JA2- WP7- SG 2 **Public consultation** **on the Core protocol Pilot for AEG**
2nd draft (July 22nd 2015)

Comments on the draft

	Author and number of comment	Page	Line	Comment	Character of comment • "major"[1] • "minor"[2] • "linguistic"[3]	Answers
1.	**ASSR 1**	General		Congratulations to the authors for the excellent work		Thank you.
2.	**SNHTA 1**	General		General: The document is a valuable new document for the EUnetHTA community. It is concrete, pragmatic and well structured. It can be used by HTA and policy-making institutions that acknowledge the concept of AEG, but lack a standardized process protocol, and by those that wish to improve existing AEG processes. We would like to congratulate the authors with their excellent achievement.	☒ major ☐ minor ☐ linguistic	Thank you.
3.	**VASPVT 1**	General		This "Core protocol Pilot for AEG" is well written and quite easy to understand, especially when there is an example technology in need of AEG identified. However, the main question is: Who has to do Core protocol for AEG (especially additional elements) in the future? Maybe the answer to this question should be written in this Pilot.		Core protocol for AEG is directed to: - HTA agencies\national bodies, which can use it as a basis to set up requirements for either a common study or multiple coordinated AEG requests; - study sponsors as guidance when drafting their study protocols Additional elements are thought to be implemented by the organism that is going to set up the study in practice.

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						This information is already presented in the text of the pilot.
4.	**HVB 1**	General		I would suggest not to put so many terms between "…" …		Thank you, this has been modified.
5.	**ASSR 2**	General section 2		Well written and comprehensive, given the difficulty of outlining a guidance that fits all.		Thank you.
6.	**SNHTA 2**	2		A structured Table of Content with page references is missing.	☐ major ☒ minor ☐ linguistic	Thank you, this has been added.
7.	**ASSR 3**	3	47	In the introduction a clearer outline of the whole objective and process of WP7 SG 2 could be provided to better convey the overall (and ambitious) aim of SG2	x major ☐ minor ☐ linguistic	Thank you, the description of all WP7 SG2 deliverables has been added to the text.
8.	**SNHTA 3**	3	52	Grammar: It should be either "Lacking or inadequate evidence…" OR "A lack or inadequacy of the evidence…	☐ major ☐ minor ☒ linguistic	Thank you, this has been modified.
9.	**EFPIA 1**	3	52-53	First sentence is confusing and should be re-written for clarity purposes. Possible suggestion that fits with the following sentences: *An often encountered obstacle to the introduction of new technologies into a health system is uncertainty relating to a lack of, or inadequate, evidence at the time of their appraisal.*	☐ major ☐ minor ☒ linguistic	Thank you, the sentence has been reformulated.

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10.	**ASSR 4**	3	55	...or prove to be even harmful. May sound better " ...or even prove to be harmful."	☐ major ☐ minor x linguistic	Thank you, this has been modified.
11.	**SNHTA 4**	3	55	Wording for potentially missed benefits should be as strong as for potential harms: ...technologies that **may** later turn out…	☐ major ☐ minor ☒ linguistic	Thank you, this has been modified.
12.	**EFPIA 2**	3	55	The either or statement as written implies that all new products that are granted access will turn out to have problems. Possible suggestion: replace "that later turn out" with "*that <u>may</u> later turn out*". This simple change balances this possibility with the risk of delaying potential benefits.	☐ major ☐ minor ☒ linguistic	Yes we agree, thank you. The sentence has been modified.
13.	**SNHTA 5**	3	58	Do you mean "outlined"?	☐ major ☐ minor ☒ linguistic	Yes, this has been rewritten.
14.	**EFPIA 3**	3	58	I think that the five-step pathway is very clear and like figure 1 which usefully depicts the information flow. I have a question with respect to the outcome of the generation of new evidence: what happens if the additional data collection study succeeds but fails to adequately resolve the uncertainty? For example the ISPOR paper on performance-based	☐ major ☒ minor ☐ linguistic	We agree that the question is really important and will be considered in future activities on AEG, as it is not in the scope of this pilot to include a discussion on that issue.

