WP5 Strand B: 2nd Pilot Draft Project Plan - Summary of public consultation comments and responses

Comments received from:

- Okke-Jaap Bosgra (Johnson& Johnson)
- François Houÿez (Eurodis)
- Michael J Lee (Beaumont Hospital)
- Gerard Goh & Anna-Maria Belli (St George's NHS Trust)
- GIUSEPPE MANCIA (University of Milano-Bicocca)
- JOSEP REDON (UNIVERSITY OF VALENCIA)
- Antonio Coca (University of Barcelona)
- Bettina Maringer (HVB)

Answered but no comments: -

Comment #	Comments received from	Page	Section	Comment	Author's Reply
1	**Okke-Jaap Bosgra (Johnson&Johnson)**	3	1	We believe that only one external reviewer is not enough given the potential European impact. We would recommend contacting more than 1 and when relevant to contact also necessary European medical societies in this specific case interventional cardiologist, interventional radiologist etc. to reflect different countries dimensions. Selection criteria for choosing external reviewer could be added.	Agreed. We will include clinical experts for external review that are representatives of acknowledged clinical societies.
2	**Okke-Jaap Bosgra (Johnson&Johnson)**	3	2	What are the rules that make a technology/procedure to be eligible to rapid core HTA? We would suggest creating explicit rule. See comments above.	Agreed. This important issue will be brought up for discussion at a general level. For this review, we have now included all the 5 systems (5 manufacturers). We would like to emphasize that these rapid reviews are pilots aimed at testing and learning.

3	**Okke-Jaap Bosgra (Johnson&Johnson)**	4	1	What are the criteria for choosing the competitors? It is not clear to us.	As above (Comment #2). In this assessment all 5 manufacturers will have the possibility to submit their documentation.
4	**Okke-Jaap Bosgra (Johnson&Johnson)**	4	1	We would also suggest that the technology is compared to the drug therapy ("standard of care"). Through the text clarification on what is competitor and comparator needs to be sorted out as we found it confusing.	Agreed. "No denervation" is now replaced by "standard of care".
5	**Okke-Jaap Bosgra (Johnson&Johnson)**	4	1	We also suggest re-phrasing following sentence "it is suggested that competitors should be approached …" A rule should exist to define how to reach to all competitors. This approach should not be subjective or different from one assessment to another. We suggest contacting all competitors that have product on the market with CE mark.	This sentence is now deleted.
6	**Okke-Jaap Bosgra (Johnson&Johnson)**	4	1	We think that competitors should be consulted otherwise the validity of any resulting report will be called into question. We also understand that the type of engagement is dependent on the type of a review performed: product-specific vs. therapy review.	As above (Comment #2). In this assessment all 5 manufacturers will have the possibility to submit their documentation.
7	**Okke-Jaap Bosgra (Johnson&Johnson)**	4	3	We believe that this section is unclear as already mentioned here above we would recommend that a more considered and comprehensive review would be undertaken, considering all potential RND technologies, with the review considering a) whether the procedure has value, and if so, then b) which of the available technologies are safe,	As above (Comment #6). No cost evaluation will be done in this rapid review nor for any of the reviews in the WP. Safety and clinical effectiveness will be assessed, and the need for future research will be covered in the discussion.

