Endovascular therapy using mechanical thrombectomy devices for acute ischaemic stroke

Project ID: WP5-SB-16

Project description and planning

Health Information Quality Authority (HIQA), Ireland

Interdisciplinary Centre for HTA and Public Health (IZPH), Germany

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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	05/05/15	PH, RG	First version of a proposed draft project plan.	
V2	05/27/15	PH	V2 of draft plan	Amended subsequent to scoping meeting with manufacturers and discussions with co-authors
V3	06/08/15	PH	V3 of draft project plan	Amended subsequent to comments of dedicated reviewers
V4	DD/MM/YY			
V5	DD/MM/YY			

B. PROJECT PLAN

1.0 PARTICIPANTS

Table 1. Project participants

#	Agency	Role in the project	Country
1.	Health Information Quality Authority (HIQA)	Author(s)	Ireland
2.	Interdisciplinary Centre for HTA and Public Health University of Erlangen-Nürnberg (IZPH)	Co-Author(s)	Germany
3.	Ludwig Boltzmann Institute for HTA (LBI HTA)	Reviewer	Austria
4.	HTA and Health Services Research, Public Health and Quality Improvement, Central Denmark Region (CFK)	Reviewer	Denmark
5.	Haute Autorité de Santé (HAS)	Reviewer	France
6.	A. Gemelli Hospital	Reviewer	Italy
7.	Health Improvement Scotland (HIS)	Reviewer	Scotland
8.	Royal College of Surgeons in Ireland Beaumont Hospital	External Reviewer(s)	Ireland
9..	Ludwig Boltzmann Institute for HTA (LBI HTA)	Project Coordination	Austria

1.1 PROJECT STAKEHOLDERS

Table 2. Project stakeholders (manufacturers)

Organisation	Contact (webpage)	Devices
Stryker Neurovascular / Concentric Medical	http://concentric-medical.com/ http://www.stryker.com/emea/Products/NeurovascularIntervention/TrevoXPProVueRetreiver/index.htm	Trevo® ProVue™ Retrieval System Merci Retrieval System
Covidien/ Medtronic	http://www.ev3.net/neuro/intl/flow-restoration/solitaire-fr-revascularization-device.htm	Solitaire™ FR Revascularization Device MindFrame CaptureTM LP System
Codman Neuro/ DePuy Synthes/ J&J	http://www.depuysynthes.com/hcp/codman-neuro/products/qs/revive-pv	REVIVE™ SE Thrombectomy Device
Balt Extrusion	http://www.balt.fr/technologie http://www.abmedica.org/productcategory/thrombektomie-aspiration/	Catch Vasco+35ASPI
Penumbra	http://www.penumbrainc.com/neuro	Penumbra System®/ACE™ (Penumbra 3D Separator)

Neuravi	http://neuravi.com/	EmboTrap
Acandis	http://www.acandis.com/acandis-aperio-thrombectomy-device	Acandis Aperio®
Phenox	http://www.phenox.net/de/produkte/preset.html	pREset, pREset® LITE, BONnet
Microvention/Terumo	http://microvention.com/index.php?id=182	SOFIA ™ distal access catheter
Microvention	http://microvention.com/index.php?id=182	ERIC® device

56 ## 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**.**

57 ## 3.0 PROJECT SCOPE AND OBJECTIVES
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	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 mechanical thrombectomy in the management of acute ischaemic stroke.	Production of a pilot rapid assessment of the respective technology/ies. The topic has been proposed for a national level HTA by the National Stroke Programme in Ireland. Its relevance is based on the significant burden of acute stroke, which is the leading cause of death and disability in the developed world. Existing therapy using systemic thrombolysis has been shown to be effective and to improve patient outcomes, however recanalisation rates of only approximately 21% in eligible patient are reported with efficacy dependent on its administration within 4.5 hours of stroke onset and the site of vessel occlusion; thromblysis increases the risk of intracranial haemorrhage and its use is contra-indicated in some patients. Endovascular therapy using mechanical thrombectomy devices provides an alternative method of revascularisation which can improve stroke outcomes without increasing risk of intracranial haemorrhage. These devices may be used in

		combination with thrombolysis (as part of standard of care), or as an alternative in those who are not candidates for thrombolysis or in whom thrombolysis appears to have failed. However, appropriate patient selection is necessary and the intervention must be delivered in a timely fashion by trained interventionalists in facitlities with the capacity for appropriate acute post-procedure care.