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				risk sharing arrangements (Garrison et al (2013) Value in Health 16: 703-719) provide a hypothetical example (Fig 2) where an additional evidence generation has reduced the variance of the evidence but moves the mean closer to the decision threshold meaning that decision uncertainty has increased. Also, in some cases, additional evidence of broad populations might usefully identify subpopulations of responders/non-responders that might not have been detected in clinical trials. My question, therefore, is whether the five-step pathway could benefit from having a feedback loop to allow for further research if required?		
15.	**ASSR 5**	3	65	Very nice picture!	☐ major ☐ minor ☐ linguistic	Thank you, it was taken from the poster developed by the French National Authority for Health (HAS) for EUnetHTA conference 2014 ”Improving additional evidence generation for health technologies”.
16.	**VASPVT 2**	3	65-82	Figure 1 could be a little bit bigger.	☐ major ☐ minor ☒ linguistic	Thank you, this has been modified.
17.	**SNHTA 6**	4	91	Wording: “Against this background…”	☐ major ☐ minor ☒ linguistic	Thank you, this has been modified.

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18.	**SNHTA 7**	4	91	Grammar: "…aimed **to suggest**…"	☐ major ☐ minor ☒ linguistic	Thank you, this has been modified.
19.	**SNHTA 8**	4	92	Grammar: " … **at** the same time…2	☐ major ☐ minor ☒ linguistic	Thank you, this has been modified.
20.	**HVB 2**	4	93	"shareable": to share does not "include" that the protocols might also be used- e.g. I would suggest to reword: applicable/utilized/employed	☐ major ☐ minor ☒ linguistic	The core items should be key and shareable among partners. It is the template that is being used\utilized. The text has been modified in order to make this clearer.
21.	**HVB 3**	4	101	I would suggest to make 2 sentences	☐ major ☐ minor ☒ linguistic	Thank you, this has been modified.
22.	**HVB 4**	4	104	.. for AEG studies: "it"???	☐ major ☐ minor ☒ linguistic	The template should be drafted\filled-in after the identification of an evidence gap and before or after the decision on coverage with evidence generation
23.	**SNHTA 9**	4	104-106	Simplify wording?: "…is directed to both HTA agencies/national bodies or to study sponsors. HTA agencies can use it… For sponsors it can serve as guidance when drafting…"	☐ major ☐ minor ☒ linguistic	Thank you, this has been modified.

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24.	**SNHTA 10**	4	127	Wording: Do you mean "complemented" instead of "Completed"?	☐ major ☐ minor ☒ linguistic	We meant that additional information, contained in additional elements, should be added to core elements in order to obtain a complete study protocol.
25.	**SNHTA 11**	4	130	Wording: "… implementation of a study"	☐ major ☐ minor ☒ linguistic	Thank you, this has been modified.
26.	**SNHTA 12**	6		Suggestion: To present the list of study protocol elements in a table format, possibly with the corresponding Core Assessment Element coding, might improve visualizing the sequence of events.	☐ major ☒ minor ☐ linguistic	Thank you for the suggestion, an image has been integrated (page 15).
27.	**HVB 5**	7	188	I would suggest to reword: to "fill" a specific gap instead of "cover"	☐ major ☐ minor ☒ linguistic	Thank you, this has been modified.
28.	**SNHTA 13**	7	191+193	Grammar: comma before " which" Line 191 2x "which" used	☐ major ☐ minor ☒ linguistic	Thank you, this has been added.
29.	**OGYEI 1**	7	194	The reference is missing.	☐ major ☐ minor ☒ linguistic	Thank you, this has been added.

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30.	**ASSR 6**	7	199 203	Not clear the use of "methodological" and "methodological appropriateness". Are the core elements related to the quality of the evidence? if so it is better to state it clearly, it is not just an issue of methods (although methods have a lot to do with it), but an issue of quality of evidence, whether data are robust or not, for effectiveness and safety	x major ☐ minor ☐ linguistic	Core elements are related to methodological appropriateness and necessary to ensure that the study will fill-in the gaps. It is true that core elements are the ones that mostly inform about the quality of the evidence generated, but they were not classified as core for that reason only.
31.	**SNHTA 14**	7	202	Wording: "… classified **as…"**	☐ major ☐ minor ☒ linguistic	Thank you, this has been modified.
32.	**ASSR 7**	7	214	".. core elements alone should be sufficient to tell if the study....." "CORE ELEMENTS ALONE SHOULD BE SUFFICIENT TO ENSURE THE STUDY ,,,,,,"	☐ major ☐ minor X linguistic	Thank you, this has been modified.
33.	**HVB 6**	7	222	Suggestion to reword: …"a list of all elements in ranked order"	☐ major ☐ minor ☒ linguistic	Thank you, this has been modified.
34.	**HVB 7**	7	226	What does "fully developed" mean in this context?	☐ major ☐ minor ☐ linguistic	It means fully described and not just listed, as it was done for additional elements.

