marked and in general use and have published data up to 18 months albeit at conferences and not in peer reviewed journals (although there are certainly publications from some manufacturers featured later in the HTA up to 6 months post procedure.	See comment 74. And a list of current status for CE is presented in Table 1. We know trials are on-going. Controlled trials are presented later in the assessment. No alterations done
76	21	497	EUCOMED	If it needs to be mentioned that systems other than the Symplicity system may present a different risk profile then it must also be mentioned that future versions of existing technology (eg next generation Medtronic systems) will also present a different risk profile and require new research to establish safety.	Yes. It refers to that different RDN systems may have different safety profiles. This will also apply to different generations of systems, and is now added in the text.

Comment #	Page	Line no.	Comment received from	Comment	Authors' reply
77	21	658	EUCOMED	This section would be a good place to state that reduction in blood pressure reduces morbidity. For instance the Norwegian cardiovascular disease model indicates that a 20mmHg increase in systolic BP results in an increased relative risk of stroke of 1.55 Wisløff T, Selmer RM, Halvorsen S, Kristiansen IS. Norwegian Cardiovascular Disease Model (NorCAD) - a simulation model for estimating health benefits and cost consequences of cardiovascular interventions. Rapport No. 23-2008. Oslo, Norway: Norwegian Knowledge Centre for the Health Services; 2008.	It is mentioned below that: "Hypertension will if untreated increase the risk of e.g. cardiovascular disease, stroke and renal failure."
78	21	667	EUCOMED	Refer to previous comments RE: Prevalence	See comment 12
79	21	684	EUCOMED	There are at least two publications which have reported potential cost-effectiveness analysis which should be mentioned here: Dorenkamp, M. *et al.* Potential lifetime cost-effectiveness of catheter-based renal sympathetic denervation in patients with resistant hypertension. *Eur Heart J* **34,** 451–461 (2013). Geisler, B. P. *et al.* Cost-Effectiveness and Clinical Effectiveness of Catheter-Based Renal Denervation for Resistant Hypertension. *Journal of the American College of Cardiology* **60,** 1271–1277 (2012).	This section only concern the burden of treatment-resistant arterial hypertension
80	22	690	EUCOMED	The approach to diagnosing hypertension may be obvious to the authors but may not be so to the reader. What the authors have not made obvious is that they are summarising the approach to diagnosis of Hypertension as described in the 2013 ESH/ESC guidelines for the management of arterial hypertension (correctly referenced as Mancia 2013) as given in the opening paragraph of chapter 3 of that document. Perhaps it would be better to describe the approach in chapter 6.14 of that document which refers to the diagnosis of resistant hypertension:	Changes made in summary and chapter 2. To summary: In diagnosing resistant hypertension first attention should be drawn to the fact that most cases of resistant hypertension originates in multifactorial factors and rarely in a solitary cause. Evaluation should verify the diagnosis of hypertension excluding pseudoresistant patients (e.g. white-coat hypertension),

Comment #	Page	Line no.	Comment received from	Comment	Authors' reply
				A correct diagnostic approach to resistant hypertension requires detailed information on the patient's history (including lifestyle characteristics), a meticulous physical examination and laboratory tests to detect associated risk factors, OD and alterations of glucose metabolism, as well as of advanced renal dysfunction opposing—via sodium retention—the effect of BP-lowering drugs. The possibility of a secondary cause of hypertension should always be considered: primary aldosteronism may be more frequent than was believed years ago,[601] and renal artery stenoses of an athero-sclerotic nature have been shown to be quite common in the elderly. Finally, ABPM should be performed regularly, not only to exclude spurious resistance but also to quantify to a better degree the BP elevation and the subsequent effect of the treatment modifications.[598,602] Of course the approach in Calhoun 2008 and JNC 7 do differ slightly from that given by ESH / ESC. Although ESC / EHA is the most recent set of guidelines.	uncover any causes of secondary hypertension and clarify cardiovascular risk, organ damage and related clinical conditions. Medical history is included in the clinical evaluation along with family history related to hypertension, as well as physical examination, laboratory investigations and further diagnostic tests.The evaluation of patients with resistant hypertension should be directed toward confirming true treatment resistance.
81	22	723	EUCOMED	As mentioned earlier, it is certainly important to measure ABPM, however it is unfortunate that most European countries do not reimburse it, The lack of reimbursement for this diagnostic tool should be mentioned.?	The current and local use, cost and reimbursement of ABPM is outside the scope of this assessment
82	23	742	EUCOMED	Given the range of publications suggesting prevalence and the well defined guideline indications for RDN it should be possible to make a conservative estimate for expected utilisation.	Change is made
83	23	744/ 747	EUCOMED	"*Data potentially indicate many candidates for renal denervation*" could you mention which data or analysis suggest this statement?	See comment 21
84	23	755	EUCOMED	For this section, including the discussion part, it would be good to get support from an expert in epidemiology for this important research question.	Thank you for your suggestions, but we are not able to do that in this assessment. No alterations done.
85	25	805	EUCOMED	Why were the websites of the other featured companies not visited? If company websites are to be used as an information source then the best way to avoid bias would be to research information from all	The web-sites that have been visited, were visited to check specific information, which could not be found in

Comment #	Page	Line no.	Comment received from	Comment	Authors' reply
				websites. Also Covidien website is http://www.covidien.com/oneshot/pages.aspx?page=OneShot	overview articles
86	25	828	EUCOMED	It is interesting to see that same technology is used but no analysis of the technicality of the systems is done to understand the effect. and be mentioned in the conclusion.	We do not understand what sentence this comment is referring to, but this rapid REA provides a general description of the working mechanism of the procedure, and does not look into the details of every system. The included studies have been used to assess the effect, which should hopefully be sufficient to understand the conclusion.
87	25	829	EUCOMED	This is a misleading statement regarding the mechanisms of renal denervation via RF ablation. Nerves are not „modulated", the tissue near the ablation electrode is heated to a carefully monitored temperature causing localised cell death, including the cells of the afferent and efferent sympathetic nerve fibres located in the arterial advantitia. The destruction of these cells causes disruption of the sympathetic nervous system, specifically the feedback mechanisms involved in blood pressure regulation.	The word 'modulated' is used in different articles. But I have added more information to the description on the working mechanism and involvement of afferent and efferent nerve fibres
88	26 Table	835	Boston Scientific	Please replace V2 with Vessix TM V2. V2 is not correct	Is changed.
89	26	835	St Jude Medical	We consider it unlikely that the Biosense ThermoCool catheter will ever be promoted for use in the renal arteries. The device is CE marked but we believe the intended use of this device is for cardiac electrophysiology mapping and ablation procedures. Furthermore, the RCT featuring the thermocool catheter was primarily designed to study the effect of Renal denervation on the long term success of cardiac ablation of atrial fibrillation.	For an assessor relying on what is written about the device this information is difficult to find out. As the device is used in trials for RD, and therefore described in the assessment

