#	Section/Page	Comment NIPH-AGENAS	Reply/Action by AGENAS and NIPHNO teams – October 2017
1	2.0 PROJECT INTRODUCTION/ RATIONALE Pag.8	Patricia Harrington: As noted in e-meeting, would be concerned about restricting the assessment to just devices from these two companies. Ideally should be class-based assessment including all CE-marked products. Obviously, the SR may only find RCT evidence to support some of the products, but commentary can be added to the effect that the evidence may not be applicable to other devices. In Europe there are at least 8 different TAVI valves approved for use; although it is noted that the Edwards Lifesciences balloon expandable Sapien 3 valve and the Medtronic Evolut self-expanding valve are the most commonly used valves.	IFU documents of all TAVI systems have been reviewed (Acurate, CoreValve, Direct Flow, JenaValve, Lotus, Portico, Sapien – as of today, Lotus is not on the market anymore). Excluding the two systems already identified during the preliminary analyses (CoreValve Evolut R and Sapien 3), all the other TAVI systems have specified within their IFU document that use is indicated in patients at high surgical risk. The meetings with manufacturers (representing 98% of the TAVI volume in Italy) held at Agenas on 5th July 2017 confirmed this situation. For the reasons above, we did not add all the TAVI systems within the project plan (PP). Rationale is given in Table 3.0 of the PP.
2	Table 3. Project Scope: PICO Pag.9	Raatz Heike: There are a variety of other ICD-10 codes that might be relevant: e.g. Nonrheumatic aortic valve stenosis with insufficiency I35.2	The suggested code (I35.2) has been added to the table. Clinical experts reviewing the draft did not suggest other amendments.
3	Table 3. Project Scope: PICO Pag.10	Raatz Heike: 1)-What do we do when both are being used. In their review 2012 Sawaya et al, suggest that the EuroSCORE may overestimate the risk of valve replacement compared to STS. See also (see ESC Rosenhek)- May be check le medecin regarding the classification of EureoSCORE and its comparability to STS. 2)- Not sure what the newer studies used but there is a new score available since 2011.	1) The issue of the scores used within the clinical studies will be discussed within the assessment, when study selection will be completed. As a general rule for study selection, we will consider any study in which the authors defined an “intermediate risk population”, regardless the score used. 2) STS, EuroSCORE II, and logistic EuroSCORE I are the only tools mentioned within the latest ESC/EACTS guidelines (2017).
4	Table 3. Project Scope: PICO Pag.10	Patricia Harrington:	1) See reply to comment #1

		1)-again, need to be certain that these are the only relevant devices Raatz Heike: 2)- Should we consider subgroups depending on the risk assessment tool used for risk assessment (see comment above?)	 2) If available data will allow it, subgroup analysis depending on the risk assessment tool will be performed.
5	Table 3. Project Scope: PICO Pag.12	Raatz Heike: 1)-Is it possible to pre-define those subgroups? 2)- There seems to be a lot of overlap in the outcomes chosen (e.g. 30 day mortality in the effectiveness will include the perioperative mortality from the safety domain, how do you differentiate between procedure related adverse events, device success, device-related adverse events, durability of the device and performance of the device). You risk loosing a lot of power because you differentiate between so many composite outcomes related to the device. I would suggest checking whether these outcomes are not similar enough for pooling and possibly doing subgroup analyses rather than splitting them right at the start. It would also facilitate weighing the pros and cons. 3)- Given that you use GRADE you should also pre-define the importance of the outcomes (critical, important, not so important) 4)- What do you mean with “rehabilitation” as an outcome? That would be an intervention for me or do you mean “recovery from symptoms”?	1) Subgroups will not be pre-defined within the PP as they will depend on the included studies. 2) Outcomes list has been reviewed and simplified following comments and suggestions from dedicated reviewers and clinical experts. 3) Outcome rating is relevant only during development of recommendations. This context is limited to retrieve and rate the evidence. 4) Removed.

