EUnetHTA JA3 WP4 - Other technologies, WP4-ACB-CA-5
Review by dedicated reviewers of the draft Project Plan for Repetitive transcranial magnetic stimulation for treatment-resistant major depressive disorder

Comments should be submitted not later than *Friday 06/01/2017*

Please use this form for submitting your comments and please return to Judit Erdos/LBI-HTA:

1. Please put each new comment in a new row.
2. Please insert the page number and section number on which your comment applies. If your comment relates to the document as a whole, please put **'general'** in this column.
3. Please provide a description of your comment as specific as possible and preferably also provide a suggestion for rewording. If you wish to draw our attention to published literature, please supply the full reference.

The draft Project Plan of the Rapid Assessment on Repetitive transcranial magnetic stimulation (rTMS) is open to review between 30/12/2016 and 06/01/2017.

Comment from *Insert your name and organisation*	**Page number** *Insert 'general' if your comment relates to the whole document*	**Line/ section number**	**Comment and suggestion for rewording** *Please insert each new comment in a new row.*	**Character of comment** • 'major'[a] =1 • 'minor'[b] = 2 • 'linguistic'[c] =3 *Please indicate your choice by writing the according number in this field, e.g. for major choose "1".*	**Author's reply**
Haffen (FSBPN)	5	Table 1	The project does not include a specialist of the discipline. It is a deliberate choice?	2	We were searching specialists of the discipline and based on suggestion of the European Psychiatric Association we contacted you and we also identified 2 more experts in the field neuropsychology.

Please add extra rows as needed.

[a] "major": the comment points to a highly relevant aspect and a thorough answer is expected from the author(s)
[b] "minor": the comment does not necessarily have to be answered in a detailed manner
[c] "linguistic": grammar, wording, spelling or comprehensibility

DD/MM/YYYY

Haffen (FSBPN)	5	Table 1	There are only three European countries that participate in the project.	2	Yes, based on requirements of the European Commission we can call it a collaborative assessment if at least 3 countries are involved, which is fulfilled, because we have 2 authoring countries and 1 of the 2 dedicated reviewers (internal review) is a third country.
Haffen (FSBPN)	8		The question: “is rTMS in patients with TRD more effective…” than what? Antidepressant treatment? ECT? tDCS? MST?	1	We would like to clarify. Therefore we would have the following questions which are also connected to comment on page 15,table 5 and to comment on page 10, table 3: -do the guidelines differ in terms of the recommended treatment pathway for TRD patients? If yes, what is the most common/best accepted among clinical experts? - Is ECT the first choice as a third-line treatment? (is it the reference treatment according to up to date high quality clinical practice guidelines?) - is it routine in clinical practice to administer no medication when rTMS or ECT is applied? -are tDCS and MST clinically available procedures that are recommended by high-quality practice guidelines as third-line treatment? Is switch to 3rd line antidepressants also supported by clinical practice guidelines? - in the light of the above, we could set up the following options: 1. rTMS (+ unchanged antidepressant medication) vs. Placebo (rTMS) (+ unchanged antidepressant medication) OR Unchanged antidepressant medication (add-on therapy) 2. rTMS vs. ECT (or the other stimulation therapies, if they are well-established)
Haffen (FSBPN)	8	Table 3	“or antidepressants are not suitable” = this is not included in the definition of TRD	2	We deleted it.

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Haffen (FSBPN)	8	Table 3	It's mentioned: "Intended use of technology: second-line treatment" but TRD patients have already received a second line of treatment (i.e. definition of TRD)	2	We corrected it to third-line.
Haffen (FSBPN)	10	Table 3	It's mentioned for comparison: "Sham stimulation (with unchanged antidepressant medication or no medication)" but, rTMS with a unchanged antidepressant treatment or no medication, it's really not the same: it's either a new strategy or a add-on strategy	1	Yes, we agree. It is either add-on or new strategy. We would like to clarify.
Haffen (FSBPN)	10	Table 3	Remission rate is only defined for HAMD. And for MADRS and QIDS?	2	We added MADRS score <7, QUIDS score<5
Haffen (FSBPN)	13	Table 4b	The number of session per day is missing	2	We amended.
Haffen (FSBPN)	15	Table 5	There is a lot of question concerning the depression for whom there is, to date, no answer: there are a lot of practice guidelines concerning TRD; the natural course of the disease is not well known; the risk factors for TRD are not well established; the epidemiology of TRD in European countries is not well defined; etc… Studies must be led to answer these questions	2	Could you please share the practice guidelines deemed most relevant by you? We would like to choose the comparator based on what the clinical practice is.
Dr. Jose M[a] Vergara Ugarriza (Miguel Servet University Hospital)	9	Table 3	Comorbidity: As it is frequent in Major Depression, which does not have a differential objective diagnosis, several characteristics can be hidden. The criteria for exclusion may need to be carefully specified.	2	We amended our definition of the target population of the assessment and now it reads: 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. This is our inclusion criteria. Therefore we exclude those who do not fall under these criteria.

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Dr. Jose M[a] Vergara Ugarriza (Miguel Servet University Hospital)	10	Table 3	I think most of the stimulators are superficial (cortical). Possibly only the Israeli has a coil for deep stimulation. Do you have this in mind?	2	We will exclude deep rTMS.
Dr. Jose M[a] Vergara Ugarriza (Miguel Servet University Hospital)		Table 3	We have a very cheap technology (TCDS) and a much more expensive one (rTMS). The levels of evidence are not very different between the two of them. Why taking care of the most expensive in these moments of unsustainability? Where is the economic aspect considered?	2	The guidelines dealing with TRD we found do not mention tCDS as a recommended treatment option. We are not assessing the economic domain of this intervention, which is out of the scope of the assessment, but we will mention economic aspects in relation to the organizational aspects.

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