This pilot rapid assessment addresses the research question whether mechanical thrombectomy plus current standard of care (that may include intravenous and/or intraarterial thrombolysis where appropriate) is more effective and/or safer than current standard of care in acute ischaemic stroke.

Table 3. Project Scope: PICO

Description	Project scope
Population	Adults aged 18 years or older with acute ischaemic stroke in the anterior and/or posterior region. ICD-10: I63 MeSH: Stroke
Intervention	Mechanical thrombectomy plus standard of care. (Mechanical thrombectomy may be used in combination with intravenous (and/or intra-arterial) thrombolysis or as an alternative to it in patients experiencing an acute ischaemic stroke who are not candidates for thrombolysis or in whom thrombolysis appears to have failed.) Fourteen CE-marked devices will be considered in this assessment: Aspiration/Suction Devices • Vasco+35ASPI • Penumbra System®/ACE™ (Penumbra 3D Separator) • Sofia™ Distal Access Catheter Stent Retrievers • Trevo® ProVue™ Retrieval System • Solitaire™ FR Revascularization Device • MindFrame CaptureTM LP System • REVIVE™ SE Thrombectomy Device • Catch • EmboTrap • Acandis Aperio®

	• pREset® LITE • BONnet • ERIC® Clot Retrievers • Merci Retrieval System MeSH-terms: Endovascular procedures; Stents; Tissue Plasminogen Activator; Angioplasty, Balloon
Comparison	Standard of care (which may include intravenous and/or intra-arterial thrombolysis where appropriate). Comparators have been chosen based on CE Mark specific indications, information in published clinical guidelines for treatment of acute ischaemic stroke and EUnetHTA guidelines.

Outcomes	**Effectiveness**:
	• Primary outcomes:
	  ○ Modified Rankin Score (mRS) at 90 days
	  ○ Mortality from ischaemic stroke
	• Secondary outcomes:
	  ○ NIHSS score change at 24 hours
	  ○ Barthel Index at 90 days
	  ○ Reperfusion at 24 hours
	  ○ Revascularisation at final angiography (TICI score)
	  ○ Health-related quality of life (EQ5D)
	  ○ All-cause mortality
	Safety:
	• Cerebral haemorrhage (symptomatic and asymptomatic) according to the ECAS III trial definition)
	• Perforation/dissection
	• Other haemorrhage
	• New ischaemic stroke in a different vascular territory
	• New ischaemic stroke in the same vascular territory
	• Any device-related adverse events
	• Any procedure-related adverse events
	
	Outcomes have been selected based on the recommendations from the clinical guidelines (ESO guidelines) and the EUnetHTA Guidelines on Clinical and Surrogate Endpoints and Safety.

Study design	**Effectiveness:**
	• Primary studies
	  ○ Randomised controlled trials
	  ○ Prospective clinical controlled studies
	• Secondary studies
	  ○ Systematic reviews
	  ○ Health Technology Assessment (HTA) reports
	
	Safety:
	• Systematic reviews
	• Health Technology Assessment (HTA) reports
	• Prospective clinical studies
	• Medical device adverse event registers

4.0 PROJECT APPROACH AND METHOD

Table 4a. Project approach and method

Project approach and method
Distribution of tasks among agencies: As Author, HIQA will: • Have a leading role in both scoping and production of the pilot; • Be responsible for management of the completed scientific work; • Have ultimate responsibility for quality assurance; • Answer comments. As Co-authors, the Centre for HTA and Public Health (IZPH) will: • Be responsible for supporting the author in all project phases; • Be responsible for writing TEC and CUR domains independently; • Answer comments. As Dedicated reviewers, A Gemelli, CFK, HAS, HIS and LBI-HTA, 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 using a systematic structured search of the literature. Searches of the following databases will be performed:
- Ovid MEDLINE;
- Embase;
- Cochrane Library;
- CRD databases (DARE, NHS EED, HTA).

