Transcatheter implantable devices for mitral valve repair in adults with chronic mitral valve regurgitation

Project ID: WP5-SB-15

Project description and planning

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Contents:

A. VERSION LOG

Version number	Date	Name (Initials)	Modification	Reason for the modification
V1	24/02/15	AM, MC, MRP, MH, TT	First version of a preliminary draft project plan.	-
V2	02/03/15	AM, MC, MRP, MH, TT	Amended draft after first e-meeting with pilot team.	Clarifications have been made after discussion among authors. Comments from pilot team have been considered and integrated.
V3	13/03/15	AM, MC, MRP, MH, TT	Amended draft after scoping meeting with manufacturers and internal discussion.	Changes have been made (mainly to the PICO) after discussion with manufacturers and among authors/co-authors. The draft has been finalised for dedicated reviewers' and external experts' review.
V4	27/03/15	AM, MC, MRP, MH, TT	Amended draft following comments by dedicated reviewers and external clinical experts.	Changes to the PICO and general improvements to the text have been made to increase clarity and readability. The draft has been finalised for public consultation.
V5	27/04/15	AM, MC, MRP, MH, TT	Final version of the Project Plan including amendments following comments received by public consultation.	Only minor amendments to increase clarity.

B. PROJECT PLAN

1.0 PARTICIPANTS

Table 1. Project participants

#	Agency	Role in the project	Individual's expertise	Country
1.	Agenzia Nazionale per i Servizi Sanitari Regionali (Agenas)	Author(s)	Biomedical engineering, medical devices, health economics	Italy
2.	Agency for Quality and Accreditation in Health Care and Social Welfare (AAZ)	Co-Author(s)	Clinical (physician-specialist in clinical pharmacology and toxicology) and methodological expertise (HTA and evidence-based medicine for SR on clinical effectiveness and safety)	Croatia
3.	Section of European Programmes and Projects -Ministry of Health of the Slovak Republic	Co-Author(s)	Health economics, methodological expertise (HTA)	Slovakia
4.	Avalia-t - Galician Agency for HTA	Reviewer	Biology, Pharmacy. Methodological expertise in evidence-based medicine, systematic reviews, health technology assessment reports and Clinical practice guidelines development	Spain
5.	French National Authority for Health (Haute Autorité de Santé) (HAS)	Reviewer	Medical devices and methodological expertise (health technology assessment, evidence-based medicine, clinical effectiveness and safety)	France
6.	Gesundheit Österreich GmbH (GÖG)	Reviewer	Methodological expertise (HTA, EBM), health economics	Austria

7.	Andalusian HTA Agency - Ministry of Equality, Health, and Social Services (AETSA)	Reviewer	Clinical (physician-specialist in preventive medicine and public health) and methodological expertise (HTA)	Spain
8.	Agency for Quality and Accreditation in Health Care and Social Welfare (AAZ)	Reviewer	Clinical (physician-specialist in clinical pharmacology and toxicology) and methodological expertise (HTA)	Croatia
9.	Health Information and Quality Authority (HIQA)	Reviewer	Methodological expertise (HTA)	Ireland
10.	Health Improvement Scotland (HIS)	Reviewer	Health Technology assessment; Systematic reviewing	Scotland
11.	NHS Lothian University of Bologna	External Reviewers	Cardiology Cardiology	Scotland Italy
12.	TBD	Medical Editor	Methodological expertise, medical writing	
13.	Ludwig Boltzmann Institute for HTA (LBI HTA)	Coordinating team	Project management	Austria

1.1 PROJECT STAKEHOLDERS

Table 2. Project stakeholders

Organisation	Contact (name, e-mail, tel)	Comments
Abbott Vascular International	Cullinganlaan 2B – 1831 Diegem – Belgium http://www.abbottvascular.com	The MitraClip® System has been selected for assessment as it received CE mark in 2008.
Cardiac Dimensions Inc.	5540 Lake Washington Blvd. NE Kirkland, WA 98033 http://www.cardiacdimensions.com	The Carillon® Mitral Contour System® has been selected for assessment as it received CE mark in 2011.
NeoChord Inc.	7700 Equitable Drive, Suite 206	The NeoChord DS1000 has been selected for

	Eden Prairie, MN 55344 http://www.neochord.com/	assessment as it received CE mark in 2013. The company has been contacted by the coordination team via telephone on the 17th of December and via e-mail on the 2nd, the 9th, the 12th and the 17th of December. No answer has been received. On 9th and 23rd March 2015, the company has been contacted again by e-mail and telephone. Information regarding the device has been submitted.

