Transcatheter aortic valve implantation (TAVI) in patients at intermediate surgical risk

Project ID: OTCA06

Project description and planning

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Contents:

A. VERSION LOG

Each (significant) modification should be marked with a new *version* number (Vx). Minor modifications may be marked within versions (Vx.y). *Each new version to be communicated with the project team.*

Version number	Date	Name (Initials)	Modification	Reason for the modification
V1	06/06/17	NV	First draft	[e.g. change of participants]
V1.1	06/07/2017	NV, MC, IA, EC, AM	Advanced draft	Review after co-author involvement
V2	30/10/17	NV, FG, IA, MC, EC	Final draft	Review after Dedicated reviewer involvement
V2.1	07/11/2017	NV	Final version PP	Review of the timeline
V3	20/12/2017	NV	Reviewd version	Review of the timeline due to extended scoping phase and review of literature
V4	DD/MM/YY			
V5	DD/MM/YY			

B. PROJECT PLAN

1.0 PARTICIPANTS

All individuals actively participating in the project.

Table 1. Project participants

#	Agency	Country	Role in the project	Individual's expertise	Distribution of work
1.	Agenzia nazionale per i servizi sanitari regionali (Agenas)	Italy	Author(s)	Health technology assessment of medical devices	Develop the first draft of EUnetHTA project plan, amend the draft if necessary. Carry out the assessment (domains EFF and SAF): answer assessment elements, fill in checklist regarding potential "ethical, organisational, patient and social and legal aspects" of the HTA Core Model® for rapid REA (see table 6). Send "draft versions" to reviewers, compile feedback from reviewers and perform changes according to reviewers' comments (domains EFF and SAF).

					Prepare final assessment and write a final summary of the assessment.
2.	The Norwegian Institute of Public Health	Norway	Co-Author(s)	Health technology assessment of medical devices	Assist to develop the first draft of EUnetHTA project plan. Carry out the assessment (domains TEC and CUR): answer assessment elements, fill in checklist regarding potential “ethical, organisational, patient and social and legal aspects” of the HTA Core Model® for rapid REA (see table 6). Compile feedback from reviewers and perform changes according to reviewers’ comments (domains TEC and CUR). Perform structured literature search for domains EFF and SAF. Assist in preparation of final assessment and final summary.

3.	KCE	Belgium	Reviewer	Clinical evaluation	Review the draft and final version of the assessment
4.	Onassis Cardiac Surgery Centre	Greece	Reviewer	Interventional Cardiology	Review the draft and final version of the assessment
5.	HIQA	Ireland	Reviewer	HTA/ health service research	Review the draft and final version of the assessment
6.	SNHTA	Switzerland	Reviewer	Clinician, Clinical epidemiologist	Review the draft and final version of the assessment
7.	Regione Veneto	Italy	Reviewer	Pharmacists and health economists	Review the draft and final version of the assessment
8.	Norwegian Radiation protection authority (NRPA)	Norway	External Expert	Radiation protection	Radiation detriment/harm analysis
9.	External Experts: Gry Dahle Reidar Bjørnerheim Svein Færestrand	Norway	External Expert	• Cardiothoracic surgeon, • Radiologist, • Cardiologist	
10.		To be defined	Patient representative		
11.		To be defined	Medical Editor		
12.	Agenas	Italy	Project coordinator		Project coordination and management

1.1 PROJECT STAKEHOLDERS

Please describe/list project stakeholders♣.

♣ Here the term “stakeholder” has a generic meaning that goes beyond (yet may include) the identified EUnetHTA Stakeholder groups (as described in the EUnetHTA Stakeholder Policy).

If you are planning to assess a single technology, please provide the names of all relevant competitors. They will be informed about the assessment as well.

Table 2. Project stakeholders

Organisation's name	**Type of organisation**
Edwards Lifesciences	Manufacturer
Medtronic	Manufacturer

2.0 PROJECT INTRODUCTION/ RATIONALE

Project introduction/ rationale
The rationale for this assessment report is to produce joint assessments that are fit for purpose, of high quality, of timely availability, and cover the whole range of non-pharmaceutical health technologies. In addition, the implementation of the joint assessment in the national/regional practice will be facilitated.