MeSH terms in Table 3 will be combined with the following terms to perform the searches: thrombectomy, embolectomy, endovascular recanalisation, endovascular embolectomy, mechanical thrombus removal, mechanical embolus removal, endovascular intervention, mechanical device.
All searches will be performed limiting the results to English language sources published between 2005 and the time of searches (July 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).

The retrieved data will be cross-checked against the submission files received from the manufacturers for completeness.
Distribution of tasks among team members:
For the 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.
Two authors (RG and LM for EFF and SAF) will screen the records by title and abstract. Disagreements will be solved by discussion. 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 by the two researchers on pre-defined extraction tables.

Methodological quality of systematic reviews will be based on the ROBIS (Risk of Bias in Systematic Reviews) tool. The methodological quality of RCTs and CCTs will be assessed using the Cochrane risk of bias tables and EUnetHTA Guidelines. The GRADE approach will be used to qualitatively summarise the results from the EFF and SAF domains. Quantitative results based on an intention-to-treat principle will be expressed as point estimates together with associated 95% confidence intervals (95% CI) and exact p-values. Pooled analysis of treatment effect using forest plots and standard meta-analytic techniques will be carried out provided sufficient study data are obtained and taking account of heterogeneity between studies. An assessment of the heterogeneity of included studies will be performed. The I^2 statistic will be examined to describe the proportion of the variability in the results that reflects real differences in effect size. Chi-squared test for heterogeneity will be performed; if significant heterogeneity is detected, possible explanations will be investigated. The clinical heterogeneity of the populations in included studies will also be assessed.
Asymmetry of the funnel plot based on the data for the primary outcome will be taken as an indication of publication bias. Studies will also be assessed to ensure all proposed outcomes in the methods section are reported in the results section to exclude selective outcome reporting. Outcomes specified in the methods that are omitted from the results will be taken as evidence that outcomes were selectively reported. If this occurs the authors of the paper will be contacted to enquire if the results are reported elsewhere.
If data permit, subgroup analysis will be performed for the following:
1) Device type
2) Age <80 years vs ≥ 80 years
3) NIHSS score at baseline 2-15, 16-19, or ≥20
4) Time to treatment and reperfusion
5) Use of image-guided patient selection.
These subgroups have been identified a-priori based on a plausible rationale. The number of subgroups is kept to a minimum and priority is given to subgroups that are of specific interest to the potential addition of mechanical thrombectomy to standard medical care in the management of acute ischaemic stroke.

Table 4b. Preliminary Evidence

Preliminary evidence table

The following information will be extracted from included primary studies:

Study general information:

- Author
- Year of publication
- Reference number
- Objectives

Study characteristics*:*

- Study design - allocation concealment (and method), randomisation (and method), blinding (outcome, assessors), intention-to-treat analysis
- Study Registration number (Registry identifier)
- Country(ies) of recruitment
- Sponsor
- Study duration (study start and completion date)

Patients groups:

- Number of patients (total and for each comparator)
- Age
- Sex
- Exclusion criteria
- Diagnosis
- Previous treatments
- Flow of patients (time from stroke onset to arrival at stroke centre, time to thrombolysis, time to procedure, duration of procedure)

Intervention

- Mechanical thrombectomy device assessed (model name and manufacturer)

Comparator(s)

Outcomes and follow-up

- Efficacy outcomes
- Safety outcomes
- Main study findings
-

Conclusions

- Authors' conclusions

Reviewers' comments.

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
- Number of studies included in the review
- Review timeframe
- Comparison(s)
- Patients groups (number of patients and device used) in the included studies

Outcomes and follow-up:

- Main outcomes reported
- Main study findings

Conclusions:

- Authors' conclusions
- Reviewers' comments.