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35.	**OGYEI 2**	8	233-244	It would be useful if the templates which are indicated in the 4-7th footnotes will be available on a website or as a background material / appendix. (cf. page 20 line 697-700)	☐ major ☒ minor ☐ linguistic	The links to the templates have been provided in the bibliography.
36.	**HVB 8**	8	242	HVB answer was missing: sorry for the delay in providing this answer. Even though we do ask for additional information, we do not have a template of a protocol for AEG or others, and we have not yet requested additional evidence generation upon new studies, it is more like additional evidence generation by literature or better documentation.	☐ major ☐ minor ☐ linguistic	Thank you for your answer.
37.	**OGYEI 3**	8	between 242-243	We recommend to amend the following sentence. Original: "TEMPLATE OF A PROTOCOLE FOR AEG OR OTHER" Modified: "TEMPLATE OF A PROTOCOL FOR AEG OR OTHER"	☐ major ☐ minor ☒ linguistic	Thank you, this has been modified.
38.	**ASSR 8**	10	297	Not sure a glossary of terms is a wise choice, as they are always incomplete. Maybe better have a list of abbreviations?	☐ major x minor ☐ linguistic	During the previous consultations, some of the partners suggested to add a glossary which might help to better understand the use of the terms into the document. Some acronyms have been added.
39.	**SNHTA 15**	10	299	Wording: "… procedure **to ensure** that one or more parties…"	☐ major ☐ minor ☒ linguistic	Thank you, this has been modified.

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40.	**SNHTA 16**	10	301-302	Please clarify: Double blinding implies that 2 people are being blinded – not three or four as suggested here. There is no consensus which two people are being blinded and hence this should be specified in any protocol.	☐ major ☒ minor ☐ linguistic	Thank you, the text has been integrated. Since there is no consensus which two people are being blinded, this should be specified in any protocol.
41.	**OGYEI 4**	10	308	We recommend to amend the following sentence. Original: "a product/therapy used as a reference a in a clinical study (…)" Modified: "a product/therapy used as a reference in a clinical study (…)"	☐ major ☐ minor ☒ linguistic	Thank you, this has been modified.
42.	**HVB 9**	10	342	RCTs are	☐ major ☐ minor ☒ linguistic	Thank you, this has been modified.
43.	**OGYEI 5**	12	361	An overall table/graph about the different elements (core/additional) could help to understand which elements are considered core and additional.	☐ major ☒ minor ☐ linguistic	Thank you for the suggestion, an image has been integrated (page 15).
44.	**Xavier Fournie**	12	362	The list of all elements of a study protocol is presented in a format which is different from current existing EU regulatory guidances for Non-interventional studies, especially when study is qualifying as a PASS. Accordingly, the bibliography given page 20 refers to EMA/623947/2012 (line 683)	☐ major ☒ minor ☐ linguistic	Thank you for the suggestion, we agree and this has been integrated.

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				and ENCePPP guidance (685). Considering that some AEG studies can be non-interventional with safety as a main objective, this could generate questions on which format and content is to be preferred/used in such case. Therefore it may be valuable to add line 362 the following information: "The list of all elements as presented in sections 1.3.1 to 1.3.3 is intended to cover both interventional and non-interventional study designs and different study objectives. It is not necessarily a standard format for the protocol presentation but rather the elements which should be addressed in a study protocol for AEG. According to study type and objectives, the use of a specific protocol presentation format may be required by regulation and regulatory guidance (e.g. when study qualifies as a PASS)."		
45.	**OGYEI 6**	12	364-406	This listing (1.3.1.) does not contain the following elements: title (1.3.2.), feasibility of the study (1.3.3.), project management (1.3.3.).	☐ major ☒ minor ☐ linguistic	Thank you, this has been modified and integrated.
46.	**OGYEI 7**	12	382	Like in the former element (research method), the subsections of Statistical aspects could be written in a listed form: Statistical aspects: • Sample size calculation • Statistical analysis	☐ major ☐ minor ☒ linguistic	Thank you, this has been modified.