				effective, and then c) for future RND technologies, what do they need to demonstrate to be considered safe and effective as those covered under 'b)'.	
8	**Gerard Goh & Anna-Maria Belli (St George's NHS Trust)**	4	Stakeholders	Stakeholders should include the Cardiovascular and Interventional Society of Europe and the European Society of Hypertension	Agreed. We will do so.
9	**JOSEP REDON (UNIVERSITY OF VALENCIA)**	4		A document missed, coming from the European Society of Hypertension, is the following: Schmieder RE, Redon J, Grassi G, Kjeldsen SE, Mancia G, Narkiewicz K, Parati G, Ruilope L, van de Borne P, Tsioufis C. ESH position paper: renal denervation -an interventional therapy of resistant hypertension. J Hypertens. 2012. May;30(5):837-41. doi: 10.1097/HJH.0b013e328352ce78. PubMed PMID: 22469838.	In what sense is this reference "missed" in the project plan? A systematic literature search will be performed, which should catch up this article. If this will be included or not in the assessment will depend on what type of publication it is, what type of study it reports etc…(i.e. if it satisfies the inclusion criteria).
10	**JOSEP REDON (UNIVERSITY OF VALENCIA)**	4		Among the non-renal denervation, the pharmacologic treatment is the adequate. Comparison with stimulation with the Rheos System, baroreceptor stimulation, is not appropriate since it is a experimental therapy today, less developed that the renal denervation.	Agreed. "Rheos System" is now deleted.
11	**Okke-Jaap Bosgra (Johnson&Johnson)**	5	Table 3	Whilst it might be justifiable to undertake either a procedure or a product review, the aim and rationale should be clearly stated. We would recommend that a more considered and comprehensive review be undertaken, considering all potential RND technologies, with the review considering a) whether the procedure has value, and if so, then b) which of the available technologies are safe, effective, and then c) for future RND technologies, what do they need to demonstrate to be considered safe and effective as	Agreed. As above (Comment #2). In this assessment all 5 manufacturers will have the possibility to submit their documentation.

				those covered under 'b)'. Without prejudice - If it is a product review, and the comparator is "No renal denervation", then we suggest the comparator is flawed. Clearly Symplicity is not the only option for patients; the choice is not between No renal denervation or Symplicity – the clinical decision is between No renal denervation and RND. Then, if RND is selected, the choice is between available products. Therefore IF you are undertaking a product review, then other RND systems HAVE to be comparators. Therefore, there should be no question to approaching them for their comments – if you are working with Medtronic, you must also approach other system providers too. However, if it is a potential 'procedure-based' review, (which we believe it should be in the first instance), then the scope should be open to all manufacturers to submit evidence. However it appears from your scope that you have only had discussions with one company in arriving at the draft scope, and so the activities undertaken so far are biased towards one manufacturer's participation in the process, even though there are several brands available on the market at this time. If it is to be product specific review, then the reason for selecting only one product from those commercially available should be justified, otherwise it appears as you are clearly favoring one company without explanation. If industry were to exclude all other competitors, we would be accused of bias. Again – this questions the appropriateness of the	

				"rapid" (and so incomplete) approach to this HTA project. For Strand B to be useful in the European space, it must recognize and address the differences between pharmaceuticals and other medical technologies. We also think that if the evaluation is product specific it should be stated what is the recommendation/consequences/requiremens for other manufacturers of the same product.	
12	**Okke-Jaap Bosgra (Johnson&Johnson)**	5	Comparison	If the comparison is no renal denervation, are the other technologies compared to pharmacological treatment too?	"No renal denervation" has been deleted and changed to "standard of care".
13	**Okke-Jaap Bosgra (Johnson&Johnson)**	5	Outcomes	We suggest that you look primarily at blood pressure decrease according to the indication mentioned in the intervention chapter ("thereby causing a reduction in blood pressure"). There is a validated correlation between blood pressure level and cardiovascular morbidity / mortality. Considering realistically the feasibility of clinical studies to evaluate the therapies, primary outcomes should not be "overall mortality and cardiovascular morbidity". Those outcomes would require a long term study of several years and a very high number of patients.	Acknowledged, but would like to keep mortality and morbidity as primary outcomes. We perfectly understand the limitations of providing data on mortality at this point, hence this needs to be stated in the review. Blood pressure decrease now figures as primary outcome in the project plan.
14	**Okke-Jaap Bosgra (Johnson&Johnson)**	5	Study design	We think that all important clinical studies should be considered despite the fact that they have or not RCTs. Maybe different studies investigate different aspects and different objective. There is not just enough evidence from RCTs. Registries and databases are important sources too.	We understand the concern however we do not state that we only will look at RCTs. However, if RCTs provide sufficient evidence of high quality for a particular outcome, we will report data from these. "Importance" of a study is perceived differently among stakeholders. Agree that registries and databases also are