Selected assessment elements

The table shows the assessment elements and the translated research questions that will be addressed in the assessment. 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", was the primary source for selecting the assessment elements (AEs). 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 if believed relevant to the present assessment.

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 mechanical thrombectomy devices and what are the comparators?	JA2-WP5 –updated assessment elements for the HTA Core Model for Rapid REA
A0020	**CUR**	Regulatory Status	For which indications has the technology received marketing authorisation or CE marking?	Yes	For which indications have the mechanical thrombectomy devices received marketing authorisation or CE marking?	JA2-WP5 –updated assessment elements for the HTA Core Model for Rapid REA
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 mechanical thrombectomy devices in relation to the comparators?	JA2-WP5 –updated assessment elements for the HTA Core Model for Rapid REA
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).	JA2-WP5 –updated assessment elements for the HTA Core Model for Rapid REA
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 undertakes mechanical thrombectomy and its comparators technologies and in what context and level of care are these technologies provided?	JA2-WP5 –updated assessment elements for the HTA Core Model for Rapid REA
B0008	**TEC**	Investments and tools required to use the	What kind of special premises are needed for the technology and the	Yes	What kind of special premises are needed to provide percutaneous mechanical thrombectomy and its comparator(s)?	JA2-WP5 –updated assessment elements for the HTA Core Model for Rapid

		technology	comparator (s)?			REA
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 to undertake mechanical thrombectomy and the comparators?	JA2-WP5 –updated assessment elements for the HTA Core Model for Rapid REA
A0021	**CUR**	Regulatory Status	What is the reimbursement status of the technology?	Yes	What is the reimbursement status of mechanical thrombectomy devices?	JA2-WP5 –updated assessment elements for the HTA Core Model for Rapid REA
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.	JA2-WP5 –updated assessment elements for the HTA Core Model for Rapid REA
A0002	**CUR**	Target Condition	What is the disease or health condition in the scope of this assessment?	Yes	What is the health condition in the scope of this assessment?	JA2-WP5 –updated assessment elements for the HTA Core Model for Rapid REA
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 an acute ischaemic stroke?	JA2-WP5 –updated assessment elements for the HTA Core Model for Rapid REA
A0004	**CUR**	Target Condition	What is the natural course of the disease or health condition?	Yes	What is the natural course of acute ischaemic stroke?	JA2-WP5 –updated assessment elements for the HTA Core Model for Rapid REA
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 acute ischaemic stroke for the patient?	JA2-WP5 –updated assessment elements for the HTA Core Model for Rapid REA
A0006	**CUR**	Target Condition	What are the consequences of the disease or health condition for the society?	Yes	What are the consequences of acute ischaemic stroke for society?	JA2-WP5 –updated assessment elements for the HTA Core Model for Rapid REA
A0024	**CUR**	Current Management of the	How is the disease or health condition currently diagnosed according to	Yes	How is acute ischaemic stroke currently diagnosed according to published guidelines?	JA2-WP5 –updated assessment elements for the HTA Core Model for Rapid

		Condition	published guidelines and in practice?			REA
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 acute ischaemic stroke currently managed according to published guidelines?	JA2-WP5 –updated assessment elements for the HTA Core Model for Rapid REA
A0007	**CUR**	Target Population	What is the target population in this assessment?	Yes	What is the target population in this assessment?	JA2-WP5 –updated assessment elements for the HTA Core Model for Rapid REA
A0023	**CUR**	Target Population	How many people belong to the target population?	Yes	How many people belong to the target population?	JA2-WP5 –updated assessment elements for the HTA Core Model for Rapid REA
A0011	**CUR**	Utilisation	How much are the technologies utilised?	Yes	To what extent is mechanical thrombectomy currently used?	JA2-WP5 –updated assessment elements for the HTA Core Model for Rapid REA
D0001	**EFF**	Mortality	What is the expected beneficial effect of the technology on mortality?	Yes	What is the expected beneficial effect of mechanical thrombectomy on mortality?	JA2-WP5 –updated assessment elements for the HTA Core Model for Rapid REA
D0003	**EFF**	Mortality	What is the effect of the technology on the mortality due to causes other than the target disease?	Yes	What is the effect of mechanical thrombectomy on mortality due to causes other than the target disease?	JA2-WP5 –updated assessment elements for the HTA Core Model for Rapid REA
D0005	**EFF**	Morbidity	How does the technology affect symptoms and findings (severity, frequency) of the disease or health condition?	Yes	How does mechanical thrombectomy impact the symptoms and severity of acute ischaemic stroke?	JA2-WP5 –updated assessment elements for the HTA Core Model for Rapid REA
D0006	**EFF**	Morbidity	How does the technology affect progression (or recurrence) of the disease or health condition?	Yes	How does mechanical thrombectomy affect progression (or recurrence) of acute ischaemic stroke?	JA2-WP5 –updated assessment elements for the HTA Core Model for Rapid REA