Comment #	Page	Line no.	Comment received from	Comment	Authors' reply
90	26	835	EUCOMED	What is the relevance of mentioning some devices without CE mark? Surely all devices should be mentioned or none. It may be more pertinent to include all devices that have published data. It is less helpful to list devices that feature on public trials databases such as clinicaltrials.gov as sometimes these devices to not reach the market and names change during development. If the proposed dates for FDA review are provided for Medtronic they should be provided for all companies. Is the planned date for FDA review really relevant to a European HTA? Certainly dates for planned IDE trials could be relevant but the dates for expected FDA review and approval are less so, these dates are often fluid anyway.	This is a good point, and will be followed up upon for future assessments. For this assessment only KONA medical will be deleted as it is not included in the synthesis of effectiveness and safety. Dates for FDA review and approval has been removed.
91	26	835	EUCOMED	It is unlikely that the Biosense ThermoCool catheter will be promoted for use in the renal arteries. It is designed and marketed for use in cardiac electrophysiology mapping and ablation procedures.	For an assessor relying on what is written about the device this information is difficult to find out. As the device is used in trials for RD, and therefore described in the assessment
92	26	835	EUCOMED	If the next generation Medtronic device is included, why not include next generation devices from other companies? There is no information conveyed to the reader by it's inclusion other than promotion of the brand name. It should be noted also that the "MarinR" catheter is actually a market released cardiac ablation catheter, it is unlikely that Medtronic are developing this catheter as their next generation RF ablation catheter.	This is a good point, which we will take into consideration for future assessments. For this assessment, MarinR was found in the search for effectiveness data, and will be maintained. However, the notion that it is Medtronic next generation device is deleted from the table.
93	26	842	Covidien	The description of the procedure for the radio-frequency devices is described for only one device not for the others. Please find below the description of the OneShot™ System and its procedure. Could you please include the following information in the HTA report? The OneShot™ System is a balloon-based radiofrequency (RF) system using a mounted spiral electrode with a unique feature of irrigation of	The aim of the rapid relative effectiveness assessment is to provide a synthesis of the available evidence on effectiveness and safety of the class of technologies, and thus support policy- and decision makers. It is projected that interested readers will try to find more detailed information on a certain type, when a regulatory or reimbursement

Comment #	Page	Line no.	Comment received from	Comment	Authors' reply
				the vessel lumen during treatment. The non-compliant balloon is inflated under low pressure (1 atm) in the renal artery. The electrode delivers RF energy to ablate adjacent nerve bundles with a single 2-minutes treatment. Characteristics of the OneShot™ System - Balloon with continuous spiral electrode - 20 mm long - 5, 6 and 7mm diameter - low pressure (<1atm) - 0.014" guidewire - 7F/8F guide catheter compatible The electrode is made of a proprietary conductive ink that is a custom formulation of a polymer that contains silver. The conductive electrode is painted onto the catheter balloon and is more flexible and robust than a standard metal electrode. The spiral electrode offers two main benefits. First, it offers 360° of ablation. Regardless of balloon orientation and position along the vessel, 360° of ablation will be achieved. The second benefit is that the potential impact of stenosis would be much less than in a circumferential ablation. If even a small amount stenosis forms along a circumferential ablation there is potential that this could significantly block the artery. If the same amount stenosis were to develop along a spiral ablation, it would be spread over 20mm and the potential impact to the flow of the artery would be less. There has been no reported case of a clinically significant stenosis requiring treatment in patients treated with the OneShot™ Renal Denervation System. Cooling of renal artery by irrigation holes placed alongside spiral electrode Saline is flowing out from 8 irrigation holes in the balloon creating a thin film of saline between the balloon and the wall; saline is	decision has to be made in a respective local context. Hence no changes have been made.

Comment #	Page	Line no.	Comment received from	Comment	Authors' reply
				conductive and will not interfere with the ablation. – protects the artery – enhances control and consistency of the treatment effect – prevents sticking of electrode to tissue The internal and external cooling of the electrode through irrigation would prevent the formation of coagulum and char even if the electrode is exposed to blood. The protection of the artery is also reported in Stabile's study which evaluates the morphological features before and after 12 renal ablations using the OneShot™ Renal Denervation System. Pre-procedural and post-procedural optical coherence tomography (OCT) pullbacks were performed and evaluated. No evidence for vasospasm, oedema or intraluminal thrombus formation was detected. It confirms that the OneShot™ Renal Denervation System is designed to deliver energy to achieve denervation of the renal arteries without heating the inner part of the vessel wall, thus preventing tissue damage. Reference: Stabile et al., Percutaneous sympathectomy of the renal arteries: the OneShot™ Renal Denervation System is not associated with significant vessel wall injury; EuroIntervention 2013;9:694-699 Summary of the advantages of the OneShot™ System · Low pressure, balloon-based system delivered over a standard 0.014" wire facilitates access and is designed to minimize arterial over stretch · Single-treatment radio frequency ablation per artery reduces procedure time (2 minutes total per artery) · Spiral electrode design offers standardized and reproducible ablation pattern · Integrated irrigation cools and protects the non-treated region of	

Comment #	Page	Line no.	Comment received from	Comment	Authors' reply
				the artery while producing deep, consistent lesions.	
94	26	847	EUCOMED	This is not true for all devices. Procedure times vary and a complete range should be provided, in fact the longest procedure times are currently associated with the Medtronic device. If procedure time is mentioned, please define when it starts and it finishes.	This information is referenced (Mahfoud) and will be maintained
95	26, 99	850, 2493	ReCor Medical	Delete „under development" in reference to Paradise System as the device is CE marked	Has been changed.
96	26,99	849, 2492	ReCor Medical	Add , without the need for direct vessel contact, „thereby minimizing damage to the arterial wall"	Current text has been maintained.
97	26	850, 2494	ReCor Medical	Add, Paradise System, „a catheter based system which utilizes a cylindrical ultrasound source centered wtihin a cooling balloon to deliver ultrasound energy circumferentially to ablate the renal sympathetic nerves while preserving the integrity of the arterial wall (ReCor Medical, source)"	Has not been added.
98	27	897	EUCOMED	Multiple ablations have an impact on procedure time but may not be an issue for the outcome. MarinR is a cardiac ablation catheter probably not a next generation device and speculation related to medtronics pipeline is not relevant to this HTA	This comment has been made earlier and answered earlier.
99	27	898	EUCOMED	Are we sure that there is continuous lesion? The aim is to create a continuous lesion but it is not possible for the operator to know that that has been achieved.	The point to be made here was that more time was required, and that development goes in the direction of less time needed.
100	27	896	EUCOMED	The regulatory pathway may not be relevant for this chapter. In general having marketing authorization for a device does not mean that the device is used in the market. The section is biased towards the development of the Medtronic system and is likely inaccurate in this respect.	Some information is now deleted, however we feel that providing information on marketing authorization provides the reader an idea of the development that is going on in the field

Comment #	Page	Line no.	Comment received from	Comment	Authors' reply
101	27	900	EUCOMED	Why mention the potential benefits of the untested next generation Medtronic system? It is likely that all the companies featured in this HTA and many that are not have next generation systems in development which all potentially improve on the current technology	The aim is to provide the reader with the development that is going on. It will become clear to the reader that there is a continuous development in this area, and that this HTA not gives any definite 'answers'.
102	27	902	Boston Scientific	Please replace V2 with Vessix TM V2. V2 is not correct	See before
103	27	906	EUCOMED	What relevance to a European network report is the approval process for Medtronic in the US? Planned IDE trials may be relevant.	We believe that the European readership is interested in the worldwide regulatory and marketing status.
104	27	913	EUCOMED	The authors should present the worldwide availability and regulatory approval status of all systems if they present Medtronic and Boston Scientific.	Agree. This has been removed.
105	28	917	Boston Scientific	Please replace V2 with Vessix TM V2. V2 is not correct	See before
106	28	921	EUCOMED	There is no reimbursement in the UK yet. See previous comments relating to this issue.	The paragraph on reimbursement will be changed on the basis of information of Eucomed.
107	28	924	EUCOMED	Pay attention that Country systems are different all around Europe and the both specific structure and process of the reimbursement for Medical Devices vary considerable. All the European Country currently provide reimbursement and fund renal denervation procedure. (For example is Spain the Renal Denervation procedure is funded and the DRG system doesn't exist and Hospitals are funded mainly through global annual budget)	The paragraph on reimbursement will be changed on the basis of information of Eucomed.