2.0 PROJECT INTRODUCTION/ RATIONALE

Project introduction/ rationale
The rationale for this pilot assessment is to test the capacity of national HTA bodies to collaboratively produce structured rapid core HTA information on pharmaceuticals (strand A) and other medical technologies, such as medical devices, surgical interventions or diagnostics (strand B). In addition, the application (translation) of those collaboratively produced HTAs in the national contexts will be tested**.**

3.0 PROJECT SCOPE AND OBJECTIVES

	List of project objectives	**Indicator (and target)**
1.	To test the capacity of national HTA bodies to collaboratively produce structured rapid core HTA	Production of 1 pilot rapid assessment according to the research question (see Table 3)
2.	To test the application of these collaboratively produced rapid assessments into a national/local context	Production of ≥1 national/local report per pilot rapid assessment.
3.	To compile a pilot rapid assessment of transcatheter mitral valve repair devices for the treatment of adults with chronic mitral valve regurgitation	Production of a pilot rapid assessment of the respective technologies. The topic has been proposed by one of the Italian regional partners of the RIHTA network (Italian network for HTA) and prioritised as “very relevant” by the RIHTA

		Prioritisation Committee. The rationale for the relevance lies on the high cost of the technology and on the potential risk of inappropriate and/or uncontrolled diffusion and extension of indications to a broader population.

The present pilot Rapid Assessment addresses two research questions:

i) Is transcatheter mitral valve repair by device implantation in adults with chronic primary mitral valve regurgitation who are surgical candidates more effective and/or safer than surgery?

ii) Is transcatheter mitral valve repair by device implantation in adults with chronic primary or secondary mitral valve regurgitation who are at high surgical risk or non-surgical candidates more effective and/or safe than pharmacological treatment (when indicated) with/without cardiac resynchronisation therapy (CRT)?

According to the Health Technology Assessment Core Model (HTA Core Model) for Rapid REA of Pharmaceuticals, the PICO and scope will be re-checked after the assessment of the first two domains *("Description and Technical Characteristics of the Technology", TEC, and "Health Problem and Current Use of Technology", CUR)*.

Table 3. Project Scope: PICO

Description	Project scope
Population	• *Mitral regurgitation (MR);* *ICD-10: I34.0 Mitral (valve) insufficiency;* *MeSH: Mitral Valve Insufficiency (C14.280.484.461); Mitral Incompetence; Mitral Insufficiency; Mitral Regurgitation; Mitral Valve Incompetence; Mitral Valve Regurgitation.* • *Adults with moderate-to-severe and severe primary/degenerative MR who are surgical candidate (i.e., NeoChord DS1000 population) and adults with moderate-to-severe and severe primary/degenerative MR or secondary/functional MR who are at high surgical risk or non-surgical candidates (i.e., Carillon and MitraClip population).* • *The interventions assessed are proposed to treat the condition.*