					important sources.
15	**Okke-Jaap Bosgra (Johnson&Johnson)**	5	Languages	What if the report is done in a language not familiar to the authors and co-authors?	We believe that any data worth being reported will at least have some kind of abstract or a summary available in one of the languages we have included. If translation is needed, we will do so.
16	**François Houÿez (Eurodis)**	5	3	In the definition, clarification as below: Patients with treatment-resistant arterial hypertension (defined as persisting hypertension despite administration of at least three antihypertensive drugs of different classes in adequate doses including a diuretic) with blood pressure ≥ 140/90 mm Hg (Calhoun 2008) and without secondary cause of hypertension. ICD-10 code: Hypertensive diseases I10 - I15	Authors do not see what this comment is about. This is what is written in the project plan. (We hope we did not miss anything).
17	**Gerard Goh & Anna-Maria Belli (St George's NHS Trust)**	5	Table 3	The procedure (renal artery denervation) as a whole should be assessed not an individual device. It is illogical to assess one device when are many CE marked renal denervation devices available that work along the same principle as the Symplicity device. Furthermore the Symplicity device is a 'generation 1' device that is soon to be superceeded by the simplicity spiral and there are several other 'generation 2' devices already CE marked that are technologically advanced compared with the simplicity. Assessing one device would seem to be anti competitive under EU competition law and several HTA bodies would want assessment of more than one device.	Agreed. As above (Comment #2). In this assessment all 5 manufacturers /technologies will have the possibility to submit evidence.

18	**Gerard Goh & Anna-Maria Belli (St George's NHS Trust)**	5	Table 3	The primary stated outcomes are currently not available in the literature. To date there is no longer term study that has examined these parameters apart from complications during or after the treatment. Furthermore it would take years for large studies to undertake these primary outcomes to produce meaningful results. Blood pressure should be stated as including office and ambulatory 24 hour blood pressure measurements.	Acknowledged, but would like to keep mortality and morbidity as primary outcomes. We perfectly understand the limitations of providing data on mortality at this point, hence this needs to be stated in the review. Blood pressure decrease now figures as primary outcome in the project plan.
19	**JOSEP REDON (UNIVERSITY OF VALENCIA)**	5		The criteria to select patients is to vague, imprecise and will include patients that do not require the procedure. Patients to be denervated should pass first a step by step protocol which include to rule out spurious BP elevation, systematic checking of factors that can maintain BP high and a protocol with medical therapeutic approach.	This comment relates more to how a proper trial should be carried out (recruitment etc.). These issues will be covered in the assessment.
20	**JOSEP REDON (UNIVERSITY OF VALENCIA)**	5		It will be very difficult to collect information about morbidity and mortality endpoints, this will require a large follow-up. As a primary endpoint, Blood pressure should be included and measured with 24-hour ambulatory BP monitoring. Secondary endpoints can be surrogate markers of organ damage in the heart (LV mass and LA volume, microalbuminuria, eGFR and pulse wave velocity.	Acknowledged, but would like to keep mortality and morbidity as primary outcomes. We perfectly understand the limitations of providing data on mortality at this point, hence this needs to be stated in the review. Blood pressure decrease now figures as primary outcome in the project plan.
21	**Okke-Jaap Bosgra (Johnson&Johnson)**	6	4	Adaptation from Cochrane and Nock checklist assessment tools the quality of systematic review should be justified.	The most commonly accepted and used source today is the Cochrane Handbook. It has its limitations but this is what we have so far. The SR-checklist can certainly be improved, and we agree that subjectivity cannot be excluded. This is why we need to state clearly on what basis we have