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47.	**OGYEI 8**	12 17	386 581	The titles of the subsection are not consequent. Here is: Study procedures and *methods* to avoid bias In the section 1.3.3. : Study procedures and *procedures* to avoid bias	☐ major ☐ minor ☒ linguistic	Thank you, this has been corrected.
48.	**OGYEI 9**	13	408	The dot (“.”) is missing (1.3.2).	☐ major ☐ minor ☒ linguistic	Thank you, this has been corrected.
49.	**OGYEI 10**	13-19	411-666	The writing of the sentences is not coherent. Sometimes the dot (“.”) is missing at the end of the sentences, sometimes not.	☐ major ☐ minor ☒ linguistic	Thank you, this has been corrected in the whole section.
50.	**VASPVT 3**	13	412-413	SYNOPSYIS SYNOPSIS	☐ major ☐ minor ☒ linguistic	Thank you, this has been corrected.
51.	**HVB 10**	13	424	Thank you very much for this clear and important remark, it is very clear and we will use it.	☐ major ☐ minor ☐ linguistic	Thank you.
52.	**SNHTA 17**	13	436	Grammar: “… in **the** light of **the** current…”	☐ major ☐ minor ☒ linguistic	Thank you, this has been modified.

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53.	**SNHTA 18**	13	441	Grammar: "… preferable **to** on-going…"	☐ major ☐ minor ☒ linguistic	Thank you, this has been modified.
54.	**SNHTA 19**	13	441-442	1. The study doesn't necessarily have to be preferable. It can also simply cover aspects not yet addressed in on-going studies. 2. You may have different scenarios regarding on-going studies and it seems questionable whether necessary and helpful to depict them here: a. You can have **no** on-going studies b. You can have on-going studies, which are not worthwhile waiting for c. You can have on-going studies, worthwhile waiting for but which don't fill all the gaps d. You can have on-going studies, worthwhile waiting for and which would fill all the gaps Only in the last case no AEG would be warranted.	☐ major ☒ minor ☐ linguistic	The discussion on whether an AEG should be warranted or not normally takes place before the protocol is drafted. That is why we think that the protocol itself should not provide guidance but should contain an explanation of why **the given study** is preferred to on-going (including the possibility that it is covering aspects not yet addressed by on-going studies). We have added a footnote with examples of different scenarios, but a complete guidance - eligibility criteria for AEG of a technology, including considerations on ongoing studies, can be found within: "EUnetHTA, Description of Criteria to select and prioritize health technologies for additional evidence generation. July 2012".
55.	**HVB 11**	13	449	448-449 Sorry, I found it difficult to understand- the rationale should be the basis and the purpose based on the rationale, right???	☐ major ☐ minor ☐ linguistic	The research question should be consistent with the rationale explained below. We have redrafted the sentence.

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56.	**OGYEI 11**	13	450	A reference for PICO format would be useful – for example an appendix or bibliography.	☐ major ☒ minor ☐ linguistic	Thank you, this has been added in the glossary.
57.	**HVB 12**	14	454 And the followi ng	I would suggest to use bullet points, as it has been done before.	☐ major ☐ minor ☐ linguistic	We used this format since it can be easily visualized within the text.
58.	**SNHTA 20**	14	461	Grammar: "…specified **whether** it is…"	☐ major ☐ minor ☒ linguistic	Thank you, this has been modified.
59.	**HVB 13**	14	465-66	? I think a word is missing	☐ major ☐ minor ☒ linguistic	Thank you, the sentence has been reformulated.
60.	**ASSR 9**	13	466	Could add another bullet point: clear commitment to dissemination of results, including publication (protocol in trial registries and full paper on results)	☐ major x minor ☐ linguistic	We feel nothing is missing; the information asked for seems to already be in the text within additional elements (page 21).