Intervention	Transcatheter mitral valve repair by device implantation in adults with chronic MR. *Three systems will be considered within the present assessment:* • *MitraClip System (Abbott Vascular) for leaflets repair;* • *CARILLON Mitral Contour System (Cardiac Dimensions) for annulus repair;* • *NeoChord DS1000 (NeoChord) for chordal repair.*
Comparison	*In patients with primary/degenerative MR who are surgical candidates, the use of the device NeoChord DS1000 will be compared to:* • *Surgery.* *In patients without heart failure, with primary/degenerative MR who are at high surgical risk or non-surgical candidates, the use of the device MitraClip will be compared to:* • *No pharmacological treatment.* *In patients with heart failure, with primary/degenerative MR who are at high surgical risk or non-surgical candidates, the use of the device MitraClip will be compared to:* • *Pharmacological treatment.* *In patients with secondary/functional MR who are at high surgical risk or non-surgical candidates, the use of the device MitraClip or the device CARILLON will be compared to:* • *Pharmacological treatment (in combination with or without CRT).* Comparators have been chosen based on CE Mark specific indications, information in published clinical guidelines for treatment of mitral valve regurgitation [1-3], EUnetHTA guidelines [4-7], and amended following comments from dedicated reviewers and external experts.
Outcomes	***Effectiveness****:* • *Primary outcomes: mortality (all-cause), cardiovascular mortality, need of cardiac transplantation, NYHA Functional Status improvement, freedom from NYHA ≥ 3, 6 minutes walking test (6MWT), reduction of hospitalisation rate, cardiovascular hospitalisation, need for mitral valve surgery,*

	quality of life. • *Secondary outcomes: improvements in echocardiographic outcomes (e.g., reduction in left ventricular volumes, improvement in left ventricular ejection fraction), procedural success rate.* ***Safety**:* • *Durability of the clip; short- and long-term adverse events (device-related as well as procedure-related): 1) any adverse event, 2) serious adverse events, 3) most frequent adverse events.* Outcomes have been selected based on the recommendations from the clinical guidelines for treatment of mitral valve regurgitation and the EUnetHTA Guidelines on Clinical and Surrogate Endpoints and Safety [1-3, 5-7] and amended following comments from dedicated reviewers and external experts.
Study design	***Effectiveness:*** • *Systematic reviews;* • *Health Technology Assessment (HTA) reports;* • *Randomised controlled trials (RCT);* • *Controlled clinical trials (CCT);* ***Safety (other than the designs already listed):*** • *Case series;* • *Medical devices adverse events registries;*

4.0 PROJECT APPROACH AND METHOD

Table 4a. Project approach and method

Project approach and method
Distribution of tasks among agencies: As Author, Agenas will: • Have a leading role in both scoping and production of the pilot; • Be responsible for management of the whole scientific work;

- Have ultimate responsibility for quality assurance;
- Answer comments.

As Co-authors, AAZ and MoH of Slovakia will:

- Be responsible for supporting the author in all project phases;
- Be responsible for writing TEC and CUR domains independently;
- AAZ will be responsible for co-authoring the EFF domain;
- Answer comments.

As Dedicated reviewers, Avalia-t, HAS, GÖG, AETSA, AAZ, HIQA, and HIS will:

- Guarantee quality assurance by thoroughly reviewing the project plan and the assessment drafts;
- Review methods, results, and conclusions based on the original studies included;
- Provide constructive comments in all the project phases.

Selection of Assessment Elements (AEs) and development of domains

A preliminary working version of the HTA Core Model® for Rapid Relative Effectiveness Assessment, based on the "HTA Core Model® for Rapid Relative Effectiveness Assessment of Pharmaceuticals 3.0", will be the primary source for selecting the assessment elements (AEs). Additionally, assessment elements from other EUnetHTA Core Model Applications will be screened and included if believed relevant to the present assessment. The REA Model Checklist will be used for potential ethical, organisational, social, and legal aspects.

The following domains will be developed within the present assessment:

- Description and technical characteristics of the technology (TEC);
- Health Problem and Current Use of Technology domains (CUR);
- Clinical effectiveness (EFF);
- Safety (SAF).

Selected AEs are presented in Table 5. Methods are described, per each domain, in the following sections.

TEC: This domain will be developed starting from the information provided by the manufacturers within the Manufacturer's Submission File. Whenever the Submission File has not been provided by the manufacturer or believed insufficient, information will be integrated with *ad hoc* PubMed and internet searches of grey literature using the Google search engine, review of the reference lists and bibliographies of studies identified through the basic systematic search, manufacturers' web sites, brochures, information for use, and regulatory bodies' databases.