					given a certain score, for instance, so that we remain verifiable and transparent. ICTRP includes Clinicaltrial.gov.
22	**Bettina Maringer (HVB)**	6	4	SRs of high quality will be included: Add the definition of high quality/ score.	See Comment #21.
23	**Okke-Jaap Bosgra (Johnson&Johnson)**	6	4	How is high quality of SRs defined? We suggest to pick one SR check-list accepted everywhere otherwise each SR will potentially have a different level of quality.	See Comment #21.
24	**Okke-Jaap Bosgra (Johnson&Johnson)**	6	4	We would expect to see Clinicaltrial.gov database among the literature search	See Comment #21.
25	**Okke-Jaap Bosgra (Johnson&Johnson)**	6	4	Information should be asked to all manufacturers of renal denervation therapies.	Agreed. As above (Comment #2). In this assessment all 5 manufacturers will have the possibility to submit their documentation.
26	**Okke-Jaap Bosgra (Johnson&Johnson)**	7	Responsibilities	"Establish contact with the manufacturer": At what stage of the project this is done. Is it only one manufacturer or all manufacturers producing the technology? "Involve clinical expert(s)": what are the criteria to determine the experts? How the choice will be justified? We would recommend contacting more than 1 and when relevant to contact also necessary European medical societies in this specific case interventional cardiologist, interventional radiologist etc. to reflect different countries dimensions.	Agreed. This is to be stated more in detail in the next reviews in the WP. The stage is at the initial stage, i.e. right from the beginning, which was done in our case with RDN and Medtronic. Now that all 5 manufacturers are involved at the same level following SAG and public consultation of the project plan, we think we have done what can be done to get on track in this regard (for this review). Ad "clinical experts": Agreed. We will include clinical experts for external review that are representatives of acknowledged

					clinical societies.
27	**Okke-Jaap Bosgra (Johnson&Johnson)**	9	Table 5	We recommend that class assessment is performed (see our general comments) so the wording is changed accordingly e.g. following needs to be deleted: “and what are the evidence based alternative” (Page 10, Section 4.0, Table 5, B0001)	Agreed. This is now a class assessment. Agreed. Where appropriate, research questions have been reformulated.
28	François Houÿez (Eurodis)	9	4	Lines A0024 and A0025 seem to be duplicates	Correct. A0025 is now deleted.
29	**Okke-Jaap Bosgra (Johnson&Johnson)**	10	Table 5, B0004	Who diagnose should be put into context with A00024 and A00025	Agreed. We need to refer to these result cards in the review.
30	**Okke-Jaap Bosgra (Johnson&Johnson)**	10	Table 5, B0009	We suggest to change “supplies” to “material”	“Supplies” is now replaced by “materials”.
31	**Okke-Jaap Bosgra (Johnson&Johnson)**	10	Table 5	Effectiveness is written sometimes with capital letter.	This is how the tool for the HTA Core Model presents the questions. But agree of course and will take this editing issue on board in future developments.
32	**Okke-Jaap Bosgra (Johnson&Johnson)**	11	Table 5, C0002	An equivalent of the “Dose-response” parameter is relevant and should be rephrased for the medical devices strand. For each device there may be a relevant dimension to qualify and quantify with a potential effect on safety and/or effectiveness. In the case of RDN this may be the amount of energy provided to a renal nerve. This needs to be further defined.	Agreed. This is reformulated in the project plan.

33	**Okke-Jaap Bosgra (Johnson&Johnson)**	11	Table 5, C0007	The manufacturer provides the device and advises to the user but does not act directly on the patients; therefore the manufacturer behavior should not be mentioned.	Is this for sure in all cases? If manufacturer behavior is irrelevant in this case, we will state so in the assessment.
34	**Okke-Jaap Bosgra (Johnson&Johnson)**	13	Table 7	We are surprise to see the 3 consultations at the same time: 1. Manufacturer 2. SAG and 3. Public. Eucomed would expect they would be sequential reviews.	Acknowledged, and will be brought into further discussions and developments within the WP. We have planned a different consultation process of the draft project plan in the future. There will only be public consultation. All comments received by public consultation will be made public within 1 month.
35	François Houÿez (Eurodis)	13	Table 6	For social and legal aspects, one question could be: if the intervention requires highly specialised surgery teams or a procedure that is not used in all Member States, or within one Member State not in all regions, it could happen that patients apply to use their rights for cross-border care to receive the medical intervention in a different country than the country of affiliation. In this case, social (reimbursement, including travel and accommodation) and legal (legal liability) consequences should be considered.	Acknowledged. We will see to that these aspects are covered in the discussion. In addition, we would like to discuss this as issues to be included in the Model.
35	**Okke-Jaap Bosgra (Johnson&Johnson)**	13,14		Manufacturer should be given appropriate time to provide information and clarification on the issue.	Agreed. More time will be given.
37	**Okke-Jaap Bosgra (Johnson&Johnson)**	14	Table 7	7 day period is not enough to review the draft report. We would suggest minimum of 2 weeks for the consultation. We would want to add section on how the comments/suggestions will be discussed and	Agreed. Same comment as for Comment # 35.

