Repetitive transcranial magnetic stimulation for treatment-resistant major depressive disorder

Project ID: OTCA05

Project plan

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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	15/12/16	JE	First version of draft project plan	
V2	21/12/16	JE	Revised draft project plan	Comments received from co-authors
V3	30/12/16	JE	Revised draft project plan	Comments received from 1 dedicated reviewer
V4	05/01//17	JE	Revised draft project plan	Comments received from both dedicated reviewers
V5	10/01/17	JE	Revised draft project plan	Comments received from external experts

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.	Ludwig Boltzmann Institute for HTA (LBI HTA)	Austria	Author(s)	Health technology assessment of medical devices	Develop first draft of EUnetHTA project plan, amend the draft if necessary. Perform the literature search Carry out the assessment: answer assessment elements, fill in checklist regarding potential "ethical, organisational, patient and social and legal aspects" of the HTA Core Model R for rapid REA (see table 6) Send "draft versions" to reviewers, compile feedback from reviewers and perform changes according to reviewers comments Prepare final assessment and write a final summary of the assessment
2.	Basque Office for Health Technology Assessment (OSTEBA). Ministry for Health. Basque Government	Basque Country (Spain)	Co-Author(s)	Health technology assessment of medical devices, Clinical Practice Guidelines, early dialogue, Health outcomes research, Variability in Practice	Review draft EUnetHTA project plan Check and approve all steps (e.g. literature selection, data extraction, assessment of risk of bias) Review draft assessment, propose amendments where necessary (perform additional hand search of literature if needed) and provide written feedback on: • information retrieval: sources and search terms for locating domain specific information, inclusion/exclusion criteria for

					studies or other information, in terms of content, methods and quality. • handling the published data: do a systematic review, cite recent reviews, “screen until saturated” etc. • finding information when there is no published data: From web sites of organisations, discussion forums, registers: Other type of own research (analysis of primary data, modelling etc). • quality assessment tools or criteria planned to be used • synthesis: evidence table, plan for meta-analysis or qualitative synthesis, use of GRADE, etc.
3.	Fundación Canaria de Investigación Sanitaria (FUNCANIS)	Spain	Reviewer	HTA of medical devices, Health Economics, GRADE, Patient and Citizen Involvement in HTA, Knowledge Management, Clinical Practice Guidelines, Health Outcomes Research, Patient Reported Outcomes, Post-Introduction Monitoring of Health Technologies, Health Systems Assessment, Project Management.	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
4.	Belgian Health Care Knowledge Centre (KCE)	Belgium	Reviewer	Development of clinical practice guidelines, Health Technology Assessment of medical technologies and	Guarantee quality assurance by thoroughly reviewing the project plan and the assessment drafts; •Review methods, results, and conclusions based on the original

				medicinal products, Health Services Research	studies included; •Provide constructive comments in all the project phases
5.	Dr. Emmanuel Haffen	France	External Expert	Professor of psychiatry, President of French Association of Biological Psychiatry and Neuropsychopharmacology (AFPBN member of the WFSBP), Head of laboratory of Neurosciences (EA 481) of the University of Franche-Comté, Head of the Clinical Investigation Centre (CIC-1431 INSERM) of the University hospital of Besançon	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
6.	Dr. Jose Mª Vergara Ugarriza	Spain	External Expert	Head of Neurophysiology of Miguel Servet University Hospital (Zaragoza), Aragon	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
7.	Ludwig Boltzmann Institute for HTA (LBI HTA)	Austria	Medical Editor	Health technology assessment of medical devices	Medical editing
8.	Ludwig Boltzmann Institute for HTA (LBI HTA)	Austria	Project coordinator	Project management, Health technology assessment of medical devices, public health	Project management

1.1 PROJECT STAKEHOLDERS

Please describe/list project stakeholders[*].