3.0 PROJECT SCOPE AND OBJECTIVES

	List of project objectives	**Indicator (and target)**
1.	To produce joint health technology assessments that are fit for purpose, of high quality, of timely availability, and cover the whole range of health technologies.	Production of 1 rapid assessment according to the research question (see Table 3).
2.	To compile a rapid assessment of transcatheter aortic valve implantation (TAVI) in patients at intermediate surgical risk.	Production of a rapid assessment of the respective technologies. During the second semester 2016, two manufacturers have obtained expanded indications for their TAVI systems. For its CoreValve Evolut R system, Medtronic obtained approval for use in patients at extreme, high and intermediate surgical risk in Europe (CE mark), while Edwards Lifesciences obtained CE mark for its Sapien 3 transcatheter heart valve for patients who are at intermediate risk for death or complications associated with open-heart surgery. These

		new indications may be linked to a high diffusion of these systems and assessing their relative effectiveness in comparison to the conventional treatment (aortic valve replacement by open-heart surgery) is then urgent and necessary.
3.	To refine the production processes of jointly produced assessment reports based on lessons learned and experiences from JA2 and probe a stepped roll-out of additional collaborative assessments yielding timely information.	Development of sustainable production processes for jointly produced assessments. Production of collaborative assessments probing a decentralised coordination process and facilitating to meet national timelines.
4.	To develop a process that facilitates the implementation of the jointly produced assessment in the national/regional practice.	Production of >2 national/local reports based on the jointly produced assessment.

This rapid assessment addresses the research question whether transcatheter aortic valve implantation (TAVI) in patients at intermediate surgical risk is more effective and/or safer than aortic valve replacement (AVR) by open-heart surgery.

Table 3. Project Scope: PICO
For more information use the HTA Core Model® for rapid REA.

Description	Project scope
Population	ICD-10 code: I35.0 - Nonrheumatic aortic (valve) stenosis; I35.2 - Nonrheumatic aortic valve stenosis with insufficiency; I06.0 - Rheumatic aortic stenosis; Q23.0 - Congenital stenosis of aortic valve. MeSH-terms: C14.280.484.150, C14.280.955.249

	The population of interest in this report is represented by patients with severe aortic stenosis (AS) at intermediate risk for death or complications associated with open-heart surgical aortic valve replacement (SAVR). The indication should at least be defined by New York Heart Association Functional class (NYHA class), and either The Society of Thoracic Surgeons' risk model score (STS score), European System for Cardiac Operative Risk Evaluation (EuroScore) or EuroSCORE II.
Intervention	Transcatheter aortic valve implantation (TAVI) as a therapeutic intervention for the defined target population. The assessment will be restricted to systems with a CE mark for the defined population. MeSH terms: E04.100.376.485.500, E04.650.410.500, E04.928.220.410.500. TAVI consists of the insertion of a prosthetic valve which functionally replaces the damaged aortic valve, using fluoroscopic and echographically-guided minimally-invasive procedures. The prosthetic valve is compressed within a dedicated delivery system and, once in place within the diseased aortic valve, its deployment allows its expansion and the compression of the native diseased valve against the wall of the aorta. Depending on patient's anatomy and device characteristics, the procedure can be performed by four different approaches: the transfemoral (TF) route is the most common while the others are performed when patient's anatomy precludes access via TF route. These approaches are the

	subclavian/transaxillary (S/T) approach, the transapical (TA) approach, and the transaortic (TAo) approach. Subgroup analysis based on the risk assessment tool used, the TAVI system used (i.e., model-dependent), and the procedural approach (i.e., TF, S/T, TA, and TAo) will be performed if data will allow that.
Comparison	Aortic valve replacement (AVR) by open-heart surgery. AVR by open surgery may be performed using different approaches (full sternotomy and more minimally invasive procedures) and with different kind of valves and valve anchoring techniques (sutured and suture-less). Subgroup analysis based on comparator will be performed if possible. MeSH terms: E04.100.376.485, E04.650.410, E04.928.220.410 Rationale: Comparator has been chosen based on information from relevant published clinical guidelines [Vahanian 2012] and EUnetHTA guidelines [Therapeutic 2015; Endpoints 2015].
Outcomes	***Efficacy Outcomes:*** • Mortality at 30 days and at the longest follow-up (all cause mortality, cardiovascular mortality, noncardiovascular mortality); • Improvement of symptoms (reduction in NYHA class);

	• Improvement in health-related quality of life indicators (e.g., EQ-5D score, SF-12 score, KCCQ score); • Procedural success (i.e., successful valve implantation); • Haemodynamic function of the valve; • ICU length of stay (days); • Hospital length of stay (days); • Rehospitalisation for myocardial infarction (*>72 h following TAVI*); • Need for permanent pacemaker implantation. ***Safety Outcomes:*** • Any major or minor adverse event (e.g., Vascular complications; Stroke; TIA; Disabling or life-threatening bleeding; Aortic valve re-intervention; Myocardial infarction ≤72 h post-procedure; New or worsening atrial fibrillation or atrial flutter; Moderate or severe aortic valve regurgitation; Acute kidney injury; Pain). • Radiation detriments/harms both to patient and staff. Rationale: Outcomes have been chosen based on information from relevant published clinical guidelines [Vahanian 2012, Piazza 2013], and EUnetHTA guidelines [Therapeutic 2015; Endpoints 2015].
Study design	**Efficacy:** • Randomised controlled trials (RCTs)

	(the most recent systematic reviews/meta-analysis of RCTs will be used to retrieve potential eligible studies and compare overall results). **Safety:** • Randomised controlled trials (RCTs) *(the most recent systematic reviews/meta-analysis of RCTs will be used to retrieve potential eligible studies and compare overall results);* • Real world data derived from published studies from prospective European ntional registries.