Comment #	Page	Line no.	Comment received from	Comment	Authors' reply
108	28	926	EUCOMED	New drug development may only be relevant if these drugs are intended to address resistant hypertension.	Agree.
109	28	936	EUCOMED	Interventional radiologists perform RDN as well.	Has been changed.
110	28	940	EUCOMED	Why is it required? by law ? by current practice? by choice of the doctor? This information is too vague. Could you please either specify or delete?	Has not been changed. In the next sentence it says that in current practice patients are prescribes a combination of (at least) three drugs.
111	28	942	EUCOMED	"To acquire expertise, centres should perform > 25 interventions per year". This statement is misleading the ESC expert consensus that this has been drawn from states that "Appropriate expertise could be assumed at centres with > 25 renal interventions per year" By renal interventions they do not mean purely renal denervation procedures but also other catheter based procedures such as renal artery stenting.	This has been changed to the statement by Mahfoud.
112	28	944	EUCOMED	Center of hypertension can be in another center collaborating with the center performing RDN. It is about the organization of the health care. Could you please rephrase this paragraph to mitigate this statement? Please refer to, for example, Andersson systematic review, NICE guidelines…	See below See comment 113
113	28	947	EUCOMED	The recommendation from Andersson et al relating to the composition of specialists involved in patient selection decisions should be above and separate to this paragraph as it is an important point and reflects current practice.	Has been changed. And sentence about centre has been deleted.
114	28	957	EUCOMED	This is a very limited perspective; it fails to account for the potential reduction in follow up costs for patients treated with renal denervation due to the improved control of their hypertension. Renal denervation is employed when other efforts at reducing blood pressure have failed. The increased cost is for a procedure to be offered to patients that have exhausted other therapeutic avenues.	At the current moment no documentation has been found backing the statement that there might be an effect on mortality and/or morbidity, and thus reducing costs.

Comment #	Page	Line no.	Comment received from	Comment	Authors' reply
115	28	972	EUCOMED	RD is used when other therapies fail. It is performed to decrease CV risk for patients. Decreasing BP by 20 mm/HG the CV risk is decreased by 50%. Clarify time horizon on which costs are calculated. RD is performed in order to treat the pts and to save lives.	See comment 114
116	29	972	EUCOMED	Although renal denervation is an add on therapy and medication use may not be reduced as a result, it should be mentioned that the successful reduction of blood pressure is likely to reduce the future cost of providing care for these patients by reducing comorbidity events such as stroke.	See comment 114
117	29	974	EUCOMED	in the discussion part, it should be mentioned that the correlation of blood pressure level and cardio-vascular morbidity and mortality and therefore the potential advantage of the decrease of the blood pressure. Reference: Giuseppe Mancia and al. 2013 ESH/ESC Guidelines for the management of arterial hypertension The relationship between BP values and CV and renal morbid-and fatal events has been addressed in a large number of observational studies. The results, reported in detail in the 2003 and 2007 ESH/ESC guidelines, can be summarized as follows: 1. Office BP bears an independent continuous relationship with the incidence of several CV events [stroke, myocardial infarction, sudden death, heart failure and peripheral artery disease (PAD)] as well as of endstage renal disease (ESRD). This is true at all ages and in all ethnic groups. 2. The relationship with BP extends from high BP levels to relatively low values of 110–115mmHg for SBP and 70–75mmHg for diastolic BP (DBP). SBP appears to be a better predictor of events than DBP after the age of 50 years, and in elderly individuals pulse pressure (the	We believe that this is answered at comment 114

Comment #	Page	Line no.	Comment received from	Comment	Authors' reply
				difference between SBP and DBP values) has been reported to have a possible additional prognostic role. This is indicated also by the particularly high CV risk exhibited by patients with an elevated SBP and a normal or low DBP [isolated systolic hypertension (ISH)]. 3. A continuous relationship with events is also exhibited by out-of-office BP values, such as those obtained by ABPM and HBPM. 4. The relationship between BP and CV morbidityn and mortality is modified by the concomitance of other CV risk factors. Metabolic risk factors are more common when BP is high than when it is low.	
118	29	977	EUCOMED	What is the relevance to this European HTA of the hypothetical assumption that following FDA approval some US physicians will use the systems off label? If the authors wish to raise the possibility of broader indications they could achieve this by pointing to the ongoing studies which you can find on the WHO ICTRP site	To inform that this might become the case in Europe.
119	29	980	EUCOMED	It is clear what is meant about the "*around the corner*". Could you specify? The indication for Renal Denervation is defined by the Scientific Society. It is not clear the link with the fact the devices are CE-market.	The sentence has been changed, but the message maintained.
120	31	1027	Covidien	In the section SAFETY "Main results": The safety outcomes of the RAPID study are missing and the outcomes of RHAS are incorrect in the tables SAF1 and SAF2. The outcomes provided on August 5 were communicated to EUnetHTA as "publically available" for consideration by the producers of the present HTA report and therefore Covidien agreed to have those data communicated in the HTA report. This is also in agreement to the EUnetHTA Joint Action WP4 – Policy for the HTA Core Model ® and core HTA information FINAL VERSION – 12 Dec 2012	The RHAS article points that most of adverse events were mostly periprocedural. For this reason we have incorporated them in the table of SAF1 (procedural). The possibility of errors in this and other studies due to inadequate data recording is accounted for in the discussion. As we have stated before, the study protocol for the safety domain only contemplates the inclusion of information retrieved from the

Comment #	Page	Line no.	Comment received from	Comment	Authors' reply
				One month follow-up outcomes were communicated on August 5. Since August, the 6 month follow-up outcomes of RAPID study were communicated at the international congress Transcatheter Cardiovascular Therapeutics 2013 (TCT). Here below is a summary of the outcomes, and for further information, please find attached the presentation at the congress by Dr Stefan Verheye. 1) RAPID study 6 months follow-up safety outcomes Reference: Verheye S., RAPID study with 6 months follow-up outcomes, podium presentation at Transcatheter Cardiovascular Therapeutics 2013 Could you please include those important outcomes in this section with at least the following information? "The RAPID study is a multi-center, prospective, non-randomized, 50 patient study using the OneShot™ Renal Denervation System. Eligible patients had: Office systolic blood pressure (SBP) ≥ 160 mmHg, three or more antihypertensive medications including a diuretic, renal artery sizes were 4-7 mm. The endpoints: · Primary: Acute and chronic procedural safety and procedural effectiveness, defined as change of office systolic blood pressure (SBP) at 6 months · Secondary: Rate of SBP at 12, 24 and 36 months, procedure time and fluoroscopy time. Safety Outcomes: Acute Procedural Safety Data	bibliographic literature search. Congress abstracts or unpublished data are not considered in the review. For this reason, these studies cannot be incorporated.

Comment #	Page	Line no.	Comment received from	Comment	Authors' reply
				No deaths, stroke, renal artery dissection, groin or vascular complications from procedure through discharge Two device and procedure related events (2/50): - Cardiac event (bradycardia) – resolved no sequelae - Flank Pain - Resolution within 72 hours Chronic Safety Data No deaths, stroke, MI or other serious events reported within the 6 month follow-up period One event reported 8 days post procedure (1/50): Inflammation at access site due to Closure device Closure device removed and patient treated with antibiotics Resolved 142 days post procedure Chronic Safety – Renal Artery Assessment 41 subjects underwent renal imaging at 6 months including CT, MRI or duplex ultrasound to assess any renal artery abnormalities Protocol required Renal imaging identified one asymptomatic patient with possible renal artery stenosis (1/50); related to device and procedure: -Site performed follow-up imaging -Stenosis deemed non-hemodynamically significant (<50%) in an asymptomatic patient	

Comment #	Page	Line no.	Comment received from	Comment	Authors' reply
				-No change in renal function -At 1 year visit, no change in patient's clinical status Overall conclusion: "Results show that the OneShot™ Renal Denervation System is safe and effective. There was a low acute Serious Adverse Event rate of 2% (1/50 – flank pain). There was a mean BP reduction of -17/-7, -17/-7 and -20/8 mmHg at 1, 3 and 6 months respectively and 24Hr ABPM reduction of -11/-6 mmHg at 6 months. Ablation time was only 2 minutes in each artery." Please note that the development of a publication in a journal is on-going. Note 1: Please note that the development of a publication is on-going. Note 2: Specific information related to RAPID study for tables SAF 1 and SAF 2 pages 34 and 35 respectively is provided in the next comment below. 2) RHAS study one year follow-up safety outcomes (Orniston et Al. 2013) Please see information in the next comment below for pages 34 – 35 (lines 1125 and 1129)	
121	31	1046	ReCor Medical	Change reference to Mabin 2012	Done.
122	32	1088	EUCOMED	Why are the references to the symplicity trials referred to by name? The referencing should follow the same structure for all references and be given by author and year. The same comment applies to the following tables.	As we have commented beforehand, in the simplicity trial authors refer to themselves as the "Symplicity HTN-2 investigators" and thus it is referenced as such. However, we have introduced the name of other trials in the description section.