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61.	**ASSR 10**	14	456	"If appropriate...." ?? Once you get to the stage of writing a protocol, you cannot do without stating the study design	☐ major ☐ minor X linguistic	Thank you, we agree and this has been modified.
62.	**EFPIA 4**	14	456	This sentence has strange wording, as it implies that if inappropriate, then the plan and design should not be described. Suggest re-wording as follows *The overall study plan and design should be described briefly but clearly in this section. We recommend reference to EUnetHTA position paper on appropriate study design.*	☐ major ☐ minor ☒ linguistic	Thank you for your suggestion, the sentence has been reformulated.
63.	**EFPIA 5**	14	459-469	It might be helpful to break the guidance on the type of study into sections based on the study type. While an adequate description of requirements is given here for RCT type studies, there is very limited guidance on alternative types of studies, such as prospective vs retrospective observational, modelling and so forth. In addition, while the comment that RCTs are the highest quality interventional study is true, this should be balanced by the fact that RCTS are often the poorest quality studies with respect to generalization and real world impact of products (i.e. effectiveness). As the uncertainty problem being addressed by the AEG may be related to effectiveness there is a need	☒ major ☐ minor ☐ linguistic	As reported in the position paper on study design, the general starting point for efficacy\effectiveness gaps would be the selection of an RCT study design. It is true that RCT are biased by the fact that they involve selected subjects, but when the gap\uncertainty is about effectiveness, the most appropriate design would be a pragmatic RCT, which is based in the real practice. However this document has been developed to capture core elements independently by the type of study, so our attention was focused on that

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				to recognise this within in this section of the guidance and provide appropriate comments about study design requirements. This issue will likely require addressing throughout the protocol document.		aspect.
64.	**ASSR 11**	14	466	" and the rational for choosing ..." THE RATIONALE	☐ major ☐ minor X linguistic	Thank you, this has been corrected.
65.	**SNHTA 21**	14	466	Typo: "… rationale**…"**	☐ major ☐ minor ☒ linguistic	Thank you, this has been corrected.
66.	**SNHTA 22**	14	467	…specified **whether**	☐ major ☐ minor ☒ linguistic	Thank you, this has been modified.
67.	**SNHTA 23**	14	469	I think "cross-sectional" is the more common designation for this kind of study design	☐ major ☐ minor ☒ linguistic	Thank you, this has been modified.
68.	**SNHTA 24**	14	470	Add hyphen: mono-	☐ major ☐ minor ☒ linguistic	Thank you, this has been added.

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69.	**SNHTA 25**	14	473	Grammar: "bias" is uncountable: ie. it should be bias and not "biases"	☐ major ☐ minor ☒ linguistic	Thank you, this has been corrected.
70.	**OGYEI 12**	14	473-474	There is no subsection for "the limitations of the study", despite there are details on page 14 line 473-474, and 1.3.1. contains a limitation subsection.	☐ major ☒ minor ☐ linguistic	Thank you this subsection was a misprint and it was removed. These aspects are developed in the text.
71.	**ASSR 12**	14	477	Whatever the study design ... I would delete this	☐ major ☐ minor X linguistic	Thank you, this has been modified.
72.	**EFPIA 6**	14	486	You could also include indication and/or biomarker-related subgroups if there is a need to assess whether such subgroups might have a differential response.	☐ major ☒ minor ☐ linguistic	Thank you for your suggestion. We have redrafted the sentence including the possibility to define other specific subgroups.
73.	**SNHTA 26**	14	487	I would suggest not to call those subgroups "subgroups by gender". Those are gender specific conditions (just like prostate cancer in men). A subgroup by gender in my understanding would be male vs. female but in the examples you give it could be pregnant vs. non-pregnant women and you are not even interested in the other gender or you may compare pregnant women vs. non-pregnant women/men and then you have one group with a mix of genders – and the gender per se is not the driving force behind the subgroups.	☐ major ☒ minor ☐ linguistic	Subgroups might be defined by gender or by specific gender conditions and this has been added in the text.