D0011	**EFF**	Function	What is the effect of the technology on patients' body functions?	Yes	What is the effect of mechanical thrombectomy on patients' body functions?	JA2-WP5 –updated assessment elements for the HTA Core Model for Rapid REA
D0016	**EFF**	Function	How does the use of the technology affect activities of daily living?	Yes	How does the use of mechanical thrombectomy affect activities of daily living?	JA2-WP5 –updated assessment elements for the HTA Core Model for Rapid REA
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 mechanical thrombectomy on generic health-related quality of life?	JA2-WP5 –updated assessment elements for the HTA Core Model for Rapid REA
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 mechanical thrombectomyon disease-specific quality of life?	JA2-WP5 –updated assessment elements for the HTA Core Model for Rapid REA
D0017	**EFF**	Patient satisfaction	Was the use of the technology worthwhile?	Yes	Was the use of mechanical thrombectomy worthwhile?	JA2-WP5 –updated assessment elements for the HTA Core Model for Rapid REA
C0008	**SAF**	Patient safety	How safe is the technology in relation to the comparator(s)?	Yes	Relative to current standard of care alone, how safe is mechanical thrombectomy (technology- and procedure-related adverse events) when used in combination with standard of care relative to standard of care? Specifically: • What is the frequency of serious adverse events (SAE)? • What are the most serious adverse events (SAE)? • What is the frequency of serious adverse events (SAE) leading to death? • What are the most frequent adverse events? • How frequently do they occur?	JA2-WP5 –updated assessment elements for the HTA Core Model for Rapid REA
C0002	**SAF**	Patient safety	Are the harms related to dosage or frequency of applying the technology?	No	Not applicable for the technology under assessment.	JA2-WP5 –updated assessment elements for the HTA Core Model for Rapid REA

C0004	**SAF**	Patient safety	How does the frequency or severity of harms change over time or in different settings?	Yes	What are the variables associated with the use of mechanical thrombectomy devices that may impact the frequency and/or severity of harms?	JA2-WP5 –updated assessment elements for the HTA Core Model for Rapid REA
C0005	**SAF**	Patient safety	What are the susceptible patient groups that are more likely to be harmed through the use of the technology?	Yes	Which patient groups are more likely to be harmed by the use of mechanical thrombectomy devices? Are there any relevant contra-indications or interactions with other technologies?	JA2-WP5 –updated assessment elements for the HTA Core Model for Rapid REA
C0007	**SAF**	Patient safety	Are the technology and comparator(s) associated with user-dependent harms?	Yes – May overlap with C0002	Are mechanical thrombectomy devices associated with user-dependent harms? Specifically, are there potential harms that can be caused by those that undertake mechanical thrombectomy? Is there a learning curve, or potential for intra- or inter-observer variation in interpretation of outcomes, errors or other user-dependent concerns in the quality of care	JA2-WP5 –updated assessment elements for the HTA Core Model for Rapid REA
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 mechanical thrombectomy devices?	JA2-WP5 –updated assessment elements for the HTA Core Model for Rapid REA