4.0 PROJECT APPROACH AND METHOD

Table 4a. Project approach and method

Project approach and method
For all domains, the selection of assessment elements will be based on the HTA Core Model Application for Rapid Relative Effectiveness (REA) Assessments (ver.4.2). The checklist for potential Ethical, Organisational, Patient and Social, and Legal aspects of the HTA Core Model for rapid REA will be filled in as well. The selected issues (generic questions) will be translated into actual research questions (answerable questions). **TEC and CUR domains** The assessment elements of TEC and CUR domains will be answered based on: • Input from manufacturers. This will in particular relate to questions on CE mark, marketing, availability and current use. Questions regarding TEC and CUR assessment elements will be formulated by the co-author (NIPHNO). Manufacturers involvement will be managed by the author (AGENAS). Manufacturers structured questionnaire and answers will be shared with the co-author (NIPHNO).

- Input from clinical experts. Questions will in particular be related to description of disease, current treatment, current use and best available epidemiological data. Experts involvement will be managed by the co-author (NIPHNO). The appointed external clinical experts will be asked to review the Project Plan (PP), verify the relevance and accuracy of information and citations of assessment elements in TEC and CUR, review the assessment drafts.
- Response from EUnetHTA partners based on a survey. Questions will in particular be related to current use, number of hospitals and organizational arrangements. The survey will be managed by the co-author (NIPHNO) and the relevance of questions will be verified by the author (AGENAS).
- Clinical guidelines. A search for clinical guidelines will be performed by the co-author (NIPHNO). Sources will be Guidelines International (G-I-N) and NICE evidence. From these, information on current recommendations as well as citations of epidemiological data we will extracted.
- Updated information from publications of prospective national registry data. Major national registries will be identified as part of the systematic search for the SAF domain. From these, information on current use including number of procedures, age, sex and operative risk, and radiation dose to patients receiving TAVI will be extracted.
- Various background literature restricted to systematic reviews and narrative reviews from 2016 and later identified from various sources including the systematic search for the EFF and SAF domains.

Data will be presented as text and tables. All information will be provided by the co-author (NIPHNO) and checked by the author (AGENAS).

EFF and SAF domains

Systematic searches

To identify relevant studies, systematic searches of the following information sources will be performed:

- Cochrane Library, Centre for Research and Dissemination (CRD), Embase, Medline;
- *Ad hoc* internet-searches (from reference list of relevant studies).

To assess efficacy outcomes, potentially relevant RCTs will be identified first. The co-author (NIPHNO) will provide a sorted list of included and excluded titles and abstracts of potentially relevant trials identified by two independent researchers according to the defined inclusion criteria. The author (AGENAS) will check the study selection process and retrieve all relevant trials in full-text. The full-text examination will be performed by two independent researchers. The author (AGENAS) will provide a sorted list of included and excluded studies after full-text examination. The list will be checked by the co-author (NIPHNO). The most updated secondary studies (systematic reviews and HTA reports) will be used only to identify potentially relevant RCTs not identified through the searches described above and to compare results. Studies were a population of intermediate operative risk patients cannot be distinguished from inoperable, high risk or low risk patients will not be included. Included studies will be extracted in full-text and assessed for methodological quality.

To assess safety outcomes, “real world data” from prospective national registries will be considered in addition to RCTs if, for the specific safety outcome measures, data are comparative and presented at a longer follow-up than in the RCTs.
Publications from the last 4 years (2013-2017) will be considered. The following sources of information will be used:

- Embase; Medline; Cochrane Library,

The co- author (NIPHNO) will provide a sorted list of included and excluded titles identified by two independent researchers according to the defined inclusion criteria. Only the most updated publication from each registry reporting on the relevant subgroup of patients will be included. The author (AGENAS) will check the study selection process and retrieve all relevant studies in full-text. The full text examination will be performed by two authors independently. The author (AGENAS) will provide a sorted list of included study after full-text examination. The list will be checked by the co-author (NIPHNO). Data extraction of included studies will be performed by the author (AGENAS) and checked by the co-author (NIPHNO). Event rates will be presented as described in the publications. No meta-analysis or assessment of strength of evidence will be performed for event rates.
The analyses of the radiation dose and risk to patient and staff will be performed by NRPA. The following sources of information will be used to collect and present estimated doses and risks as available in literature:

- *Ad hoc* internet-searches (from reference list of relevant studies and articles).