Table 2. Project stakeholders

Organisation's name	Type of organisation
Magstim	Manufacturer
MagVenture	Manufacturer
Mag & More GmbH	Manufacturer
Neurostar	Manufacturer
Neurosoft	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 repetitive transcranial magnetic stimulation	Production of a rapid assessment of the respective technology.
3.	To refine the production processes of joint 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 joint assessments. Production of collaborative assessments probing a decentralized coordination process and facilitating to meet national timelines.
4.	To develop a process that facilitates the	Production of >2 national/local reports based on the joint assessment.

[*] 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).

	implementation of the joint assessment in the national/regional practice.	

This rapid assessment addresses the research question:

1, Is high-frequency repetitive transcranial magnetic stimulation (rTMS) in patients with treatment-resistant major depression more effective or as effective as and safer than or as safe as sham stimulation?
2, Is high-frequency repetitive transcranial magnetic stimulation (rTMS) in patients with treatment-resistant major depression more effective or as effective as and safer than or as safe as electroconvulsive therapy (ECT)?

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

Description	Project scope
Population	Adult patients (>18 yrs) with **treatment resistant major depressive disorder (TRD)** as defined by DSM IV-TR or ICD-10 and which is characterized by: • syndrome of unipolar depression with or without psychotic features and • lack of clinically meaningful improvement despite the use of at least 2 antidepressant agents from different pharmacological classes with each antidepressant medication trial being adequate in terms of dose, duration, compliance and tolerability [1, 2] Intended use of technology: third- or subsequent-line treatment MeSH terms: Major depressive disorder F03.600.300.375, Depressive disorder, treatment-resistant: F03.600.300.387 ICD-10 categories: F32 Depressive episode, F33 Recurrent depressive disorder Rationale: population has been chosen based on information from the relevant published clinical guidelines [3-5].

Intervention	Repetitive transcranial magnetic stimulation (rTMS) as a therapeutic intervention MeSH term: E02.621.820 The following intervention will be considered: • **High-frequency** (≥5 Hz) rTMS of the **left** dorsolateral prefrontal cortex (DLPFC) as monotherapy or add-on therapy Products to be included: o MagStim: Magstim Rapid2, Super Rapid2 and Super Rapid2 Plus1 o Magventure: MagVita TMS Therapy system o Neurostar: NeuroStar TMS therapy system o Mag & More: PowerMAG, Different versions: PowerMAG Clinical 30, PowerMAG Clinical 100, PowerMAG CLincal 100 PU, PowerMAG Research 30, PowerMAG Research 100, PowerMAG Research 100 ppTMS, PowerMAG Research 100 PU, PowerMAG Research 100 ppTMS PU o Neurosoft: Neuro-MS o Brainsway Rationale: relevant published clinical guidelines [3, 4] issued level A recommendation only for the use of high-frequency rTMS of the left DLPFC, for the use of low-frequency rTMS of the right DLPFC level B recommendation (probable effect) has been issued. If there is data available we conduct a subgroup analysis regarding the additive and potentiating antidepressant effect in patients receiving antidepressants.
Comparison	Sham rTMS (with unchanged antidepressant medication or no medication)

	ECT (with unchanged antidepressant medication or no medication) Rationale: Comparator has been chosen based on information from relevant published clinical guidelines [3, 4] and EUnetHTA guidelines [6, 7].
Outcomes	*Clinical endpoints:* *Primary* Change in depression score (measured on one of the followings: Hamilton Depression Rating Scale/HAMD, Montgomery-Asberg Depression Rating Scale, Beck Depression Inventory, or Quick Inventory of Depressive Symptomatology) • Response rate (>=50% reduction in the depression scores) • Remission rate (HAMD score <7, MADRS score <7, QUIDS score <5) • Relapse rate *Secondary* Adverse events: • Seizure • Syncope (fainting) • Scalp discomfort or pain • Transient induction of hypomania • Transient hearing loss • Transient impairment of working memory • Induced currents in implanted devices • Headache • Facial twitching • Vertigo • Device-related insomnia/drowsiness • Mild confusion Patient satisfaction Quality of life in depression scale Rationale: outcomes have been chosen based on information from relevant published clinical guidelines [2-4, 8] and EUnetHTA guidelines [6, 7].