CUR: This domain will be developed starting from the information provided by the manufacturers within the Manufacturer's Submission File. Whenever the Submission File has not been provided by the manufacturer or believed insufficient, information will be integrated with basic systematic searches, *ad hoc* PubMed and internet searches of grey literature using the Google search engine, review of the reference lists and bibliographies of studies identified through the basic systematic search, manufacturers' web sites, brochures and information for use.

EFF and SAF: These domains will be developed starting from the information provided by the manufacturers within the Manufacturer's Submission File. Whenever the Submission File has not been provided by the manufacturer or believed insufficient, information will be integrated by systematic structured searches. Comprehensiveness of the search strategy implemented by the manufacturers will be reviewed by the pilot team and used as criterion to decide on the completeness of evidence provided.

Literature searches will be performed in the following databases:

- Ovid MEDLINE;
- Embase;
- Cochrane Library;
- CINAHL;
- CRD databases (DARE, NHS EED, HTA).

MeSH terms in Table 3 will be combined with the following terms to perform the searches: *mitral valve repair; mitraclip; leaflets repair; percutaneous edge-to-edge repair; transcatheter edge-to-edge repair; carillon; annulus repair; percutaneous annulus repair, transcatheter annulus repair; neochord; transapical chordal repair; transapical mitral valve repair; transapical chordal replacement; percutaneous chordal repair; transcatheter chordal repair.*

All searches will be performed limiting the results to English language sources published between 2005 and the time of searches (March 2015).

In addition, the following clinical trials databases will be searched to identify ongoing trials or studies:

- ClincalTrials.gov;
- ISRCTN;
- EU Clinical Trials Register;
- *meta*Register of Controlled Trials (*m*RCT);
- International Clinical Trials Registry Platform (ICTRP).

Distribution of tasks among team members:

Two authors (Antonio Migliore and Mirjana Huic for EFF and Antonio Migliore and Mirella Corio for SAF) will screen the records by title and abstract. Disagreements will be solved by discussion with a third party (Maria Rosaria Perrini for both EFF and SAF). Potentially relevant studies will be retrieved in full-text and reconsidered for actual inclusion in the present evidence review. Data extraction will be performed independently on pre-defined extraction tables.

For TEC and CUR domains no quality assessment tool will be used, but multiple sources will be used in order to validate individual, possibly biased, sources. Descriptive analysis will be performed on different information sources.

Methodological quality of secondary studies will be assessed by using the R-AMSTAR tool [8]. Methodological quality of RCTs and CCTs will be assessed using the criteria from the Cochrane Handbook for Systematic Reviews of Interventions and EUnetHTA Guidelines [9-11]. The GRADE methodology will be used for qualitatively summarising the results from the domains EFF and SAF [12].

Quantitative results will be expressed as point estimates together with associated 95% confidence intervals (95% CI) and exact p-values.

Table 4b. Preliminary Evidence

Preliminary evidence table

The following information will be extracted from included secondary studies:

Study general information:

- Author

- Year of publication
- Reference number
- Study objectives

Study characteristics:

- Study types included in the review
- Databases consulted by the authors
- Number of studies included in the review
- Review timeframe
- Comparison(s)
- Patients groups (number of patients, patient characteristics, device used)

Outcomes and follow-up:

- Main outcomes reported
- Main study findings

Conclusions:

- Authors' conclusions
- Reviewers' comments.

The following information will be extracted from included primary studies:

Study general information:

- Author
- Year of publication
- Reference number
- Objectives

Study characteristics*:*

- Study design
- Study Registration number (Registry identifier)
- Country(ies) of recruitment
- Sponsor
- Study duration (study start and completion date)

Patients groups:

- Number of patients
- Age
- Sex
- Diagnosis
- Previous treatments
- Patients flow

Intervention

- Implantable device assessed (model name and manufacturer)

Comparator(s)

Outcomes and follow-up

- Efficacy outcomes
- Safety outcomes

Conclusions

- Main study findings
- Authors' conclusions
- Reviewers' comments.