To describe upcoming evidence, relevant ongoing RCTs will be identified by searching the following information sources:

- International Clinical Trials Registry Platform (ICTRP).

Assessment of methodological quality of included studies

Assessment of methodological quality of included studies will be performed by the author (AGENAS) and checked by the co-author (NIPHNO). Disagreements will be resolved by consensus. The methodological quality of included RCTs will be assessed in accordance with the criteria established by the Cochrane tool for assessing risk of bias [Higgins, 2011]. The following domains for the risk of bias will be considered: i) Random sequence generation (selection bias); ii) Allocation concealment (selection bias); iii) Blinding of participants and personnel (performance bias); iv) Blinding of outcome assessment (detection bias); v) Incomplete outcome data (attrition bias); vi) Selective reporting (reporting bias). In case of observational studies, the body of evidence will by default be rated as “low” but the quality can be upgraded based on the presence of the following three factors: (a) a strong or very strong association, (b) a dose–effect relationship, and (c) all plausible confounding may be working to reduce the demonstrated effect or increase the effect if no effect was observed [Abraha 2015].

Data extraction, analysis, presentation of results and assessment of strength of evidence

Data extraction will be performed by the author (AGENAS) and checked by the co-author (NIPHNO). If possible, a meta-analysis of the included RCTs will be performed. All analysis will be performed by the author (Agenas) and checked by the co-author (NIPHNO). Review Manager (Revman 5.3) will be used for data synthesis. Data will be pooled using both the random-effects model and the fixed-effect model to ensure robustness. Subgroup analyses will be performed based on TAVI model used and implantation technique. A table of findings will be prepared for presenting results coming from selected studies. Dichotomous outcomes results will be expressed as risk ratio (RRs). Where continuous scales of measurement are used to assess the effects of treatment, the mean difference (MD) will be used; the standardised mean difference (SMD) will be used if different scales have been used. All RRs, MDs and SMDs will be presented with 95% confidence intervals (CIs). Analysis will be performed according to an intention-to-treat principle.

For missing data, trial authors will be contacted or sensitivity analyses will be performed. Heterogeneity will be evaluated using a Chi^2 test with N-1 degrees of freedom, with an alpha of 0.10 used for statistical significance and with the I2 test [Higgins 2011]. Source of heterogeneity will be sought by assessing the participants, the intervention, the comparison group, and the outcomes and by visually assessing the forest plots. For time to event data (survival, freedom from adverse events), hazard ratios will be used to calculate the magnitude of effect. The hazard ratio and variance corresponding to the published survival data will be used. Where this will not be directly available from the published version the authors of the study will be contacted. Otherwise, hazard ratio and variance will be estimated using log rank P-value, number randomised, events, or survival curves where available [Tierney, 2007]. Where data are available cumulative event rate will be calculated. Assessment of the strength of evidence will be performed using “Grading of Recommendations, Assessment, Development and Evaluation” – GRADE approach. Disagreements will be resolved by consensus.

Table 4b. Preliminary Evidence

Preliminary evidence table – Primary studies Please provide information on what kind of data your planning to extract from the studies included. The following resources provide useful insights to presenting data in tabular format: The Cochrane Handbook for Systematic Reviews of Interventions, http://www.cochrane.org/training/cochrane-handbook and http://handbook.cochrane.org/ , particularly chapter 11.5 “Summary of findings tables” Sign 50: A Guideline Developer’s Handbook, http://www.sign.ac.uk/guidelines/fulltext/50/index.html NICE: The Guidelines Manual 2012, appendices J-K, http://publications.nice.org.uk/the-guidelines-manual-appendices-jk-pmg6c
Author, Year, Reference Number
Study Registration Number (Registry Identifier)
Country
Sponsor
Comparator

Number of Patients
Patient Characteristics (age, sex, risk score, NYHA class, comorbidities)
Inclusion Criteria
Follow-up Duration (weeks)
Loss-to-follow-up (n, %)
Access Approach
TAVI valve used (model and manufacturer)
Outcomes
Efficacy
Mortality at the longest follow-up (all cause mortality, cardiovascular mortality, noncardiovascular mortality);
Improvement of symptoms (reduction in NYHA class);
Improvement in health-related quality of life indicators (e.g., EQ-5D score, SF-12 score, KCCQ score);
Procedural success (i.e., successful valve implantation);
Haemodynamic function of the valve;
ICU length of stay (days);
Hospital length of stay (days);
Rehospitalisation for myocardial infarction (>72 h following TAVI);
Need for permanent pacemaker implantation.
Safety
Any major or minor adverse event (e.g., Vascular complications; Stroke; TIA; Disabling or life-threatening bleeding; Aortic valve re-intervention; Myocardial infarction ≤72 h post-procedure; New or worsening atrial fibrillation or atrial flutter; Moderate or severe aortic valve regurgitation; Acute kidney injury; Pain)
Radiation detriments/harms both to patient (skin burns and risk of cancer induction) and staff (induction of cataract, finger doses and risk of cancer induction).