Study design	Efficacy: Systematic reviews and meta-analysis of RCTs RCTs Safety: Systematic reviews and meta-analysis of RCTs RCTs

4.0 PROJECT APPROACH AND METHOD

Table 4a. Project approach and method

Project approach and method
The selection of assessment elements will be based on the HTA Core Model Application for Rapid Relative Effectiveness (REA) Assessments (4.2). The checklist for potential ethical, organizational, 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). Given the extensive body of evidence (randomized controlled trials and systematic reviews) a systematic search for published systematic reviews of RCTs will be conducted first. The following sources of information will be used: • Cochrane Library, Centre for Research and Dissemination (CRD), Embase, Medline. • Handsearch (in reference list of relevant studies), internet-search We will consider systematic reviews published in the last 5 years (2012-2016). The systematic reviews will be assessed using the AMSTAR tool and the best quality systematic review will be taken as a basis and will be updated. For the update a literature search for RCTs published since the literature search of the chosen systematic review will be performed. The following sources of information will be used: • Embase, Medline • Clinical trial registries will be assessed for registered ongoing clinical trials: ClinicalTrials.gov, International Clinical Trials Registry Platform (ICTRP) • Handsearch (in reference list of relevant studies), internet-search Literature selection: the author (LBI-HTA) will include and exclude studies and the co-author(s) (OSTEBA) will check the selection, independently from each other. Any disagreements will be resolved by consensus. All reporting of clinical effectiveness and safety data will be done according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA Statement 2012).

Data extraction: the author will extract the data and the co-author(s) control the extracted data.

AMSTAR tool will be used to assess the quality of identified systematic reviews. Cochrane risk of bias assessment approach will be used to assess RCTs (ACROBAT-NRSI tool), according to the EUnetHTA Guidelines on Therapeutic medical devices [6]. Assessment of the strength of evidence will be using "Grading of Recommendations, Assessment, Development and Evaluation" – GRADE approach. These steps will be performed by the author independently from the co-author(s). Any disagreements will be resolved by consensus.

For Description and Technical Characteristics of Technology (TEC) and Health Problem and Current Use of the Technology (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 of different information sources will be performed. The completed EUnetHTA submission file from the manufacturers will be used as starting point.

Quantitative data will be pooled in statistical meta-analysis. Effect sizes expressed as odds ratios and weighted mean differences and their 95% confidence intervals will be calculated for analysis. Heterogeneity will be assessed statistically using the standard chi-square test. Where statistical pooling is not possible, the findings will be presented in narrative form including tables and figures to aid data presentation where appropriate.

Table 4b. Preliminary Evidence

Quality assessment of identified systematic reviews (SR)

rTMS vs. sham stimulation

Study	Type of review	Aim of the study	N studies (N participants)	Inclusion/exclusion criteria	Key outcomes	AMSTAR Score	Period searched
HQO/2016 etc.	SR, MA						

rTMS vs. ECT

Study	Type of review	Aim of the study	N studies (N participants)	Inclusion/exclusion criteria	Key outcomes	AMSTAR Score	Period searched
HQO/2016 etc.	SR, MA						

Preliminary evidence table 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
Study design
Number of patients
Patient characteristics (age, sex, previous therapy, depression score at baseline)
Inclusion criteria
Exclusion criteria
Follow-up duration (weeks)
Loss-to-follow-up, n (%)
Depression scale used
Frequency (Hz) applied
Type of the stimulation (unilateral or bilateral), side of the stimulation if unilateral
Number of sessions
Intensity of the stimulation (% RMT)
Outcomes
Efficacy
Depression score (at follow-up)
Response
Relapse
Remission
Quality of life in depression scale (QLDS)
Patient satisfaction
Safety
Seizure
Headache

Syncope (fainting)
Scalp discomfort
Pain
Facial twitching
Vertigo
Device-related insomnia/ Drowsiness
Induced currents circuits in implanted devices
Transient induction of hypomania
Transient impairment of working memory
Mild confusion
Transient hearing loss