<table>
<tr><th>Comment #</th><th>Page</th><th>Line no.</th><th>Comment received from</th><th>Comment</th><th>Authors' reply</th></tr>
<tr><td>123</td><td>32-33</td><td></td><td>Medtronic</td><td>All of the comments above need to be applied to the repeat presentation of the data presented on these pages.</td><td>OK</td></tr>
<tr><td>124</td><td>33</td><td>1114</td><td>EUCOMED</td><td>Clarify if these are procedure related events</td><td>Done.</td></tr>
<tr><td>125</td><td>34</td><td>1125</td><td>EUCOMED</td><td>a patient can have several adverse events... It seems that report authors consider number of adverse events as number of patients experiencing adverse events.</td><td>We have reviewed the study and verified that it made reference to patients experiencing adverse events. The only inconsistency could be the RHAS study which does not specify if it is patients or adverse events or if they are procedural or not. We have introduced a footnote in the table to specify this point.</td></tr>
<tr><td>126</td><td>34
35</td><td>1125
1129</td><td>Covidien</td><td>Could you please consider the two following comments for the table SAF1 and SAF2:

1) The safety outcomes for the RHAS study (Orniston et Al. 2013) are incorrect in tables SAF1 and SAF2. This might due to the fact that one patient can more than one adverse events.

Please find below the correction for this study in both tables SAF1 and SAF2

- Table SAF1. Frequency of device- or procedure-related adverse events

<table>
<tr><th></th><th></th><th></th><th colspan="8">Minor</th><th colspan="5">Major</th><th></th></tr>
<tr><th></th><th></th><th>N</th><th>Hypotensive events</th><th>hematoma</th><th>BC</th><th>Femoral artery PA</th><th>Renal artery spasms</th><th>TVR</th><th>Other</th><th>Total</th><th>Renal artery dissection</th><th>Poas hematoma</th><th>Respiratory and CC depression</th><th>Severe artery spams</th><th>Total</th><th>Total AEs</th></tr>
<tr><td>Ormiston</td><td>Case series</td><td>9</td><td>0</td><td>2(22.2%)</td><td>0</td><td>0</td><td>0</td><td>0</td><td>1(11.1%)</td><td>2(22.2%)</td><td>0</td><td>0</td><td>0</td><td>0</td><td>0</td><td>2(22.2%)</td></tr>
</table>
Note: The percentage given in table is by subject. Two subjects had three procedure-related events (one numb foot, and one subject had hematoma).</td><td>The safety outcomes provided in the tables are not in accordance with what is published in this paper. The paper does not make reference to any angina and documents 4 hematomas.</td></tr>
</table>

Comment #	Page	Line no.	Comment received from	Comment	Authors' reply
				SAF2. Frequency of follow up (post procedure) adverse events	

				Minor			Major				
		N	Follow up	Hypotensive events	Other	Total	Nausea and/or oedemas	Hypertensive episodes	angina	TIA	Progress of existing stenosis
Ormiston	Case series	9	12	0	6(66.7%)	6(66.7%)	0	0	1 (11.1%)	0	0

Note: The percentage given in table is by subject.

2) **The safety outcomes of the RAPID study are missing.** Please find below the information to be reported in the respective tables:

SAF1. Frequency of device- or procedure-related adverse events (up to 1 Month)

			Minor							Ma		
		N	Hypotensive events	hematoma	BC	Femoral artery PA	Renal artery spasms	TV R	Other	Total	Renal artery dissection	Poas hematoma	R
RAPID I	Case series	50	0	0	0	0	0	0	6(12%)	6(12%)	0	0	

Note: The percentage given in table is by subject.

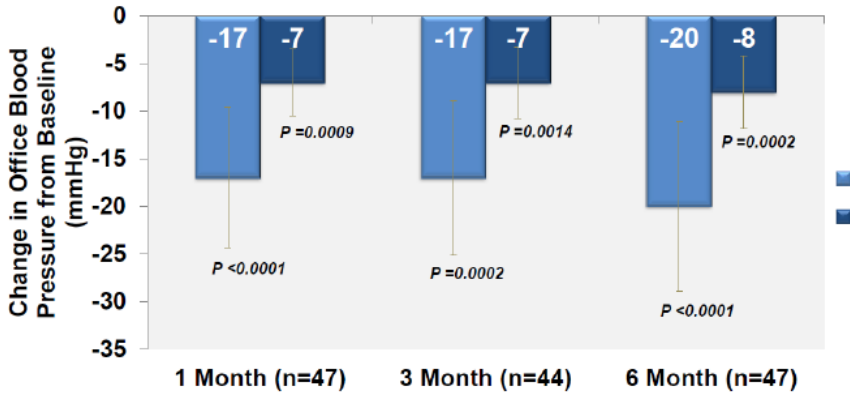
SAF2. Frequency of follow up (post procedure) adverse events (up to 1 Month)

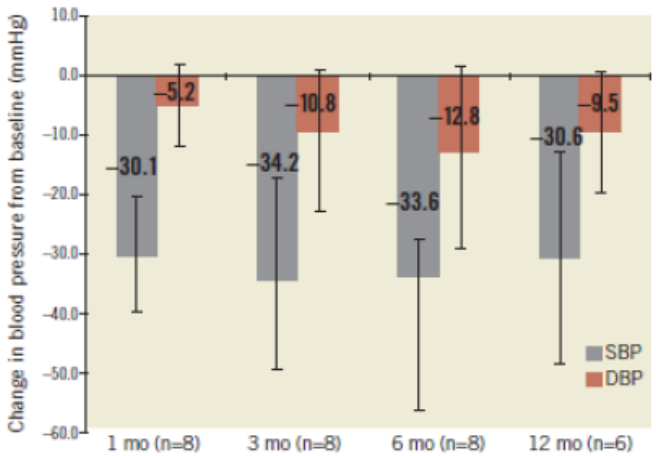
				Minor			Major					
		N	Follow up	Hypotensive events	Other	Total	Nausea and/or oedemas	Hypertensive episodes	angina	TIA	Progress of existing stenosis	Prog of r dise
RAPID I	Case series	50	12	1(2%)	11(22%)	12(24%)	0	1(2%)	0	0	0	

Note: The percentage given in table is by subject.

Comment #	Page	Line no.	Comment received from	Comment	Authors' reply
127	37	1189	EUCOMED	Why is Ardian mentioned here and not Medtronic as indicated in the rest of the document? 1038 also	Amended.
128	37	1189	EUCOMED	This paragraph should be changed according to the new conclusion.	We have not incorporated the new conclusion suggested by EUCOMED, hence no changes in this paragraph.
129	37	1209	EUCOMED	Most of the studies are funded by the Manufacturers and are all scientifically approved. Also, there are few independent studies We suggest to re-phrase: *Significant Conflict of Interests*	Re-phrased as potential conflict of interest.
130	38	1228	EUCOMED	there should be guideline for assessment of intervention including medical devices. Pharmaceutical assessment is very different.	No alteration done. Text refers to how we identified outcomes.
131	38	1215	Covidien	Regarding the section clinical effectiveness: The effectiveness outcomes of the RAPID (Verheye et al.2013) and RHAS (Orniston 2013) studies are missing in the HTA report. The outcomes provided on August 5 were communicated to EUnetHTA as "publically available" for consideration by the producers of the present HTA report and therefore agree to have those data communicated in the HTA report. This is also in agreement to the EUnetHTA Joint Action WP4 – Policy for the HTA Core Model ® and core HTA information FINAL VERSION – 12 Dec 2012 One month follow-up outcomes of RAPID study and one year follow-up of RHAS study were communicated on August 5. Since this communication, the 6 month follow-up outcomes of RAPID study were communicated at the international congress Transcatheter Cardiovascular Therapeutics 2013 (TCT). Here below is a summary of the outcomes, and for further information, please find attached the presentation at the congress TCT 2013 by Dr Stefan	The indicated studies does not include a control group, hence it is outside the inclusion criteria/scope for evaluation of clinical effectiveness in this rapid assessment.