6	Table 3. Project Scope: PICO Pag.12	Raatz Heike: 1) Aortic valve re-interventions would also be counted among the serious adverse events as you have a surgical intervention due to complications / device failure. 2) Judging whether and adverse event is related to a procedure or intervention is very arbitrary and may differ significantly between studies. I think it is important to assess ALL adverse and serious adverse events. 3) Why only major vascular complications? If we want to limit this then we should be clear that we only want to look at Serious Adverse events? I would look at both though ALL adverse events and ALL serious adverse events. If you are dead you don't care whether your physician thinks that this is related to the procedure or not. 4) See comment regarding the procedure related adverse events - 5) Degeneration of the device may be an even more important issue in patients with only intermediate surgical risk – especially if they are younger (see appended document EuroPCR 2016, may be worthwhile to check for a full publication) 6) Durability would be an effectiveness outcome. For it to be a safety issue it should be something like "device failure", which is just a surrogate outcome for adverse events or SAE if an re-operation is necessary.	1) Amended. 2) Amended. 3) Amended. 4) Amended. 5) The outcome defined as "aortic valve re-intervention" will include events related to degeneration of device and device failure. 6) The outcome defined as "aortic valve re-intervention" will include events related to degeneration of device and device failure.

		7) Performance also sounds like an outcome of effectiveness. And how do you differentiate it from device success? I suspect that there may be a lot of overlap with the other outcomes as mentioned above.	7) New outcomes has been added: “Procedural success” and “Haemodynamic function of the valve”.
7	Table 3. Project Scope: PICO Pag.13	Raatz Heike: 1)-Do you mean the consensus paper in the European Journal of Cardio-Thoracic Surgery? That is from 2012 pS45-S60	1) The proper reference was added: Piazza N, Kalesan B, van Mieghem N, et al. A 3-center comparison of 1-year mortality outcomes between transcatheter aortic valve implantation and surgical aortic valve replacement on the basis of propensity score matching among intermediate-risk surgical patients. .JACC Cardiovasc Interv. 2013 May;6(5):443-51.
		Eva Godske Friberg: 2)-Radiation dose and risk is normally not included in RCTs. Other types of studies need to be included to address this issue. Separate search for studies covering radiation dose and risk.	2) Amended.
		Lauvrak Vigdis: 4) We have been discussing if we should include studies of data from prospective registries to ensure real world safety data. We have seen from the latest publications of registry data that there has been a trend towards using TAVI for an intermediate risk population. Have you discussed this. To restrict workload: We might refer to selected registries from the SAF domain and use in the CUR/TEC domain and comment on this in the discussion	4) Agreed. Studies from selected registries will be used in CUR domain final discussion.

8	4.0 PROJECT APPROACH AND METHOD Pag.13	Eva Godske Friberg: Include questions on typical doses to patients and staff related to the different procedures (echography vs. fluoroscopy) and four approaches (TF, S/T, TA, TaO)	Amended.
9	4.0 PROJECT APPROACH AND METHOD Pag.14	Raatz Heike: 1)- Registries from any country? That could mean a lot of work if there are many registries and data may not be relevant for Europe. 2)- How do you choose your literature? I am not an expert in qualitative research but there are also criteria for when you stop looking for further studies.	1)-2)- Inclusion will be limited to data from national registries in line with PICO (i.e., studies were data on safety outcomes from a medium risk population may be extracted). We consider these studies as best available real world data on adverse events.
10	4.0 PROJECT APPROACH AND METHOD Pag.15	Raatz Heike: But if you do that then the list of outcomes you have defined may be completely different from that of the systematic review you plan to update? I would have thought that there are not many RCTs to be expected on patients with intermediate operative risk given that it was only recently given the okay by the FDA – why don't you simply search for RCTs in the first place? (The systematic review from 2016 in the BMJ by Siemieniuk only included 4 trials).	Outcomes list has been reviewed and simplified following comments and suggestions from dedicated reviewers and clinical experts. The description of methodology has been amended.
11	4.0 PROJECT APPROACH AND METHOD Pag.17	Raatz Heike: How do you classify the types? By manufacturer?	The term "type" was used as synonym of "model". Clarified within the text.
12	4.0 PROJECT APPROACH AND METHOD Pag.18	Raatz Heike: May be extract co-morbidities? The ejection fraction always seems to be an important clinical factor for	Amended.

		the operative risk and in deciding regarding the management.	
13	AE Safety Pag.23	Raatz Heike: This question implies that we don't just look at device or procedure related side effects as I suggested above.	Amended.