Selected assessment elements

The table 5 shows the assessment elements and the translated research questions that will be addressed in the assessment. They are based on the assessment elements contained in the preliminary working version of the "HTA Core Model® for Rapid Relative Effectiveness Assessment", based on the "HTA Core Model® for Rapid Relative Effectiveness Assessment of Pharmaceuticals 3.0", incorporating changes collected during the first pilots. Additionally, assessment elements from other EUnetHTA 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	Domain	Topic	Issue	Relevance in this assessment Yes/No	Reason for non-relevance/ Preliminary research question(s)	Source of assessment element
B0001	**TEC**	Features of the technology	What is the technology and the comparator(s)?	Yes	What are the technologies and what are the comparators?	Preliminary Model for Rapid Relative Effectiveness Assessment of Pharmaceuticals
A0020	**CUR**	Regulatory Status	For which indications has the technology received marketing authorisation or	Yes	For which indications has the technology(ies) received marketing authorisation or CE marking?	Preliminary Model for Rapid Relative Effectiveness

			CE marking?			Assessment of Pharmaceuticals
B0002	**TEC**	Features of the technology	What is the claimed benefit of the technology in relation to the comparators?	Yes	What are the claimed benefits of the technology(ies) in relation to the comparators?	Preliminary Model for Rapid Relative Effectiveness Assessment of Pharmaceuticals
B0003	**TEC**	Features of the technology	What is the phase of development and implementation of the technology and the comparator(s)?	No	Not relevant for the present assessment: the analysis has been limited to technologies marketed within the European context (i.e., CE marked). Analyses and discussions of the phase of development of the different devices were performed in the scoping phase.	Preliminary Model for Rapid Relative Effectiveness Assessment of Pharmaceuticals
B0004	**TEC**	Features of the technology	Who administers the technology and the comparators and in what context and level of care are they provided?	Yes	Who administers the technology(ies) and the comparators and in what context and level of care are they provided?	Preliminary Model for Rapid Relative Effectiveness Assessment of Pharmaceuticals
B0008	**TEC**	Investments and tools required to use the technology	What kind of special premises are needed for the technology and the comparator (s)?	Yes	What kind of special premises are needed for the technology(ies) and the comparator(s)?	Preliminary Model for Rapid Relative Effectiveness Assessment of Pharmaceuticals
B0009	**TEC**	Investments and tools required to use the technology	What supplies are needed for the technology and the comparator(s)?	Yes	What supplies are needed for the technology(ies) and the comparators?	Preliminary Model for Rapid Relative Effectiveness Assessment of Pharmaceuticals
A0021	**CUR**	Regulatory Status	What is the reimbursement status of the technology?	Yes	What is the reimbursement status of the technology(ies)?	Preliminary Model for Rapid Relative Effectiveness Assessment of

						Pharmaceuticals
A0001	**CUR**	Utilisation	For which health conditions, and for what purposes is the technology used?	No	The AE may have overlaps with A0020 and B0002.	Preliminary Model for Rapid Relative Effectiveness Assessment of Pharmaceuticals
A0002	**CUR**	Target Condition	What is the disease or health condition in the scope of this assessment?	Yes	What is the disease in the scope of this assessment?	Preliminary Model for Rapid Relative Effectiveness Assessment of Pharmaceuticals
A0003	**CUR**	Target Condition	What are the known risk factors for the disease or health condition?	Yes	What are the known risk factors for developing chronic mitral valve regurgitation?	Preliminary Model for Rapid Relative Effectiveness Assessment of Pharmaceuticals
A0004	**CUR**	Target Condition	What is the natural course of the disease or health condition?	Yes	What is the natural course of chronic mitral valve regurgitation?	Preliminary Model for Rapid Relative Effectiveness Assessment of Pharmaceuticals
A0005	**CUR**	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 chronic mitral valve regurgitation for the patient?	Preliminary Model for Rapid Relative Effectiveness Assessment of Pharmaceuticals
A0006	**CUR**	Target Condition	What are the consequences of the disease or health condition for the society?	Yes	What are the consequences of chronic mitral valve regurgitation for society?	Preliminary Model for Rapid Relative Effectiveness Assessment of Pharmaceuticals