Selected assessment elements

The table shows the assessment elements and the translated research questions that will be addressed in the assessment. They are based on the assessments elements contained in the 'Model for Rapid Relative Effectiveness Assessment'. Additionally, assessment elements from other HTA Core Model Applications (for medical and surgical interventions, for diagnostic technologies or for screening) have been screened and included/merged with the existing questions if deemed relevant.

Table 5. Assessment elements and translating research questions

ID	Topic	Topic Issue	Relevance in this assessment Yes/No	Research question(s) or reason for non-relevance of 'mandatory' elements
Description and technical characteristics of technology				
B0001	Features of the technology and comparators	What is the technology and the comparator(s)?	Yes	What is TAVI? What is the indication for this review? What are the current treatment alternatives for the indication (what are the comparator(s))? Are there different producers and models of equipment for TAVI? Are there different procedural approaches for TAVI? Are there different producers and models of equipment for the SAVR? Are there different procedural approaches for SAVR? Who administers TAVI and SAVR and in what context and level of care are they provided? What kind of special premises are needed to use TAVI and SAVR?
A0020	Regulatory Status	For which indications has the technology received marketing authorisation or CE marking?	Yes	For which indications has TAVI received marketing authorisation or CE marking?
B0002	Features of the technology and comparators	What is the claimed benefit of the technology in relation to the comparator(s)?	Yes	What is the claimed benefit of TAVI technology in relation to SAVR? What might be the potential harms or risks of the technology in relation to SAVR?
B0003	Features of the technology	What is the phase of development and implementation of the technology and the comparator(s)?	Yes	What is the phase of development and implementation of TAVI and SAVR?

ID	Topic	Topic Issue	Relevance in this assessment Yes/No	Research question(s) or reason for non-relevance of 'mandatory' elements
B0004	Features of the technology	Who administers the technology and the comparator(s) and in what context and level of care are they provided?	Yes	Overlaps with B0001, answer provided in B0001
B0008	Investments and tools required to use the technology	What kind of special premises are needed to use the technology and the comparator(s)?	Yes	Overlaps with B0001, answer provided in B0001
B0009	Investments and tools required to use the technology	What equipment and supplies are needed to use the technology and the comparator(s)?	Yes	Overlaps with B0001, answer provided in B0001
A0021	Regulatory Status	What is the reimbursement status of the technology?	Yes	What is the reimbursement status of TAVI across European countries?
Health problem and current use of technology				
A0002	Target Condition	What is the disease or health condition in the scope of this assessment?	Yes	What is severe aortic stenosis with intermediate risk for death or complications? How is the condition defined?
A0003	Target Condition	What are the known risk factors for the disease or health condition?	Yes	What are the known risk factors for the severe aortic stenosis?
A0004	Target Condition	What is the natural course of the disease or health condition?	Yes	What is the natural course of severe aortic stenosis?
A0005	Target Condition	What are the symptoms and the burden of disease or health condition for the patient?	Yes	What are the symptoms and the burden of severe aortic stenosis for the patient?
A0006	Target Condition	What are the consequences of the disease or health condition for the society?	No	Overlapping with A0004, no need for further explanation.
A0024	Current Management of the Condition	How is the disease or health condition currently diagnosed according to published guidelines and in practice?	No	Overlapping with A0002 and described there

ID	Topic	Topic Issue	Relevance in this assessment Yes/No	Research question(s) or reason for non-relevance of 'mandatory' elements
A0025	Current Management of the Condition	How is the disease or health condition currently managed according to published guidelines and in practice?	Yes	Are there European professional society guidelines describing best practice for treatment of severe aortic stenosis at intermediate operative risk?
A0007	Target Population	What is the target population in this assessment?	No	Same as target condition: A0002
A0023	Target Population	How many people belong to the target population?	Yes	How many people with severe aortic stenosis and intermediate operative risk are there in Europe?
A0011	Utilisation	How much are the technologies utilised?	Yes	How much is TAVI used in Europe?
A0020	Regulatory Status	For which indications has the technology received marketing authorisation or CE marking?	No	Described in the TEC domain
A0021	Regulatory Status	What is the reimbursement status of the technology?	No	Described in the TEC domain
Clinical effectiveness				
D0001	Mortality	What is the expected beneficial effect of the intervention on mortality?	Yes	What is the expected beneficial effect of TAVI on mortality (disease-specific and all-cause) in patients with severe aortic stenosis at intermediate surgical risk?
D0005	Morbidity	How does the technology affect symptoms and findings (severity, frequency) of the disease or health condition?	Yes	How does TAVI affect symptoms and findings (severity, frequency) of aortic stenosis?
D0006	Morbidity	How does the technology affect progression (or recurrence) of the disease or health condition?	Yes	How does TAVI affect progression of aortic stenosis?
D0011	Function	What is the effect of the technology on patients' body functions?	Yes	What is the effect of TAVI on patients' body functions?
D0016	Function	How does the use of technology affect activities of daily living?	Yes	How does TAVI affect activities of daily living?