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74.	**ASSR 13**	14	489	Suggest to report the flow chart of population selection and allocation	x major ☐ minor ☐ linguistic	Thank you, it has been added to the document. In particular, an example of flowchart has been added in section 2.
75.	**ASSR 14**	15	491	In this section ~~it seems useful to provide~~....a description of risks and benefits related to the study population SHOULD BE PROVIDED.	x major ☐ minor ☐ linguistic	Thank you, it has been reformulated.
76.	**HVB 14**	15	496	I would suggest to reword: these risks might be covered by.. (I think risks might be "avoided" rather than prevented or you can "meet" a risk but not "prevent it" as such??!	☐ major ☐ minor ☒ linguistic	Thank you, this has been modified.
77.	**HVB 15**	15	520	… and a link to clinical relevance given…	☐ major ☐ minor ☒ linguistic	Thank you, this has been reformulated.
78.	**SNHTA 27**	15	521	The Cochrane handbook (chapter 5.4.1) uses the term clinical outcomes in the same sense as you have defined it in the glossary and separates it from surrogate outcomes. Calling surrogate outcomes "surrogate **clinical** outcomes" is confusing in my opinion.	☐ major ☒ minor ☐ linguistic	According to Cochrane handbook, outcomes in the text are defined as surrogate outcome and clinical outcome.
79.	**ASSR 15**	15	525	" -- helpful to describe alternatives rejected" "... HELPFUL TO DESCRIBE REJECTED ALTERNATIVES"	☐ major ☐ minor X linguistic	Thank you, this has been corrected.

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80.	**OGYEI 13**	15	532	The 10th footnote is not completed.	☐ major ☐ minor ☒ linguistic	Thank you, this has been completed.
81.	**SNHTA 28**	17	586	Grammar: …, and analyzing…	☐ major ☐ minor ☒ linguistic	Thank you, this has been modified.
82.	**SNHTA 29**	17	587	Typo: "… outcome parameters…" OR "…outcomes, parameters and…"	☐ major ☐ minor ☒ linguistic	Thank you, this has been corrected.
83.	**HVB 16**	18	651	I would suggest to reword employed	☐ major ☐ minor ☒ linguistic	Thank you, this has been modified.
84.	**OGYEI 14**	20	688	Is there any availability of these guidelines? (online or published)	☐ major ☒ minor ☐ linguistic	They can be found online at https://www.seattlechildrens.org/doc/guidelines-for-protocol-writing.doc
85.	**ASSR 16**	General section 2	General section 2	Very clear and well written: takes into account all relevant aspects. My major suggestion is to highlight more the role of the evidence profiling and mapping, which is at the basis of declaring and proving the evidence gaps (I might be biased by the fact that this is how I tend to do it : -)		Thank you for your suggestion.

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86.	**SNHTA 30**	General section 2	General section 2	We want to put into question the clinical relevance of 5 mmHg as primary outcome for the treatment of resistant hypertension. 1. We consulted a hematologist posing the question of clinical relevance of a 5 mmHg reduction within the context of treatment resistant hypertension. He confirmed the evidence as presented in the literature: a 5 mmHg change has no clinical relevance short-term and that its clinical relevance long-term is unclear. 2. In addition, the change in blood pressure is a surrogate/indirect outcome. Direct outcomes of the presumed increased cardiovascular risk in people with resistant hypertension are cardiovascular-related mortality and morbidity. For these outcomes the available evidence is currently absent and too little, respectively. Finally: the available evidence is inconsistent as to whether renal RD is superior to standard of care (medical therapy) to treat resistant hypertension. Given the uncertainty of the clinical relevance of a 5 mmHg blood pressure change to reduce cardiovascular risk, the indirectness of the outcome as such and the lack of superiority evidence of RD versus optimal medical treatment for this outcome, blood pressure reduction of ≥ 5 mmHg should be reconsidered as the primary outcome for this study. NOTE I: RD seems a rather drastic treatment given		This issue was already discussed between authors and reviewers: 1. The clinically meaningful value of 5 mmHg is supported by literature (Bhatt, 2014; Whelton, 2002) and confirmed by a small panel of clinicians that we have consulted. 2. Assessing cardiovascular mortality and morbidity is important to directly evaluate cardiovascular risk reduction for patients with resistant hypertension. It is also true that for these outcomes the evidence is currently absent or too little, respectively, however their assessment would require a large scale and long-term study. Taking into consideration BP reduction outcome and looking at the available evidence, it can be observed that there is an evidence gap. It is also interesting the fact that BP reduction is usually accepted as surrogate endpoint for fatal and non-fatal cardiovascular diseases. However, beyond the fact that BP