A0024	**CUR**	Current Management of the Condition	How is the disease or health condition currently diagnosed according to published guidelines and in practice?	Yes	How is chronic mitral valve regurgitation currently diagnosed according to published guidelines?	Preliminary Model for Rapid Relative Effectiveness Assessment of Pharmaceuticals
A0025	**CUR**	Current Management of the Condition	How is the disease or health condition currently managed according to published guidelines and in practice?	Yes	How is chronic mitral valve regurgitation currently managed according to published guidelines?	Preliminary Model for Rapid Relative Effectiveness Assessment of Pharmaceuticals
A0007	**CUR**	Target Population	What is the target population in this assessment?	Yes	What is the target population in this assessment?	Preliminary Model for Rapid Relative Effectiveness Assessment of Pharmaceuticals
A0023	**CUR**	Target Population	How many people belong to the target population?	Yes	How many people belong to the target population?	Preliminary Model for Rapid Relative Effectiveness Assessment of Pharmaceuticals
A0011	**CUR**	Utilisation	How much are the technologies utilised?	Yes	How much is the technology used?	Preliminary Model for Rapid Relative Effectiveness Assessment of Pharmaceuticals
D0001	**EFF**	Mortality	What is the expected beneficial effect of the technology on mortality?	Yes	What is the expected beneficial effect of the technology on mortality?	Preliminary Model for Rapid Relative Effectiveness Assessment of Pharmaceuticals
D0003	**EFF**	Mortality	What is the effect of the technology on the mortality	Yes	What is the effect of the technology on the mortality due to causes other than the target	Preliminary Model for Rapid Relative

			due to causes other than the target disease?		disease?	Effectiveness Assessment of Pharmaceuticals
D0005	**EFF**	Morbidity	How does the technology affect symptoms and findings (severity, frequency) of the disease or health condition?	Yes	How does the technology impacts on symptoms and severity of chronic mitral valve regurgitation?	Preliminary Model for Rapid Relative Effectiveness Assessment of Pharmaceuticals
D0006	**EFF**	Morbidity	How does the technology affect progression (or recurrence) of the disease or health condition?	Yes	How does the technology affect progression (or recurrence) of chronic mitral valve regurgitation?	Preliminary Model for Rapid Relative Effectiveness Assessment of Pharmaceuticals
D0011	**EFF**	Function	What is the effect of the technology on patients' body functions?	Yes	What is the effect of the technology on patients' body functions?	Preliminary Model for Rapid Relative Effectiveness Assessment of Pharmaceuticals
D0016	**EFF**	Function	How does the use of the technology affect activities of daily living?	Yes	How does the use of the technology affect activities of daily living?	Preliminary Model for Rapid Relative Effectiveness Assessment of Pharmaceuticals
D0012	**EFF**	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 the technology on generic health-related quality of life?	Preliminary Model for Rapid Relative Effectiveness Assessment of Pharmaceuticals
D0013	**EFF**	Health-related quality of life	What is the effect of the technology on disease-specific quality of life?	Yes	What is the effect of the technology on disease-specific quality of life?	Preliminary Model for Rapid Relative Effectiveness Assessment of

						Pharmaceuticals
D0017	**EFF**	Patient satisfaction	Was the use of the technology worthwhile?	Yes	Was the use of the technology worthwhile?	Preliminary Model for Rapid Relative Effectiveness Assessment of Pharmaceuticals
C0008	**SAF**	Patient safety	How safe is the technology in relation to the comparator(s)?	Yes	How safe is the technology in relation to the comparators: - What is the frequency of adverse events (any) of the transcatheter mitral valve repair (technology and procedure) in relation to comparator(s)? - What is the frequency of serious adverse events of the transcatheter mitral valve repair (technology and procedure) in relation to comparator(s)? - What is the frequency of serious adverse events leading to death for the transcatheter mitral valve repair (technology and procedure) in relation to comparator(s)? - What are the most frequent adverse events of the transcatheter mitral valve repair (technology and procedure) in relation to comparator(s)?	Preliminary Model for Rapid Relative Effectiveness Assessment of Pharmaceuticals
C0002	**SAF**	Patient safety	Are the harms related to dosage or frequency of applying the technology?	No	Not applicable for the technology under assessment.	Preliminary Model for Rapid Relative Effectiveness Assessment of Pharmaceuticals
C0004	**SAF**	Patient safety	How does the frequency or severity of harms change over time or in different settings?	Yes	Which aspects may affect frequency and/or severity of harms?	Preliminary Model for Rapid Relative Effectiveness Assessment of Pharmaceuticals
C0005	**SAF**	Patient safety	What are the susceptible patient groups that are	Yes	Which patient groups are more likely to be harmed by the use of the technology?	Preliminary Model for Rapid Relative