Comment #	Page	Line no.	Comment received from	Comment	Authors' reply
				Verheye. **1) RAPID study 6 months follow-up effectiveness outcomes (Verheye et al. 2013)** **Reference:** Verheye S., RAPID study with 6 months outcomes, podium presentation at Transcatheter Cardiovascular Therapeutics 2013 Could you please include those important outcomes in this section with at least the following information? "The RAPID study is a multi-center, prospective, non-randomized, 50 patient study using the OneShot™ Renal Denervation System. Eligible patients had: Office systolic blood pressure (SBP) ≥ 160 mmHg, three or more antihypertensive medications including a diuretic, renal artery sizes were 4-7 mm. The endpoints: · Primary: Acute and chronic procedural safety and procedural effectiveness, defined as change of office systolic blood pressure (SBP) at 6 months · Secondary: Rate of SBP at 12, 24 and 36 months, procedure time and fluoroscopy time. **Blood Pressure Reduction at 6 months:** **There was a mean BP reduction of -17/-7, -17/-7 and -20/8 mmHg at 1, 3 and 6 months respectively (also presented in the figure below for illustration) and 24Hr ABPM reduction of -11/-6 mmHg at 6 months.**	

Comment #	Page	Line no.	Comment received from	Comment	Authors' reply
				 Overall conclusion: Results show that the OneShot™ Renal Denervation System is safe and effective. There was a low acute Serious Adverse Event rate of 2% (1/50 – flank pain). There was a mean BP reduction of -17/-7, -17/-7 and -20/8 mmHg at 1, 3 and 6 months respectively and 24Hr ABPM reduction of -11/-6 mmHg at 6 months. Ablation time was only 2 minutes in each artery." Please note that the development of a publication is on-going. Note 1: Please note that the development of a publication is on-going. **2) RHAS study one year follow-up outcomes (Orniston et al. 2013):** Reduction in Blood Pressure at Follow-Up Visits presented in the figure below:	

Comment #	Page	Line no.	Comment received from	Comment	Authors' reply
				 The OneShot™ Renal Denervation System produced in the 8 treated subjects a substantial and significant reduction in the office SBP at one month (-30.1mmHg ; p=0.006) that sustained over time (at one year follow-up: - 30.6 mmHg) .	
132	40	1284	EUCOMED	Why are so few studies considered to assess the effectiveness?	Inclusion criteria/scope for evaluation of clinical effectiveness was required a control group. We did not identify further studies than those included.
133	43	1383	EUCOMED	There has been one published report concerning health-related quality of life following renal denervation which should be reviewed and included: Lambert, G. W. *et al.* Health-Related Quality of Life After Renal Denervation in Patients With Treatment-Resistant. *Hypertension* **60,**	See comment 55 No alterations done to text in this section.

Comment #	Page	Line no.	Comment received from	Comment	Authors' reply
				1479–1484 (2012).	
134	43	1386	EUCOMED	For this section, more than the initial selected studies in line 1284 are reported. Could you please report efficacy/effectiveness outcomes for all studies from the literature?	We refer to the individual studies included in the systematic reviews in addition to referencing the systematic review (also see Table 12). To report what has been the outcomes reported in all these studies are beyond the scope of this rapid assessment. We report data according to our aim.
135	43	1401	EUCOMED	Mortality is always captured by the clinical studies	No alterations done. See comment 36
136	50	1680	EUCOMED	How many people belong to the target population? NO" This should be yes incidence and prevalence are important to highlight in any HTA	Answer to the question is given in:" The burden of treatment-resistant arterial hypertension for society in terms of prevalence, incidence and costs (A0006)"
137	54	1741	EUCOMED	Please show references	No alterations done. These are flow charts of study selection based on PRISMA. Indicating all references would clutter the overview-format.
138	55	1744	EUCOMED	Please show references	See comment 137
139	80 Table	1872	Boston Scientific	Please add the ongoing Clinical Study Reduce HTN of Vessix V2 (Boston Scientific) http://clinicaltrials.gov/ct2/show/NCT01541865?term=vessix&rank=1 http://clinicaltrials.gov/ct2/show/NCT01541865?term=reduce-	No alterations done. The study is described as single group assignment. The table only include studies with a control group

Comment #	Page	Line no.	Comment received from	Comment	Authors' reply
				htn&rank=1 ClinicalTrials.gov Identifier: NCT01541865 Please replace V2 with Vessix TM V2. V2 is not correct	V2 replaced using search-replace
140	81	1881	EUCOMED	See previous comments RE comparators	See comment 6
141	84	A0002	EUCOMED	The authors might consider listing all the definitions for resistant hypertension here (see previous comment)	No changes made
142	87	2111	EUCOMED	It might be a good idea to show all the comorbidities associated with untreated or poorly controlled hypertension here, not just a few examples.	No changes made
143	89	A0006	EUCOMED	See previous comments relating to prevalence, and cost effectiveness publications.	Answer given above
144	93	2330	EUCOMED	This question should be completed with some epidemiologic analysis. So far, the research is incomplete, so the conclusion should not be transferable as it is.	Can't find the question
145	97	2452	EUCOMED	Diagnosis and management of resistant hypertension vary across Europe. It is nice to have a recommendation but one needs to look at the reality and current practice! Please see other sources such as the Andersson systematic review for example (which is already considered by EUnetHTA)	No changes made
146	98 Table	2480	Boston Scientific	Please replace V2 with Vessix TM V2. V2 is not correct	See comment 139

Comment #	Page	Line no.	Comment received from	Comment	Authors' reply
147	98	2471	EUCOMED	This chapter is incomplete. Information provided is unbalanced across the different technologies. See above.	Will be taken into consideration for a next assessment
148	98	2472	EUCOMED	See previous comments relating to the description of the therapy.	See previous responses
149	101	2582	EUCOMED	See comment above, although renal denervation is an additional therapy and may not reduce prescribed medication. The aim of the therapy and its potential benefit is not related to reducing medication costs but to reducing morbidity and mortality by reducing blood pressure. The question here (B0002) is „What is the approved indication and claimed benefit of renal denervation and the treatment alternatives" The authors have ignored the claimed benefit (reduction of morbidity and mortality related to uncontrolled hypertension) and not mentioned the demonstrated benefit of blood pressure reduction. The authors also imply that blood pressure reduction is slow, published evidence shows that blood pressure reduction occurs in the first month following the procedure and is further reduced as time goes on. It should also be mentioned that there is no alternative therapy available to patients with resistant hypertension.	See responses above. We have not been able to verify effects on mortality/morbidity.
150	101	2602	EUCOMED	Can it be ensured that physicians across Europe apply this recommendation? Considering the current practice in each country, this is only partly transferable.	It is not clear which recommendation is referred to.
151	102	2623	Boston Scientific	Please replace V2 with Vessix TM V2. V2 is not correct	See comment 139
152	102	2638	Boston Scientific	Please replace V2 with Vessix TM V2. V2 is not correct	See comment 139
153	102	B0003	EUCOMED	See previous comments	See comment 150
154	104	2685	EUCOMED	this information is currently incomplete	See comment 150