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' and other HTA Core Model® Applications.
In the 'Procedure Manual for the rapid relative effectiveness assessment of other technologies' information can be found on assessment elements considered 'mandatory' and 'non-mandatory' for individual types of technologies. In general, 'mandatory' elements are likely to be relevant for all assessments of a certain type of technology. The 'non-mandatory' elements may be relevant for specific assessments only. 'Mandatory' assessment elements have to be considered by the authors. If they do not wish to provide an answer to 'mandatory' questions, they need to provide a justification in the right column below. 'Non-mandatory' assessment elements can be included in the assessment, based on the experiences and preferences of the assessment team. No justification needs to be provided for excluding these 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 are rTMS, sham stimulation and ECT?
A0020	Regulatory Status	For which indications has the technology received marketing authorisation or CE	Yes	For which indications rTMS received marketing authorisation or CE marking?

ID	Topic	Topic Issue	Relevance in this assessment Yes/No	Research question(s) or reason for non-relevance of 'mandatory' elements
		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 rTMS in relation to sham stimulation and ECT?
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 rTMS and ECT?
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	Who administers rTMS and ECT and in what context and level of care is it provided?
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	What kind of special premises are needed to use rTMS and ECT?
B0009	Investments and tools required to use the technology	What equipment and supplies are needed to use the technology and the comparator(s)?	Yes	What equipment and supplies are needed to use rTMS and ECT?
A0021	Regulatory Status	What is the reimbursement status of the technology?	Yes	What is the reimbursement status of rTMS?
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 treatment-resistant major depressive disorder?
A0003	Target Condition	What are the known risk factors for the disease or health condition?	Yes	What are the known risk factors for treatment-resistant major depressive disorder?
A0004	Target Condition	What is the natural course of the disease or health condition?	Yes	What is the natural course of treatment-resistant major depressive disorder?
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 treatment-resistant major depressive disorder for the patient?
A0006	Target Condition	What are the consequences of the disease or health condition for the society?	Yes	What are the consequences of treatment-resistant major depressive disorder for the society?

ID	Topic	Topic Issue	Relevance in this assessment Yes/No	Research question(s) or reason for non-relevance of 'mandatory' elements
A0024	Current Management of the Condition	How is the disease or health condition currently diagnosed according to published guidelines and in practice?	Yes	How is treatment-resistant major depressive disorder currently diagnosed according to published guidelines and in practice?
A0025	Current Management of the Condition	How is the disease or health condition currently managed according to published guidelines and in practice?	Yes	How is treatment-resistant major depressive disorder currently managed according to published guidelines and in practice?
A0007	Target Population	What is the target population in this assessment?	Yes	What is the target population in this assessment?
A0023	Target Population	How many people belong to the target population?	Yes	How many people belong to the target population?
A0011	Utilisation	How much are the technologies utilised?	Yes	How much is rTMS utilised?
Clinical effectiveness				
D0001	Mortality	What is the expected beneficial effect of the intervention on mortality?	Yes	What is the expected beneficial effect of rTMS on mortality?
D0005	Morbidity	How does the technology affect symptoms and findings (severity, frequency) of the disease or health condition?	Yes	How does rTMS affect symptoms and findings (severity, frequency) of treatment-resistant major depressive disorder?
D0006	Morbidity	How does the technology affect progression (or recurrence) of the disease or health condition?	Yes	How does rTMS affect progression (or recurrence) of treatment-resistant major depressive disorder?
D0011	Function	What is the effect of the technology on patients' body functions?	Yes	What is the effect of rTMS on patients' body functions?
D0016	Function	How does the use of technology affect activities of daily living?	Yes	How does the use of rTMS affect activities of daily living?
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 rTMS 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 rTMS on disease-specific quality of life?