			more likely to be harmed through the use of the technology?			Effectiveness Assessment of Pharmaceuticals
C0007	**SAF**	Patient safety	Are the technology and comparator(s) associated with user-dependent harms?	Yes	Are the technology and comparators associated with user-dependent harms?	Preliminary Model for Rapid Relative Effectiveness Assessment of Pharmaceuticals
B0010	TEC	Investments and tools required to use the technology	What kind of data/records and/or registry is needed to monitor the use of the technology and the comparator?	Yes	What kind of data and/or registry is needed to monitor the use of the technology?	Preliminary Model for Rapid Relative Effectiveness Assessment of Pharmaceuticals

Checklist for potential ethical, organisational, social and legal 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, social and legal aspects.

1. **Ethical**	
1.1. Does the introduction of the new technology and its potential use/nonuse instead of the defined, existing comparator(s) give rise to any new ethical issues?	Yes

1.2. Does comparing the new technology to the defined, existing comparators point to any differences which may be ethically relevant?	Yes
Information about the severity level of the disease and extent to which the patient would be considered at high risk from conventional surgery could be important to decision-makers when making decisions about whether or not to implement a technology. **F0100:** At what severity level of the disease is the technology directed?	
2. **Organisational**	
2.1. Does the introduction of the new technology and its potential use/non-use instead of the defined, existing comparators require organisational changes?	Yes
2.2. Does comparing the new technology to the defined, existing comparators point to any differences which may be organisationally relevant?	No
Organisational aspects are likely to play a relevant role for those settings that will provide the procedure. Whatever is the comparator of choice (pharmacological therapy or surgery), the technology will completely reshape the clinical pathway for both the provider and the patients within the target population. Proper analyses need to be developed to assess, for example, the impact of the technology on the needs of specialised human resources and their training. **G0003:** What processes are required to ensure proper education and training for staff?	
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
3.2. Does comparing the new technology to the defined, existing comparators point to any differences which may be socially relevant?	No
4. **Legal**:	
4.1. Does the introduction of the new technology and its potential use/nonuse instead of the defined, existing comparator(s) give rise to any legal issues?	No
4.2. Does comparing the new technology to the defined, existing comparators point to any differences which may be legally relevant?	No

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	**28/10/2014**	**28/09/2015**
Scoping phase	**28/10/2014**	**30/04/2015**
Identification and confirmation of manufacturer(s) and external experts, contacting manufacturers	28/10/2014	18/12/2014
Completion of Submission file template by manufacturers	19/12/2014	09/02/2015
Draft Project Plan 1st version and e-meeting pilot team/ consultation of draft project plan with co-authors and dedicated reviewers	10/02/2015	27/02/2015
Scoping meeting with manufacturer(s)	04/03/2015	05/03/2015
Modification of submission file by manufacturers	06/03/2015	20/03/2015
Consultation of project plan by dedicated reviewers	16/03/2015	20/03/2015
Final Draft Project Plan	23/03/2015	27/03/2015
Consultation of draft Project Plan (public consultation including WP5 SAG, SF and manufacturer(s))	30/03/2015	22/04/2015
Final Project Plan	23/04/2015	30/04/2015
Assessment phase	**04/05/2015**	**Week of 7th September 2015**
First draft available	04/05/2015	05/06/2015