Comment #	Page	Line no.	Comment received from	Comment	Authors' reply
155	104	2702	EUCOMED	What about the interventional radiologist? See previous comments, interventional radiologists should always be included.	Has been changed
156	105	2731	EUCOMED	Although the information conveyed may be transferable it is certainly not complete.	It is not clear what this comment is referring to.
157	105	2749	EUCOMED	Depending on the health care organization. the hypertension expert can be outside the center where the RDN surgery is done. Could you please change the sentence? (please note that the author in reference works in one the biggest European center of excellence of hypertension)	Has been changed
158	106	2765	EUCOMED	Although the information conveyed may be transferable it is certainly not complete. This research question is insufficiently informed and is currently misleading.	Has not been changed.
159	108	2836	EUCOMED	This is incomplete. The full procedure should be described.	Has not been changed.
160	109	2867	EUCOMED	This is incomplete. B0011 presents one option and is insufficiently presented. Could you please be specific on the alternatives with their pros and cons and make a recommendation on the design of the monitoring?	This might be true, but was based on literature.
161	115	3109	EUCOMED	Although the information conveyed may be transferable it is certainly not complete as some studies are not reported.	See comments above regarding inclusion criteria.
162	115	3109	Covidien	The chapters corresponding to the section "C0001: What are the adverse events and serious adverse events in patients treated with renal denervation?" are incomplete. Could you please complete the corresponding chapters in the report with the outcomes presented in the comments above?	See comments above regarding inclusion criteria.
163	121	3335	EUCOMED	This is incomplete. Only HTN 2 study data are presented and nothing from other clinical studies. Why?	Cards have been reviewed. They include data from all published studies that comply with inclusion criteria. Data from unpublished results cannot be

Comment #	Page	Line no.	Comment received from	Comment	Authors' reply
					incorporated.
164	122	3355	EUCOMED	Although studies have not been completed which assess impact on mortality and morbidity compared to pharmacological therapy. The evidence available certainly indicates that renal denervation does not increase mortality and morbidity.	See comment 36 and 61
165	123	3387	EUCOMED	same comment as for D0001	See comment 165
166	124	3430	EUCOMED	Not all studies are reported. Could you please report information for all studies?	Cards have been reviewed. They include data from all published studies that comply with inclusion criteria. Data from unpublished results cannot be incorporated.
167	126	3505	EUCOMED	Although the information conveyed may be transferable it is certainly not complete. this is about the same research question as in comment line 3430. Because only a limited number of studies are considered, this research question is insufficiently answered.	See comment 131
168	129	3508 3618	Covidien	The chapters corresponding to the section D0006: "How does renal denervation affect progression of treatment-resistant arterial hypertension?" should be completed with all available efficacy/effectiveness outcomes in renal denervation therapy. Regarding outcomes supporting OneShot™ Renal Denervation System effectiveness, the outcomes of two studies are available: one year follow-up for RHAS study (Orniston et al. 2013) and the 6 month follow-up of RAPID study (Verheye S. 2013)	See comment 131
169	136	D0012	EUCOMED	See previous comment relating to health related quality of life assessment.	See comment 55
170	147	4084	J&J/Biosense Webster	We noticed the request for feedback by EUnetHTA was submitted to a non-personal generic email account as found on a website in the US. We kindly suggest to evaluate how stakeholders are defined, how communication lines are established and then maintained throughout	A valid point. Your suggestion will be discussed within members of the work package.

Comment #	Page	Line no.	Comment received from	Comment	Authors' reply
				the context of the rapid HTA process.	For future pilots, the coordination team will try to identify contact persons at the beginning of the pilot process, but we assumed that contacting manufacturers without known contact persons yet by using their generic e-mail would lead to identification of a personal contact.
171	158	4136	EUCOMED	the assessors would have probably benefited from the insight of the medical societies representatives, specialists within the industry, and also patients having received the RDN treatment (which is something some HTA assessors do in some countries)	Your suggestion will be discussed within members of the work package. See comment 3 and 4
172	general		Medtronic	The document fails to put adverse events into context. Hypotension or hypertension requiring hospitalization, renal artery stenosis, and bradycardia occur commonly in the hypertensive patient population on multiple anti-hypertensive medications (as is the population under study) so attributing these events to the procedure presents the adverse events out of context.	This conclusion is based on the results of the 4 comparative trials. However, taking into account the uneven reporting on cases and controls it is difficult to make firm conclusions regarding this point. We have added the following phrase to leave this clear "Results suggest that RDN treated patients could have more problems with the regulation of their blood pressure, which could result in more hospital admissions due to hypotensive and hypertensive emergencies. However, this is to be confirmed in trials adequately designed. With the available evidence it is impossible to make any conclusion with respect to the frequency of follow up complications".
173	general		Medtronic	The document is correct that no studies are designed or powered for clinical endpoints, but it needs to be pointed out that blood pressure reduction is the best established surrogate for reduction in clinical endpoints of death, CV death, MI, stroke, & renal insufficiency. Even the US FDA formally acknowledges this in their guidance documents	No alterations done. Please note that we also received other comments specially asking for clinical

Comment #	Page	Line no.	Comment received from	Comment	Authors' reply
				and in publications they have authored.	endpoints like mortality and morbidity.
174	general		EUCOMED	When a comment is made in one section, the same comment is not repeated in the section repeating the same information.	Response – not applicable
175	General		EUCOMED	It would be better to use numbered referencing throughout the document. It would be much easier for the reader to follow references given in this way. If name and date of publication referencing is preferred, a full reference list should still be provided at the end of the document For example "..three controlled studies including 158 patients in total ….(two RCTs and one non RCT) …." does not provide enough information to the reader to understand which studies were considered in the discussion.	Thank you for a constructive comment. How we use/display references will be discussed shortly as we are currently evaluating the template used for pilot rapid assessments.
176	general		EUCOMED	we think that the lack of physicians involvement is concerning	See comment 3
177	general		Covidien	Covidien agrees with the comments sent by EUCOMED on the behalf of the EUCOMED Renal Denervation Working Group. The comments below are specific to Covidien OneShot™ Renal Denervation System.	Response – not applicable
178	general		Covidien	When a comment is made in one section, the same comment is not repeated in the section repeating the same information.	Response – not applicable
179	general		J&J/Biosense Webster	As one might expect for a new indication such as denervation of the renal arteries for the treatment of resistant hypertension (often known as renal denervation), many technologies to treat this disease state are either new technologies in the early phase of product development, (i.e. pre-CE Mark), or are technologies that may be on the market (i.e. have CE Mark), where the technology is used in alternate indications (i.e. ablation therapy for the treatment of Atrial Fibrillation) and are now considered as technologies for the treatment of renal denervation. In both of these scenarios, there is little clinical	Response – not applicable

Comment #	Page	Line no.	Comment received from	Comment	Authors' reply
				evidence that can be found as a part of this review. Consequently, at this point in time it is too early to extensively comment on the content of the body of evidence. We congratulate EUnetHTA that they have been able to apply a consistent methodology on this literature search.	