ID	Topic	Topic Issue	Relevance in this assessment Yes/No	Research question(s) or reason for non-relevance of 'mandatory' elements
D0017	Patient satisfaction	Were patients satisfied with the technology?	Yes	Were patients satisfied with rTMS?
Safety				
C0008	Patient safety	How safe is the technology in relation to the comparator(s)?	Yes	How safe is rTMS in relation to sham stimulation and ECT?
C0002	Patient safety	Are the harms related to dosage or frequency of applying the technology?	Yes	Are the harms related to dosage or frequency of applying rTMS?
C0004	Patient safety	How does the frequency or severity of harms change over time or in different settings?	No	Not applicable in the current assessment.
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 the use of rTMS?
C0007	Patient safety	Are the technology and comparator(s) associated with user-dependent harms?	Yes	Are rTMS, sham stimulation and ECT 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 rTMS and ECT?

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?	Yes/No
rTMS is indicated for those patients with major depressive disorder who remain disabled despite the use of antidepressants or because of their inability to tolerate medication side effects and who are unable to tolerate or refuse ECT. If rTMS could not be used, those who belong to the latter group (unable to tolerate or refuse ECT) would be left without any treatment option.	
1.2. Does comparing the new technology to the defined, existing comparators point to any differences that may be ethically relevant?	Yes/No
There is little knowledge about the exact patient group that could benefit the most from the new technology, but there might be a group where the efficacy and safety undoubtedly favours rTMS.	
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/No
rTMS requires a physician with specialised knowledge, a silent room where the patient can lie down and the stimulator can be applied. Personnel skilled in the management of syncope and seizure are required. The technology is relatively staff intensive.	
2.2. Does comparing the new technology to the defined, existing comparator(s) point to any differences that may be organisationally relevant?	Yes/No
The new technology does not require anaesthesia. Nevertheless, the patients need to go to the hospital 5 times a week for at least 2 weeks and get the treatment, which requires free capacities at the hospital in terms of personnel and space.	
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?	Yes/No
3.2. Does comparing the new technology to the defined, existing comparator(s) point to any differences that may be socially relevant?	Yes/No
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?	Yes/No
4.2. Does comparing the new technology to the defined, existing comparator(s) point to any differences that may be legally relevant?	Yes/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	**[28/11/2016]**	**[31/03/2017]**
Scoping phase	[28/11/2016]	[06/01/2017]
Identification of manufacturers	[28/11/2016]	[30/11/2016]
Scoping and development of draft Project Plan	[28/11/2016]	[06/01/2017]
Internal Scoping e-meeting (optional)	*[12/12/2016]*	*[16/12/2016]*
Consultation of draft Project Plan with dedicated reviewers	[21/12/2016]	[29/12/2016]
Amendment of draft Project Plan & final Project Plan available	[30/12/2016]	[14/01/2017]

Send request for draft Submission file template to manufacturer(s) (optional)	*[05/12/2016]*	*[07/12/2016]*
Completion of Submission file template by manufacturer(s) (optional)	*[08/12/2016]*	*[06/01/2017]*
Clarifying further questions concerning draft Submission file (optional)	*[09/01/2017]*	*[13/01/2017]*
Final submission file (optional)	*[15/01/2017]*	*[20/01/2017]*
Assessment phase	[09/01/2017]	[24/03/2017]
Writing first draft rapid assessment	[09/01/2017]	[24/02/2017]
Review by dedicated reviewer(s)	[27/02/2017]	[03/03/2017]
Writing second draft rapid assessment	[06/03/2017]	[10/03/2017]
Review by ≥ 2 external clinical experts (and by other potential stakeholders)	[10/03/2017]	[17/03/2017]
Writing third draft rapid assessment	[20/03/2017]	[24/03/2017]
Medical editing	[10/03/2017]	[17/03/2017]
Writing of final version of rapid assessment	[20/03/2017]	[24/03/2017]
Formatting	[24/03/2017]	[29/03/2017]
Final version of REA		**[week** from 27/03/2017 - to 31/03/2017]
Local Reports (if applicable)		
Local (national or regional) REA N^{o}1 [*OSTEBA, Spain*]		
Local (national or regional) REA N^{o}2 [*KCE, Belgium*]		
Local (national or regional) REA N^{o}3 [*FUNCANIS, Spain*]		