Review by dedicated reviewers	08/06/2015	17/06/2015
Second draft available	18/06/2015	24/06/2015
Review by ≥ 1 external clinical expert, manufacturer(s), by Strand B members and other potential stakeholders	25/06/2015	16/07/2015
Third draft available	17/07/2015	31/07/2015
Medical Editing	03/08/2015	17/08/2015
Fourth draft available	24/08/2015	28/08/2015
Formatting	31/08/2015	04/09/2015
Final pilot assessment		**Week of 7th September 2015**
Local Reports		
Local (national or regional) REA N°1 – Agenas	To be defined	To be defined
Local (national or regional) REA N°2 – LBI-HTA	To be defined	To be defined
Local (national or regional) REA N°3 – AAZ	To be defined	To be defined
Local (national or regional) REA N°4 – MoH Slovakia	To be defined	To be defined
Local (national or regional) REA N°5 – HAS	To be defined	To be defined
Local (national or regional) REA N°6 – HIQA (?)	To be defined	To be defined
Local (national or regional) REA N°7 – HIS	To be defined	To be defined
Local (national or regional) REA N° 8 - AETSA	To be defined	To be defined

5.2 MEETINGS

An e-meeting will be held with the pilot team (27th of February 2015), prior to the Scoping face-to-face meeting with the manufacturers (4th and 5th of March 2015). Interim e-meetings with co-authors and coordination team will be scheduled at some steps of the project. Additional e-meetings with co-authors, coordination team and manufacturer(s) may be scheduled if deemed necessary.

6.0 COMMUNICATION

Table 8. Communication

Communication Type	Description	Date	Format	Participants/ Distribution
Draft Project Plan with timelines	Review of methods and assessment elements chosen, discussion of time-lines, preparation for scoping meeting	27/02/2015	e-meeting	Authors, Co-authors, dedicated reviewers, Coordinating Team
Final Project Plan	Review of methods and assessment elements chosen, discussion of time-lines considering comments from Stakeholder Advisory Group, public, manufacturer	23/04/2015	E-mail	Author(s), Co-author(s), dedicated reviewers, Coordinating Team
First draft of the pilot assessment	To be reviewed by dedicated reviewers	08/06-17/06/2015	E-mail	Dedicated reviewers
	To discuss comments of dedicated reviewers (optional)	18/06/2015-24/06/2015	E-Mail	Author(s), co-author(s), dedicated reviewers

Second draft of the pilot assessment	To be consulted with ≥1 clinical expert, WP5 members, manufacturer(s), other potential stakeholders	25/06/2015-16/07/2015	E-mail	≥1 clinical expert, WP5 members, manufacturer(s), other potential stakeholders
Final pilot rapid assessment	Medical editing by external editor	03/08/2015-17/08/2015	E-Mail	Medical Editor

6.1 DISSEMINATION PLAN

The final pilot rapid assessment will be distributed as laid-out in the Work Plan of WP5.

7.0 COLLABORATION WITH STAKEHOLDERS

The manufacturers are asked to provide information via the submission file template developed by WP4 SG7.

A public consultation of the draft Project Plan will be conducted. The draft Project Plan will be made publicly available on the EUnetHTA website for a period of 15 days. The WP5 SAG, the Stakeholder Forum as well as the manufacturers will be invited to comment on the draft Project Plan for this pilot rapid assessment.

Collaboration with other stakeholders (external to SAG)

Patient representative associations related to the target population will be identified by the coordination team and involved as invited reviewers to the public consultation of the draft Project Plan as well as to the review of the second draft of the assessment.

8.0 COLLABORATION WITH EUnetHTA WPs

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

9.0 RESOURCE PLANNING

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	30 person days	30 person days	-
Reviewer	3 person days each	3 person days each	-
External reviewer	10 person days	-	10 person days
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 pilot assessments. 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 pilots.

If external experts are involved in WP5 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 pilots.

11.0 EXPECTED OUTCOME(S)

Project outcome(s)
The capacity of national HTA bodies to collaboratively produce structured rapid core HTA and the translation into local reports will have been proven. Redundancies will have been reduced and therefore efficiency gains achieved. Applicability of the HTA Core Model for rapid REAs to other technologies will have been elicited and the Model accordingly adapted.

C. REFERENCES

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