				added to the draft report.	
38	**Okke-Jaap Bosgra (Johnson&Johnson)**	15	7	Does one manufacturer will be asked for further information or all the contacted manufacturers?	All contacted ones (all 5 manufacturers).
39	**Antonio Coca (University of Barcelona)**	16		Add a new reference: 2013 ESH/ESC Guidelines for the management of arterial hypertension. J Hypertens 2013;June online. Concerning the draft of the proposal, the only reference of the paper of David Calhoun "Resistant hypertension: diagnosis, evaluation, and treatment: a scientific statement from the American Heart Association Professional Education Committee of the Council for High Blood Pressure Research" published in Circulation 2008;117(25):e510-26 is not enough (it was published 5 years ago). We must add a new reference of the most recent and important Hypertension Guidelines concerning this issue: The European Guidelines.	Agreed. Reference is now added.

40	**Okke-Jaap Bosgra (Johnson&Johnson)**	**general**		As stated in many comments of Eucomed before we believe that in general it is not possible to apply a pharma model to medical devices. We support the underlying concept from EUnetHTA to separate the review of pharmaceuticals from medical devices, through the separate strands of WP5 as Strands A & B. Whilst we support the principle of the need to demonstrate the value of medical technologies, the process and methods need to be fit for purpose. We have been raising awareness of the contextual issues for medical devices for a while, and are pleased that the EUnetHTA process has started to recognize this. We do however feel that the processes so far put in place under Strand B do not fully appreciate the issues, and appear to miss some of the most critical ones. As such we would ideally seek a meeting between the industry and EUnetHTA representatives to discuss the issues in a more generic way. However in the meant-time we reference the issues below in response to the specific consultation on Renal Sympathetic Denervation. The rationale for undertaking this review as "rapid" assessment is unclear and potentially unjustified, and we would support a more robust and comprehensive review of the procedure and potential technologies available. Referring to previous comments submitted in response to the April SAG Strand B consultation, we reiterate that the concept of "rapid HTA" of this technology at this point in time makes little sense. Indeed, it actually is counter-intuitive given the other reviews already publically available. The 'Strand A' rapid REA of	Agreed. This is a pilot (with what it implies in terms of need for improvements). Apparently changes/adjustments are needed to fit devices. Ad "We do however feel…": Agreed. Again, this test (pilot) raises a series of questions of principles, which need to be brought further at a general level. Ad "rapid": we agree that this might not be a suitable term, at least when thinking rapid in the sense of "urgent", as for pharmaceuticals. However, assessments should be produced in a timely manner, since national/local reports based on these assessments need to address questions relevant for decision-makers at time-points relevant for them.

				pharmaceuticals have a clear objective: providing guidance in a timely manner alongside the EMA regulatory path, and potentially as the first REA published among member state associations. The rapid review proposed here however has no such benefits. As you indicate from your GOOGLE search, there are already 4 HTA reviews published. "Urgency" therefore cannot be claimed as a key driver in this review. If a combined EUnetHTA review is justified, surely it is from a considered, well-evidenced based approach encompassing all relevant view-points, technologies, and adhering to HTA best practices? A rushed, incomplete review, as would likely be the result of this proposed approach, is unlikely to provide a comprehensive and insightful addition to the current evidence base. It is our consideration that the protocol proposed is therefore not fit for purpose. We are not however suggesting that a review is not warranted. We would recommend that a more considered and comprehensive review be undertaken, considering all potential RND technologies, with the review considering a) whether the procedure has value, and if so, then b) which of the available technologies are safe, effective, and then c) for future RND technologies, what do they need to demonstrate to be considered safe and effective as those covered under 'b)'. We recognize this is a significant departure from you original proposal. However we have been trying to air the issue that it is not possible to simply lift expectations, procedures, and methods from pharmaceuticals and apply	