5.2 MEETINGS

An e-meeting may be held with the assessmentteam 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.	[15/12/2016]	E-meeting	Author(s), co-author(s), CT

	To discuss scoping and further handling of the submission file by manufacturers.	*[21/12/2016-29/12/2016]*	*E-mail/E-meeting*	*Author(s), co-author(s), dedicated reviewer(s), CT*
	To discuss and reach the consensus on the scoping.	*[30/12/2016-09/01/2017]*	*E-meeting/E-mail*	*Author(s), co-author(s), CT*
Feedback on submission file (optional)	*To formulate clarifying questions on draft submission file from the manufacturers*	*[DD/MM/YYYY]*	*E-mail*	*Authors, Co-authors, CT*
	To discuss the handling of data in the submission file	*[DD/MM/YYYY]*	*E-mail*	*CT, manufacturers*
Draft Project Plan with timelines	Review of methods and assessment elements chosen, discussion of time-lines	*[21/12/2016-29/12/2016]*	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.	[14/01/2017]	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)	[27/02/2017]	E-mail (e-meetings to be planned here -optional)	Dedicated reviewer(s)
	To discuss comments of dedicated reviewers (optional)	[07/03/2017]	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 (other potential stakeholders)	[10/03/2017]	E-mail	≥2 clinical experts (other potential stakeholders)
Final rapid assessment	Medical editing by external editor	[10/03/2017]	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

The 2nd draft version of the assessment will be reviewed by external experts and by manufacturers for a factual accuracy check.

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	20 person days	20 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)
A collaborative assessment that is fit for purpose, of high quality, and of timely availability will be produced. The assessments will be used in the national/local context. Production processes for collaborative assessment reports will be refined based on lessons learned and experiences from JA2. The decentralized approach for producing collaborative assessments will be probed. The implementation of the collaborative assessment in

the national/local context will be facilitated.

C. REFERENCES

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

1. Wijeratne C and Sachdev P: *Treatment-resistant depression: critique of current approaches.* Australian and New Zealand Journal of Psychiatry, 2008. **42**: p. 751-762.
2. European Medicines Agency: *Guideline on clinical investigation of medicinal products in the treatment of depression*. 2013 30.12.2016]; Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/05/WC500143770.pdf.
3. Lefaucheur JP, André-Obadia N, Antal A, Ayache SS, Baeken C, Benninger DH, Cantello RM, Cincotta M, de Carvalho M, De Ridder D, Devanne H, Di Lazzaro V, Filipovic´ SR, Hummel FC, Jääskeläinen SK, Kimiskidit VK, Koch G, Langguth B, Nyffeler T, Oliviero A, Padberg F, Poulet E, Rossi S, Rossini PM, Rothwell JC, Schönfeldt-Lecuona C, Siebner HR, Slotema CW, Stagg CJ, Valls-Sole J, Ziemann U, Paulus W, and Garcia-Larrea L: *Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS).* Clinical Neurophysiology, 2014. **125**: p. 2150-2206.
4. Leitliniengruppe Unipolare Depression, DGPPN, BÄK, KBV, AWMF, AkdÄ, BPtK, BApK, DAGSHG, DEGAM, DGPM, DGPs, and DGRW: *S3-Leitlinie/Nationale VersorgungsLeitlinie Unipolare Depression – Langfassung, 2. Auflage. Version 4.*, 2015.
5. NICE: *Repetitive transcranial magnetic stimulation for depression. Interventional procedure guidance 542*, 2015.
6. EUnetHTA: *Guideline. Therapeutic medical devices*, 2015.
7. EUnetHTA: *Guideline. Endpoints used for Relative Effectiveness Assessment: Clinical Endpoints*, 2015.
8. Rossi S, Hallett M, Rossini PM, and Pascual-Leone A: *Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research.* Clin Neurophysiol., 2009(12): p. 2008–2039.