PATIENT REPRESENTATIVE

Comments were received from:

Agency
European Organisation for rare diseases (EURORDIS)

Comment #	Page	Line number	Comment	Authors' reply
1		general/374	This comment applies everywhere in the document when the quality of evidence is rated. The quality of evidence is reported as very low, low or moderate. There is no scale: are there other possible rates like high or excellent, or only these 3? There is no explanation how to interpret "very low", "low" or "moderate".	Added under methods in summary and under methods/analysis in result section: The resulting classification and definitions of the quality of the evidence include: high (We are very confident that the true effect lies close to that of the estimate of effect), moderate (We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different), low (Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect) and very low (We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect).
2	6 to 13	General, line 157 to 503	Summary appears to be too long depending on the target audience. Typically for other users than HTA bodies or industry (healthcare professionals, patients) a 2-3 pages summary would be optimum. As the information is detailed in following sections (pages 18 to 43), there are many repeats and the main elements appear to be diluted in details that are not immediately needed (the reader can always read more in relevant sections of the document pages 18 to 43).	Thank you for a very constructive comment. There is currently ongoing a revision of the template for the pilot rapid assessment. The information will be directed to that process. No alterations done.
3	8	226-243	Description of technology:	That is right. The description has been based on written documents, which all describe the procedure in general terms. For this rapid

Comment #	Page	Line number	Comment	Authors' reply
		(also p. 25, 829-859)	This does not precisely describe the procedure: how many staff are involved in total? A cardiologist or an angiologist, plus one or several nurses, anaesthesia nurse? Should the patient be hospitalised one day before or longer, and how long should the stay last for in total (average)… This could also be explained in organisational aspects, even though it may vary from one care setting to the other.	assessment no other sources than written sources have been used, due to time limits.
4	12	434	"Germany and part of the UK are currently reimbursing the procedure": this is vague. Part of the UK, does it mean England but not Wales and not Scotland, or another distribution? What is meant by "are reimbursing"? Is it 100% covered? Are there conditions, restrictions to some patients and not all with condition?	The reimbursement paragraph is to be rewritten based on due information from Eucomed and Medtronic.
5	13	491-502	Efficacy of Simplicity is commented, but not its safety profile. For other methods, the safety profile is mentioned but regarding efficacy the reader needs to deduce there are no efficacy yet as more information is expected in the coming years. It would be fair to add one sentence about Simplicity overall safety, and to make it clearer that for other methods, it is premature to evaluate their efficacy at this stage.	A general comment has been introduced
6	14	504	The list of abbreviations should come earlier, before the first abbreviations are used in the document, i.e. before the summary.	Thank you for a very constructive comment. There is currently ongoing a revision of the template for the pilot rapid assessment. The information will be directed to that process. No alterations done.
7	30	988 (in fact general comment)	The table of research questions is excellent (not only for the domain of safety, but also to the population or to the clinical effectiveness…), and it could be useful to add one column in the table on the degree of satisfaction, or how well the question	Thank you for a very constructive comment. There is currently ongoing a revision of the template for the pilot rapid assessment. The information will be directed to that process.

Comment #	Page	Line number	Comment	Authors' reply
			could be answered too, depending on the available data. Writers could come to an agreement, for example stating that the question "What are the minor and major adverse events in patients treated with renal denervation?" could be responded to fairly well or completely, or on the contrary poorly etc.	No alterations done.

EXTERNAL REVIEWERS

Comments were received from:

Name	Agency
Giuseppe Boriani MD, PhD	Professor of Cardiology, University of Bologna, Italy
Jan Erik Nordrehaug	Professor of Cardiology, Department of Clinical Science, University of Bergen, Bergen. Norway

Comment #	Page	Line number	Comment received from	Comment	Authors' reply
1	6	171	G Boriani	In describing the disease it is reported "Treatment-resistant hypertension describes a condition where the conventional/traditional treatment measures are inadequate in treating the patients' hypertension –this is also described as true resistant hypertension." and "The condition resistant hypertension appears when appropriate treatment including lifestyle measures and three antihypertensive drugs (one of them being a diuretic) fails to lower systolic blood pressure (BP) and diastolic BP values to 140 and 90 mm Hg respectively." I think that even in this preliminary description of the medical condition object of this HTA and considered for renal denervation it should be stressed that secondary form of hypertension need to be appropriately excluded. At line 179 it is reported that "Known categories of risk factors for treatment-resistant arterial hypertension are... undetected secondary forms of hypertension.. " but this is a crucial point that need to be stressed for defining since the beginning the appropriate setting for considering renal denervation.	Changes have been made

Comment #	Page	Line number	Comment received from	Comment	Authors' reply
2	6	185	G Boriani	The text reports „The natural course for resistant hypertension has been inadequately appraised. Hypertension will if untreated increase the risk of e.g. cardiovascular disease, stroke". It would be essential to define the outcome of patients with resistant hypertension. This is crucial for anyone trying to predict the benefit or advantages of renal denervation in terms of outcomes and cost effectiveness. At least one study, reporting on the high risk for future adverse cardiovascular events should be quoted (Daugherty SL, et al.. Incidence and prognosis of resistant hypertension in hypertensive patients. Circulation. 2012;125:1635–1642.)	See comment 77 from manufacturers
3	8	234	G Boriani	The text reports that "The comparator treatment is pharmaceutical treatment of a combination of more than three drugs." This statement may easily lead to a misunderstanding. Renal denervation is an add-on treatment, on top of at least 3 anti- hypertensive agents, that need to be continued. For this reason the comparison is between no change or potentiation of medical treatment versus continuation of medical treatment plus renal denervation. This is an important point, stressed by the Expert consensus document of ESC (F. Mahfoud et al. European Heart Journal (2013) 34, 2149–2157) that reports "Renal denervation does not reduce pill burden in most patients and is not a cure for hypertension. Neither in the Symplicity HTN-1 nor in the HTN-2 a reduction in antihypertensive background medication has been investigated as an endpoint. "I think this is an important point that need some more detailed explanation.	Agree. The sentence has been changed to: Current treatment consists of a combination of at least 3 anti-hypertensive agents. Renal denervation will be an add-on treatment to pharmaceutical treatment. We can't explain why those studies have not included this outcome. However, information is available from other studies (see section "Change-in-management in terms of decrease in number of medications")
4	11	389-400	JE Nordrehaug	It would be relevant to mention both the effects on office BP and on ambulatory BP, the latter could be less exposed to bias than the former. The authors seem to focus mostly on office BP.	A very valid point. Our included SR (Davis et al.) report that the methods used for BP measurement in analysis in the controlled trials were office based BP. We note that some (but far from all) ongoing

Comment #	Page	Line number	Comment received from	Comment	Authors' reply
					studies report use of ABPM in their primary objective.
5	11	389-400	JE Nordrehaug	The problem with nonresponders seen with drug therapy is relevant to discuss, is this a problem also with RDN, or is it nonexistant so far with this intervention.	We agree, but have not included outcomes like % with reductions in BP or need for re-doing the procedure.
6	12	444 and following	G Boriani	In the discussion section it will be important to highlight that a proper assessment of this technology would require an outcome study, where the effect of this add-on treatment will be evaluated in terms of capacity to improve morbidity (stroke, Mi, cardiovascular hospitalizations, etc) or mortality. Renal denervation is a treatment on top of medications.	It is a fine line between stating what the evidence is and giving recommendations as to what are necessary or required studies in the future. We have chosen to start the discussion (the referenced section) with clear statements as to what data that is not available yet instead of starting with available evidence. However, as add-on pharmaceutical may reach the marked based only on intermediate/surrogate outcomes so there may not be a direct requirement for other interventions to show actual improvement in morbidity and mortality. Even if this is an ideal situation.
7	13	484-489 and 965	JE Nordrehaug	(1)Is there any evidence that the BP reducing effect (slowly progressive resetting of sympathetic neural regulation) may continue over time, and thereby appear as a „complication" if BP drops too low even when medication is stopped. (2) Is there any longterm evidenc or suggestion that this may happen? (3)Is it realistic to imagine so? (4) Is this a potential ethical question when designing follow-up of studies, should a longterm follow-up always be implemented/demanded for instance for the active arm of the RCTs, when the control group is allowed to cross over if short-term (12 months) study end?	For 1-2 (our numbering for reference): For effectiveness we only included controlled trials. Based on the narrative summary by Gosain and colleagues it would not seem to be a major issue as they did not report a large reduction in use of antihypertensive, which would have been done first (see D0023). For 3-4: Even if we only included CT in the effectiveness part, we did notice that several of the studies used extensions or otherwise followed-up on their patient in longer term setting. Like the reviewer states it is important to gather more