				them without consideration to other technologies. This proposal has highlighted some of the issues. We are willing to work with you to identify an appropriate path forward. EUnetHTA should be striving to set new methods and demonstrating leadership in best practice in HTA. This is a clear opportunity to do so in the field of non-drug medical technologies, and we hope the opportunity is seized.	
41	**Michael J Lee (Beaumont Hospital)**	general		Ideally, the program should cover all new devices for renal denervation and not just one device. I believe, that there are now 5 or 6 devices that are CE marked. Other technologies such as AV fistula creation (Rox coupler) and others	Agreed. All products available on the market are now included. AV fistula creation (Rox coupler) does not seem to be a RDN procedure, but an alternative treatment (which is included as comparator in the PICO). Thus this should be covered.

42	Michael J Lee (Beaumont Hospital)	general		The endpoint of cardiovascular events or mortality will be very difficult to arrive at without long term follow-up. These technologies are relatively new. Effect on hypertension would be a more reasonable endpoint.	Acknowledged, but would like to keep mortality and morbidity as primary outcomes. We perfectly understand the limitations of providing data on mortality at this point, hence this needs to be stated in the review. Blood pressure decrease now figures as primary outcome in the project plan.
43	Michael J Lee (Beaumont Hospital)	general		Multidisciplinary entry of patients into these new treatments would be best to prevent self-referral. These new treatments should be limited to trials until more information is obtained	Acknowledged, but we do not see how this comment may affect the project plan of this review.
44	**Gerard Goh & Anna-Maria Belli (St George's NHS Trust)**	general		When the report finds that there is not much available evidence there is no indication of possible recommendations (eg more RCTs, combination of trials etc.). The National Institute of Health and Care Excellence, UK, has examined this topic and produced a document in April 2012. http://guidance.nice.org.uk/IPG418	This review will not provide any kind of recommendations. We will include a section in the discussion on need for further research and refer to ongoing trials.
45	**GIUSEPPE MANCIA (University of Milano-Bicocca)**	general		Emphasis should be given to assessment of renal denervation as a therapeutic approach, rather than to differences between devices. The latter is premature	The review is now a class review (5 manufacturers) on the effect of renal denervation/renal nerve ablation for drug-resistant hypertension.
46	**GIUSEPPE MANCIA (University of Milano-Bicocca)**	general		Choice of Endpoints: This is a difficult and highly debated issue. I agree that assessing the beneficial effect of renal denervation on events (morbid, not only legal events) is difficult. Yet, it is an easy prediction that there will be a growing pressure from the scientific community (and as a reflection from the regulatory agencies) to do something because a) this has been required for drug treatment b) blood pressure reduction is a good	Acknowledged, however mortality and morbidity *are* the primary outcomes. Blood pressure decrease is mainly what has been recorded so far, so this is what we have to report then. We perfectly understand the limitations of providing data on mortality at this point, hence this needs to be stated in the review.

				but not an infallible biomarker of events and c) other biomarkers, e.g. changes in organ damage function or structure are under discussion because data on their predictive ability are inconsistent. Pressure will be applied also because being resistant hypertension a high risk condition a trial might involve a relatively limited number of patients for a not too long follow-up.	
47	**GIUSEPPE MANCIA (University of Milano-Bicocca)**	general		Comparator: Comparing the effect of renal denervation with a background baroreceptor stimulation makes no sense.	Agreed. Deleted.
48	**JOSEP REDON (UNIVERSITY OF VALENCIA)**	general		The project should be considered the evaluation of a therapy (RDN) and not a device since several devices are today available with rapid technological development.	Agreed. The review will now be a class review (see comments above).