ID	Topic	Topic Issue	Relevance in this assessment Yes/No	Research question(s) or reason for non-relevance of 'mandatory' elements
D0012	Health-related quality of life	What is the effect of the technology on generic health-related quality of life?	Yes	What is the effect of TAVI on generic health-related quality of life?
D0013	Health-related quality of life	What is the effect of the technology on disease-specific quality of life?	Yes	What is the effect of TAVI on disease-specific quality of life?
D0017	Patient satisfaction	Were patients satisfied with the technology?	No	Not relevant for the present assessment. TAVI and its comparator (conventional open-heart surgery) have very different level of invasiveness
Safety				
C0008	Patient safety	How safe is the technology in relation to the comparator(s)?	Yes	How safe is TAVI in relation to surgical aortic valve implantation?
C0002	Patient safety	Are the harms related to dosage or frequency of applying the technology?	Yes	Are the harms device-related?
C0004	Patient safety	How does the frequency or severity of harms change over time or in different settings?	Yes	How does the frequency or severity of harms change in different settings?
C0005	Patient safety	What are the susceptible patient groups that are more likely to be harmed through the use of the technology?	Yes	What are the susceptible patient groups that are more likely to be harmed through TAVI?
C0007	Patient safety	Are the technology and comparator(s) associated with user-dependent harms?	Yes	Are TAVI and surgical aortic valve implantation associated with user-dependent harms?
B0010	Safety risk management	What kind of data/records and/or registry is needed to monitor the use of the technology and the comparator(s)?	Yes	What kind of data/records and/or registry is needed to monitor the use of TAVI?

Checklist for patient and social aspects

The following checklist should be considered in order to determine whether there are specific ethical, organisational, social and legal aspects which also need to be addressed. Since the assessment is comparative in nature, only new issues should be dealt with, which arise from a difference between the technology to be assessed and its major comparator(s). Already known problems/issues with regard to ethical, organisational, social and legal aspects which are common to the technology to be assessed and its comparator(s) will, as a rule, not be addressed, as it is not to be expected that the addition of a new technology will lead to changes.
If a question is answered with 'yes', further analysis of these issues may be warranted. If they are answered with no, the domains need not be dealt with further.

Table 6. Checklist for potential ethical, organisational, patient and social and legal aspects.

1. Ethical	
1.1. Does the introduction of the new technology and its potential use/non-use instead of the defined, existing comparator(s) give rise to any new ethical issues?	No
If answered with 'yes', please provide a short statement explaining why. *Example:* Routine introduction of prenatal genetic screening tests, which could lead to pregnancy termination, may cause ethical issues for the couple as well as for the health-care provider.	
1.2. Does comparing the new technology to the defined, existing comparators point to any differences that may be ethically relevant?	No
If answered with 'yes', please provide a short statement explaining why. *Example:* The marketing authorisation holder claims that its product is superior, but has decided to limit the amount of the new medicine, which means that it has to be rationed and not all patients who need it can receive it. The comparator is freely available.	
2. Organisational	
2.1. Does the introduction of the new technology and its potential use/non-use instead of the defined, existing comparator(s) require organisational changes?	Yes

If answered with ‘yes’, please provide a short statement explaining why. The intervention requires: A broader surgical heart team involving more radiologists; surgical back up; hybrid operating rooms/suites or catheterisation laboratory facilities; increased radiations exposure of staff/personnel.	
2.2. Does comparing the new technology to the defined, existing comparator(s) point to any differences that may be organisationally relevant?	Yes
If answered with ‘yes’, please provide a short statement explaining why. The intervention may lead shorter length of hospital stay and rehabilitation, this may lead to excess capacity in relevant areas.	
3. **Social**	
3.1. Does the introduction of the new technology and its potential use/non-use instead of the defined, existing comparator(s) give rise to any new social issues?	No
If answered with ‘yes’, please provide a short statement explaining why. *Example:* A new technology allows patients to return to the workplace, but since the technology can be seen by co-workers, it may lead to stigmatisation.	
3.2. Does comparing the new technology to the defined, existing comparator(s) point to any differences that may be socially relevant?	No
If answered with ‘yes', please provide a short statement explaining why. *Example:* A technology, which is widely used by persons with abuse problems, colours the tongue blue, thus, immediately identifying the user. Comparators do not have this property.	
4. **Legal**	
4.1. Does the introduction of the new technology and its potential use/non-use instead of the defined, existing comparator(s) give rise to any legal issues?	No
If answered with ‘yes’, please provide a short statement explaining why.	