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)	No

give rise to any new ethical issues?	
1.2. Does comparing the new technology to the defined, existing comparators point to any differences which may be ethically relevant?	No
2. Organisational	
2.1. Does the introduction of the new technology and its potential use/nonuse 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?	Yes
Endovascular stoke therapy has major implications for stroke services and for triaging decisions by emergency medical services. Ideally, this procedure should be undertaken within six to eight hours of stroke onset in comprehensive stroke centres by trained interventional (neuro)radiologists. Trial data also suggest a requirement for rapid access to neuroimaging to identify eligible patients with large-vessel occlusion. These criteria require substantial stroke-workflow efficiencies and organisation of specialist stroke services that may not be readily available in many regions.	
3. **Social**:	
3.1. Does the introduction of the new technology and its potential use/nonuse instead of the defined, existing comparator(s) give rise to any new 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

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5.0 ORGANISATION OF THE WORK

5.1 MILESTONES AND DELIVERABLE(S)

Table 7. Milestones and Deliverables

Project duration	**03.2015**	**12.2015**
Pilot's team building	11.03.	07.04
Scoping phase	**07.04**	**24.07**
Identification & contact of manufacturer(s) and external clinical experts	07.04	24.04
Contacting SAG/SF for manufacturer identification	08.04	24.04
Draft Project Plan 1st version + e-meeting pilot team	27.4.	11.5.
Scoping (e-)meeting with manufacturers	20th and 21st of May; e-meeting on 27th of May	
Consultation of project plan with dedicated reviewers	25.5.	28.5.
Draft Project Plan 2nd version	29.5.	4.6.
Consultation of draft Project Plan (public consultation including WP5 SAG, SF)	9.6.	29.6.
Final Project Plan	29.6.	3.7.
Completion of Submission file template by manufacturer(s)	6.7.	24.7.
Formulation of questions regarding missing information in submission file	27.7.	31.7.
Clarification of open questions with manufacturers	3.8.	7.8.
Assessment phase	**10.8.**	**14.12**
First draft available	10.8.	11.9.
Review by dedicated reviewers	14.9.	22.9.
Second draft available	23.9.	6.10.
Review by ≥ 1 external clinical expert, manufacturer(s), by Strand B members and other potential stakeholders	7.10.	28.10.
Third draft available	29.10.	12.11.
Medical Editing	13.11.	26.11.
Fourth draft available	27.11.	8.12.
Formatting	9.12.	15.12
Final pilot assessment		**week from 14.12 - 18.12**
Local Reports (if applicable)	TBD	

5.2 MEETINGS

An e-meeting will be held with the pilot team, prior to the scoping meeting with the manufacturer(s)t. Either an e-meeting or a face-to-face meeting will be held with the (co-)authors, the coordination team and the manufacturer(s).

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
Draft Project Plan with timelines	Review of methods and assessment elements chosen, discussion of time-lines	May 2015	E-mail (e-meetings to be planned here - optional)	Author(s), Co-author(s), 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	29/06 - 03/07 2015	E-mail (e-meetings to be planned here - optional)	Author(s), Co-author(s), dedicated reviewers, Coordinating Team
First draft of the pilot assessment	To be reviewed by dedicated reviewers	14/09 - 22/09 2015	E-mail (e-meetings to be planned here -optional)	Dedicated reviewers
	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 pilot assessment	To be consulted with ≥1 clinical expert, WP5 members, manufacturer(s), other potential stakeholders	07/10 - 28/10 2015	E-mail	≥1 clinical expert, WP5 members, manufacturer, other potential stakeholders
Final pilot rapid assessment	Medical editing by external editor	13/11 - 26/11 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

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.
In addition, the manufacturers will be asked to attend a scoping (e-)meeting with the authors and co-authors and to submit the submission file developed by WP7 SG4. The 2nd draft version of the assessment will be reviewed by external experts, manufacturers and other potential stakeholders.

Collaboration with other stakeholders

If eligible patient representatives are identified, they are planned to be involved in the public consultation of the draft project plan and in the review of the 2nd draft version 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	5 person days	-	5 person days
Layout	4 person days	-	4 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 declarations 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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