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				the uncertainties associated with its clinical efficacy evidence. NOTE II: The fact that most clinical RD studies present a change in blood pressure as a surrogate outcome of decreasing cardiovascular risk in patients with resistant hypertension, does not exempt us from questioning this outcome as primary outcome for assessing efficacy and safety of RD. NOTE III: We asked ourselves whether this discussion was held among the contributors/authors. And if yes, how their conclusion and choice came about.		reduction gives an indirect measure of the reduction in cardiovascular risk, it is the first outcome that needs to be firmly proved considering the existing evidence gaps. The choice of this outcome was shared and discussed with a small panel of experts in the field and this proposal has to be surely confirmed by a larger panel of experts. We underline that the second section of the document is an exercise on a chosen technology in need of AEG and thus it should help to test if we really captured all core elements in the section 1. We have redrafted some of the parts of the rationale section (section 2) in order to better explain the choice of the outcome.
87.	**ASSR 17**	21	707	Web links to the two papers could be added	☐ major x minor ☐ linguistic	Links to the two position papers have been added in the bibliography.
88.	**ASSR 18**	21	710	"...existing HTA report" it is actually a Rapid Relative Effectiveness Assessment using HTA Core Model	☐ major ☐ minor X linguistic	Thank you, this detail has been modified in the footnote.

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89.	**SNHTA 31**	21	723	GRADE assesses the quality of the evidence not of individual studies	☐ major ☒ minor ☐ linguistic	GRADE was applied to evaluate the quality of the evidence. In particular, we evaluated the quality of the updated studies since the previous ones were already assessed in the HTA report.
90.	**VASPVT 4**	22	747-748	SYNOPSYIS SYNOPSIS	☐ major ☐ minor ☒ linguistic	Thank you, this has been corrected.
91.	**HVB 17**	22	759-761	I is not clear to me- "optimal" dosing might not be the highest tolerable dose?!	☐ major ☐ minor ☒ linguistic	This sentence has been reformulated.
92.	**SNHTA 32**	22	776	If you allow that sleep apnoea may be a co-morbidity but untreated OSA (obstructive sleep apnoea) needs to be excluded prior making the diagnosis of treatment-resistant hypertension then it might be worthwhile to defined when OSA is "sufficiently treated" for those patients to be considered	☐ major ☒ minor ☐ linguistic	In the inclusion criteria, we have reported that secondary forms of hypertension (including OSA) have to be excluded. The definition when OSA is "sufficiently treated" is out of scope.
93.	**HVB 18**	23	789	I would suggest to reword: as an accepted		Thank you, this has been modified.
94.	**HVB 19**	23	792	I would suggest to reword "impact" instead of importance		Thank you, this has been modified.
95.	**ASSR 19**	23	813	In my opinion, before the literature overview and update, the EVIDENCE PROFILE, needs to be stated and explained.(Appendix 3 Rationale and Evidence Profile at page 68). This is important because it makes the whole analysis transparent, by stating -	x major ☐ minor ☐ linguistic	Thank you, it has been modified according to this proposal.

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				before looking at the evidence - what is necessary to know to assess the technology (it is a core part of the whole endeavour). So I suggest to move the table from the appendix to here.		
96.	**HVB 20**	23	830	What does "imparted" mean here?		In this study (Bhatt, 2014) it means that the effect of renal denervation was not significant between-groups, but if considering only non-African American patients, renal denervation **caused** a statistically significant reduction in systolic BP compared with control (p=0.012)."
97.	**VASPVT 5**	24	852-854	Left ventricular hypertrophy was assessed in four published studies, but left ventricular mass was measured differently, so maybe there is a need to specify the measurement in Core protocol.	☒ major ☐ minor ☐ linguistic	Tools to be used to measure outcomes have to be discussed with experts, and are out of scope of this exercise.
98.	**ASSR 20**	25	899	Again before going on to explain the rationale of the study, the summary of the available evidence against the Evidence Profile is a necessary step to sustain what is argued afterwards. It is by showing the mapping of the evidence that evidence gaps become evident (suggest to move here table of Appendix 3 page 69: results of literature review charted on the evidence profile.	x major ☐ minor ☐ linguistic	Thank you. As already stated, the text has been modified according to this proposal.