Example: The comparator for the new technology is a pharmaceutical that is not licensed for the indication of concern, but is widely in use.	
4.2. Does comparing the new technology to the defined, existing comparator(s) point to any differences that may be legally relevant?	No
If answered with 'yes', please provide a short statement explaining why. *Examples:* • The comparator for the new technology is a controlled, restricted substance, but the new medicine is not. • The most appropriate comparator for the new technology is available as a pharmacy-compounded medicine, but not as a finished product with marketing authorisation. *Note:* The assessment should not address patent-related issues.	

5.0 ORGANISATION OF THE WORK

5.1 MILESTONES AND DELIVERABLE(S)

Table 7. Milestones and Deliverables

Milestones/Deliverables	**Start date**	**End date**
Project duration	**08/05/2017**	**15/03/2018**
Scoping phase	**08/05/2017**	**30/06/2017**
Identification of manufacturers and external experts; *optional: identification of patients*	[08/05/2017]	[08/05/2017]
Scoping and development of draft Project Plan incl. preliminary PICO	01/06/2017	10/06/2017

Share the preliminary PICO with external experts *(and patients)* for comments	10/06/2017	25/06/2017
Internal Scoping e-meeting with the assessment team	10/06/2017	30/06/2017
Scoping (e-) meeting with manufacturer(s) (optional)	*[DD/MM/YYYY]*	*[DD/MM/YYYY]*
Send the preliminary PICO for comments (in case there is no scoping meeting planned) and the request for the completion of the Submission file template to manufacturer(s) (optional)	[DD/MM/YYYY]	[DD/MM/YYYY + 5 working days]
Consultation of draft Project Plan with dedicated reviewers	30/06/2017	15/07/2017
Consultation of draft Project Plan with external experts *(and patients)* and fact check by manufacturers	20/06/2017	30/10/2017
Amendment of draft Project Plan & final Project Plan available	15/07/2017	30/10/2017
Completion of Submission file template by manufacturer(s) + Clarifying further questions concerning draft Submission file) (optional)	*[DD/MM/YYYY]*	*[DD/MM/YYYY + at least 30 working days]*
Assessment phase	[DD/MM/YYYY]	[DD/MM/YYYY]
Writing first draft rapid assessment	30/10/2017	19/01/2018
Review by dedicated reviewer(s)	19/01/2018	30/01/2018
Writing second draft rapid assessment	01/02/2018	07/02/2018
Review by ≥ 2 external clinical experts and fact check by manufacturers	07/02/2018	20/02/2018
Writing third draft rapid assessment	20/02/2018	23/02/2018
Medical editing	23/02/2018	28/02/2018
Writing of final version of rapid assessment	01/03/2018	07/03/2018
Formatting	07/03/2018	10/03/2018
Final version of REA		15/03/2018
Local Reports (if applicable)		
Local (national or regional) REA N°1 [*Institution, country*]		
Local (national or regional) REA N°2 [*Institution, country*]		

5.2 MEETINGS

An e-meeting may be held with the pilot team during the Scoping phase. Whenever needed, further e-meetings can be scheduled.

6.0 COMMUNICATION

Please define the communication requirements for the project and how information will be distributed to ensure project success.
Here's an example of organisation of communication - please choose and edit those relevant and add other types as needed.
In case of several authors and co-authors we urge you to schedule e-meetings in temporal relationship with major milestones (e.g. finalization of project plan). The coordination team will assist in setting up e-meetings.

Table 8. Communication

Communication Type	Description	Date	Format	Participants/ Distribution
Scoping	To discuss and reach the consensus on the scoping. *As a preparation to the scoping meeting with manufacturers (optional).*	[DD/MM/YYYY]	E-mail	Author(s), co-author(s), CT
	To discuss scoping and further handling of the submission file by manufacturers, as a preparation to the scoping meeting with manufacturers (optional).	*[DD/MM/YYYY]*	*E-meeting*	*Author(s), co-author(s), dedicated reviewer(s), CT*
	To discuss and reach the consensus on the scoping, as a preparation for the final Project Plan (optional).	*[DD/MM/YYYY]*	*Face-to-face meeting*	*Author(s), co-author(s), CT, manufacturers*
Feedback on draft submission file (optional)	*To formulate clarifying questions on draft submission file before sending it to the manufacturers*	*[DD/MM/YYYY]*	*E-mail*	*Authors, Co-authors, CT*