Comment #	Page	Line number	Comment received from	Comment	Authors' reply
					long term data- both to check if the reduction in BP sustains and to check if it continues to decrease.
8	13	491 and following	G Boriani	The conclusion section should include the issue of cost. Renal denervation is an add-on treatment and, as reported in the ESC Expert consensus (F. Mahfoud et al. European Heart Journal (2013) 34, 2149–2157) a specific follow up is needed. This point is stressed in others section of the HTA document, i.e. line 951 where the document reports "There will be a slight increase in the demand for functional and morphological diagnostic procedures of the renal arteries (MRI, CT, Doppler-ultrasound) as this is part of the routine protocol prior to RDN (Andersson 2013). In the CADTH assessment it is concluded that RDN is associated with additional health care resources in terms of the cost of the system, the training of specialist staff, and the use of hospital radiology services during the procedure, as RDN is currently used as an adjunct to available therapies for hypertension". The conclusion section should deal with the cost issue and also stress that, at present, the lack of data on hard outcomes make not possible any estimate on the cost-effectiveness of renal denervation. This point is debated also at line 972 ("It is an add-on therapy, thus leading to additional health care resources in terms of the cost of the system, the training of specialist staff, and the use of hospital radiology services during the procedure (CADTH 2013)." But it is worth to include this point in the Conclusions.	Agree, have added the following sentence to conclusion in summary: In terms of budget impact: renal denervation will be an add-on therapy, thus leading to additional health care resources in terms of the cost of the system, the training of specialist staff, and the use of hospital radiology services during the procedure (CADTH 2013). We agree that cost and other resource utilization is important in decision making. However, these issues are very sensitive to setting and local practice. These issues are outside the scope of this rapid assessment. All rapid assessment needs to be locally adapted, and would then in many cases include cost or cost-effectiveness.
9	13	496	G Boriani	It is absolutely important to stress that in order to draw conclusions on the role of renal denervation, on its implementation in daily practice and specifically on its cost-effectiveness profile, data derived from outcome-based RCTs are needed. For some antihypertensive drug regimens a benefit in terms of outcome has been quantified, in specific setting of hypertensive patients. For instance, in the	See comment 8

Comment #	Page	Line number	Comment received from	Comment	Authors' reply
				setting of isolated systolic hypertension in the elderly Kostis et al (JAMA. 2011;306(23):2588-2593) found that at long term every day of pharmacological treatment translates into an additional day of life saved. Although outcome improvement is expected for renal denervation, if substantial blood pressure reduction is obtained and maintained at long term, the outcome benefit need to be demonstrated and measured. Blood pressure reduction is only an outcome surrogate. The outcome benefit will be the basis for appropriate assessment of the cost effectiveness profile and the affordability of implementation of this new technology (as add-on treatment) in specific settings. I think that this HTA document should include these considerations on the resent status of our knowledge on renal denervation.	
10	26	842	JE Nordrehaug	Description of the procedures should include information on the size of the catheters used (diameter given as French (Fr) units).	Acknowledged, and have looked into this, and have seen that size is variable dependent on vessel size. We think it will become too detailed information for the main target group of this assessment. And will thus keep the description as it is.
11	32	1067	JE Nordrehaug	The information on Fr diameter will make the femoral artery aneurysm occurrence and bleeding easier to interprete and compare between studies, as these variables are often positively linked. Is a femoral artery closure system adviced after withdrawal of catheters, and were such systems used in the RCTs?	The comparison of different systems is impossible with available information. It is true that the OneShot (9 Fr) and Enlight (8 Fr) seem to have more pseudoaneurysms than the Symplicity catheter (6 Fr) but it is difficult to come to any conclusion taking into account that the first studies only include 9 and 46 patients. We have highlighted in this discussion that size could determine effect but no other analysis is possible. We acknowledge that these systems exist but RCT do not make reference to them.
12	127-130		JE Nordrehaug	Same argument as on page 11 regarding office BP versus ambulant (24 hour) BP and bias discussion.	See comment 5

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

9. Details on sources of information and literature search strategies provided?					
Search strategy	Databases	Year range	Language restriction	Primary data	Other kind of information resources
O	O	O	O	O	O
Boriani: Yes, provided **Nordrehaug: Yes**					

10. Information on basis for the assessment and interpretation of selected data and information?		
Method of data extraction described?	Critical appraisal method (for quality assessment of the literature) described?	Method of data synthesis described?
O	O	O
Boriani: Yes, information provided **Nordrehaug: Yes**		

	Yes	**Partly (please specify)**	**No (please specify)**	**Other (please specify)**
Part II: Results (See Domain Reports)				
Health problem and current use of the technology				
1. Does the section describe the health issue including incidence and prevalence, how it occurs, who is affected (including high-risk groups, vulnerable/disadvantaged populations, where it occurs, how it is diagnosed, symptoms and consequences)?	Nordrehaug	**Boriani: No data on outcome of resistant hypertension** **A:** We think the information provided is sufficient for this assessment.		
2. Are the supporting references current and do they provide an international picture of the problem?	Nordrehaug	**Boriani: I would include refs on outcome of resistant hypertension** **A:** See above		
Description and technical characteristics of the technology				

	Yes	Partly (please specify)	No (please specify)	Other (please specify)
3. Does the section describe the intervention under review including how it works and how it may have an impact on potential recipients?	Boriani Nordrehaug			
4. Does the section describe the comparator(s) under review including how it works and how it may have an impact on potential recipients?	Boriani Nordrehaug			
5. Are the supporting references current and do they provide an international picture of the problem?	Boriani Nordrehaug			
Safety and effectiveness	Boriani Nordrehaug			
6. Is the risk of bias clearly reported?	Boriani Nordrehaug			
7. Is quality of data sufficiently evaluated?	Boriani			
8. Are both relative and absolute effect measures presented for each dichotomous outcome?	Boriani Nordrehaug			
9. Are continuous data reported according to appropriate statistics (e.g. 'standardised mean difference' or 'weighted mean difference')?	Boriani Nordrehaug			
10. In case of time-to event analysis, are hazard ratios (HR) and ratios of medians presented?	Nordrehaug			Boriani :NA
11. Are measures of the precision of the effect estimates presented or, in case of absence of this essential information, is this fact reported?	Nordrehaug			Boriani :NA
12. Is frequency of adverse events, frequency of occurrence, relative risk or number needed to harm (NNH) presented for the safety data?	Nordrehaug		**Boriani : NO, no NNH reported**	

	Yes	Partly (please specify)	No (please specify)	Other (please specify)
			A: Safety was not the main endpoint in any of the included studies and outcomes for controls were incompletely recorded in all of the studies (see risk bias tables). For this reason, it is impossible to calculate NNT or any other aggregate measure.	
13. In cases where adverse events are incorporated in utility values of quality of life, is the source of quantification accessible?	Nordrehaug			Boriani :NA
14. Was the transformation of the surrogate outcomes into patient-relevant final outcomes considered (if relevant)?	Nordrehaug		Boriani	
General				
15. Do you agree that the data extracted are relevant to the research questions formulated in the beginning and that analysed and synthesised data still answer the question?	Boriani Nordrehaug			
16. Can the results be applied to the intended population?	Nordrehaug	**Boriani: outcome studies needed** A: See comment 6		
17. Is the assessment sufficiently transparent and evidence ('facts') distinguished from judgements (including values and preferences)?	Boriani Nordrehaug			

	Yes	Partly (please specify)	No (please specify)	Other (please specify)
Part III: Summary of Relative Effectiveness				
1. Does the summary present a balanced representation of the content of the report?	Nordrehaug	**Boriani: see comments** **The issue of cost and cost effectiveness need to be mentioned** A: See comment 8 (The conclusion now includes a general notion on budget impact. Costs and CEA are to be included in local assessments)		
2. Does the discussion of the summary clearly address the uncertainty in the available evidence, the evidence gaps and the applicability of the evidence?	Nordrehaug	**Boriani: the same as before**		
Part IV: Other Considerations				
1. Have all relevant ethical, organisational, social and legal aspects been considered? (See Appendix 3 of the Pilot assessment)	Nordrehaug			**Boriani: NA, not treated**