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99.	**ASSR 21**	25	911	As the authors point out, the choice of the surrogate outcome as primary outcome might turn out to be controversial. The insertion of the evidence mapping, as suggested above, could help to show in a more immediate way the reasons for this choice. The discussion on the population characteristics of the ongoing studies is also interesting . May be some of these comments should be better reflected in the inclusion criteria, as at the moment do not seem very different from those of ongong studies. If this is a crucial aspect maybe population of trial should be more painstakingly described. Should they be recruited only in highly specialized hypertension treatment centres?	x major ☐ minor ☐ linguistic	The reported elements (selection of patients in hypertension specialized centers, optimization of the drug therapy prior to randomization, monitoring of the adherence) are already mentioned within the document.
100.	**HVB 21**	25	917	I would suggest to specify what is meant with "some details"		The details we meant are for example the selection of patients in hypertension specialized centers, the optimization of the drug therapy prior to randomization, the monitoring of the adherence. This information seems already to be in the text.
101.	**SNHTA 33**	26	Table	Change "contrasting" to contradictory or inconsistent depending on how important you deem the differences between the results	☐ major ☐ minor ☒ linguistic	Thank you, this has been modified.
102.	**VASPVT 6**	27	964	Sodiumintake diet sodium intake diet	☐ major ☐ minor ☒ linguistic	Thank you, this has been corrected.

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103.	**VASPVT 7**	27	986-987	Description of subgroups, of risks and benefits to subjects, early withdrawal criteria as well as further ethical considerations all require additional expertise, and are therefore out of scope of this exercise. Description of subgroups is not always necessary, so in page 14 (lines 486–488) should be written "If needed".	☒ major ☐ minor ☐ linguistic	Thank you, it has been added to the document.
104.	**VASPVT 8**	29	1055-1069	Secondary outcome also could be "Change in left ventricular mass (for left ventricular hypertrophy)"	☐ major ☒ minor ☐ linguistic	This outcome has been added.
105.	**SNHTA 34**	29	1057ff	Might it be worthwhile to look at the percentage of patients with controlled hypertension (i.e. BP <140/90)?	☒ major ☐ minor ☐ linguistic	The outcomes reported here have been defined on the basis of the evidence profile, which is based on a systematic literature review. Other outcomes might of course be valuable, but do not arise from this exercise.
106.	**ASSR 22**	29	1058	The clinically significant difference of 5 mmHg could be made explicit in the list of outcomes	x major ☐ minor ☐ linguistic	We analyzed in more detail what is clinically significant for the primary outcome; further insights might be provided also for secondary outcomes, but for the moment they are considered out of scope for this exercise.
107.	**ASSR 23**	30	1125	Why is it suggested to exclude drop outs?	x major ☐ minor ☐ linguistic	This was an error. It has been removed.

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108.	**VASPVT 9**	31	1136-1137	Patients are followed for 2 years and blood pressure measurements are performed at baseline and after 6 months. at baseline and after every 6 months.	☐ major ☒ minor ☐ linguistic	Thank you, this was a typo. Patients are followed for 2 years and blood pressure measurements are performed at baseline and after each 6 months.
109.	**ASSR 24**	31	1137	How do you justify main analysis at only 6 months and not also at 12 months ?	x major ☐ minor ☐ linguistic	Thank you for this comment. Patients are followed for 2 years and blood pressure measurements are performed at baseline and after each 6 months. Difference in BP reduction from baseline to 6 months has been considered as primary outcome. The evaluation of the outcome at 12, 18, 24 months has been considered as secondary outcome.
110.	**VASPVT 10**	60	1613	low - high ? unclear If there is an explanation of signs, maybe it could be after every table. However, every sign (+ - ?) should be explained.	☐ major ☐ minor ☒ linguistic	A legend has been added.
111.	**HVB 22**	61	Table 4	I am sorry, for me it is not clear in how far it can be stated that it is “no serious imprecision”, would it be possible to but this in a positive rather than a negative wording?		The wording of the GRADE profiles has been reported according to the wording of the GRADE profile in the EunetHTA report.
112.	**ASSR 15**	68 + 69		Move the two tables from Appendix 3 to the main text (see above)	x major ☐ minor ☐ linguistic	Thank you, it has been moved.

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