	To point out the requirements for the final submission file by manufacturers	*[DD/MM/YYYY]*	*E-mail*	*CT, manufacturers*
Draft Project Plan with timelines	Review of methods and assessment elements chosen, discussion of time-lines	[DD/MM/YYYY]	E-mail (e-meetings to be planned here - optional)	Author(s), Co-author(s), dedicated reviewer(s), CT
Final Project Plan	Review of methods and assessment elements chosen, discussion of time-lines.	[DD/MM/YYYY]	E-mail (e-meetings to be planned here - optional)	Author(s), Co-author(s), dedicated reviewers, CT
First draft of the rapid assessment	To be reviewed by dedicated reviewer(s)	[DD/MM/YYYY]	E-mail (e-meetings to be planned here -optional)	Dedicated reviewer(s)
	To discuss comments of dedicated reviewers (optional)	[DD/MM/YYYY]	E-Mail (e-meetings to be planned here -optional)	Author(s), co-author(s), dedicated reviewers
Second draft of the rapid assessment	To be consulted with ≥2 clinical expert	[DD/MM/YYYY]	E-mail	≥2 clinical experts (other potential stakeholders)
Final rapid assessment	Medical editing by external editor	[DD/MM/YYYY]	E-Mail	Medical Editor

6.1 DISSEMINATION PLAN

The final rapid assessment will be distributed as laid-out in the Work Plan of WP4.

7.0 COLLABORATION WITH STAKEHOLDERS

Please describe the planned stakeholder involvement in the project.
The 2nd draft version of the assessment will be reviewed by external experts, and there will be a fact check by manufacturers.

Collaboration with other stakeholders

Whenever feasible, please describe any foreseen collaboration with other stakeholders (e.g. European Federations of Physicians or/and Patients).

8.0 COLLABORATION WITH EUnetHTA WPs

For the individual rapid assessment, no collaboration with other WPs is planned.

9.0 RESOURCE PLANNING

Please estimate the expected input in terms of human and financial resources necessary to achieve the project objectives.

9.1 HUMAN RESOURCES

Table 9. Human resources

Role	Total number of person days	Source	
		Staff of participating organisations	Subcontracting
Author	60 person days	60 person days	-
Co-Author	60 person days	60 person days	-
Reviewer	5 person days each	5 person days each	-
External reviewer	5 person days each	-	5 person days each
Medical Editor	10 person days	-	10 person days
Layout	5 person days	-	5 person days

10.0 CONFLICT OF INTEREST MANAGEMENT

Conflicts of interest will be handled according to EUnetHTA JA2 Conflict of Interest Policy. As conflict of interest may be topic dependent, conflict of interest declarations will be collected from authors and reviewers involved in a specific assessment via the Declaration of interest and confidentiality undertaking (DOICU) form. Authors and reviewers who declare a conflict of interest will be excluded from parts of, or the whole work under this specific topic. However, they may still be included in other assessments.

If external experts are involved in WP4 a conflict of interest declaration will be collected from them regarding the topic. External experts who declare a conflict of interest will be excluded from parts of, or the whole work under this specific topic. However, they may still be included in other assessments.

11.0 EXPECTED OUTCOME(S)
Please briefly describe the expected project outcomes, i.e., changes that occur as a result of the project when the objectives are reached.

Project outcome(s)
Joint assessments that are fit for purpose, of high quality, of timely availability, and cover the whole range of non-pharmaceutical health technologies will have been produced. These assessments will have been used in the national/local context. Production processes for joint assessment reports will have been refined based on lessons learned and experiences from JA2. The decentralized approach for producing collaborative assessments will have been probed. The implementation of joint assessments in the national/local context will have been facilitated.

C. REFERENCES

Please include any documents supporting the project rationale/implementation in numbered format.

Marquis-Gravel G, Redfors B, Leon MB, Généreux P. Medical Treatment of Aortic Stenosis. Circulation. 2016;134:1766–1784.

Vahanian A, Alfieri O, Andreotti F, et al. Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC) European Association for Cardio-Thoracic Surgery (EACTS). Guidelines on the management of valvular heart disease (version 2012). Eur Heart J2012;33:2451-96.

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

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Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Abraha I, Cruz-Jentoft A, Soiza RL, et al. Evidence of and recommendations for non-pharmacological interventions for common geriatric conditions: the SENATOR-ONTOP systematic review protocol BMJ Open 2015;5:e007488.

Tierney JF, Stewart LA, Ghersi D, Burdett S, Sydes MR. Practical methods for incorporating summary time-to-event data into meta-analysis. Trials 2007, 8:16.