National Institute for Health and Care Excellence

IP346/2– Repetitive transcranial magnetic stimulation for depression

Consultation Comments table

IPAC date: Thursday 15 October 2015

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
1	Consultee 1: Private Sector Professional	**1**	1. We fully support the recommendations for treatment, further research, procedure, efficacy and safety. As regards the variability in response, in our research we use quantitative EEG (QEEG) to guide the application of TMS and so far we have treated 66 patients with a response rate of 60%. This is superior to 30% response rate using left frontal stimulation typically used in America. Therefore using QEEG we consider the variability can be reduced, offering patients an improved probability of response. The recommendation is highly significant because as more clinicians use the procedure this will help foster research to optimise treatment parameters, try out other forms such as theta burst, and use imaging to target specific brain areas.	**Thank you for your comment** The Committee is pleased to have received the views of individuals and/or organisations that perform rTMS

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2	Consultee 2: Manufacturer	**1.1**	Thank you for giving us the opportunity to comment on the provisional recommendations and information on Repetitive Transcranial Magnetic Stimulation for Depression. We have read the Consultation document, the overview document and SAQs, and find all documents comprehensive and in accordance with our view on rTMS for Depression. We have no further comments.	**Thank you for your comment**
3	Consultee 5: NHS professional	**1.1**	Interventional procedure consultation: Repetitive transcranial magnetic stimulation for depression (GID-IP2802 & IP346/2). We welcome the provisional recommendations made in the consultation document, which supports the informed use of TMS for depression with normal clinical governance arrangements in place. We consider this timely especially as we see a considerable increase in the interest on TMS among patients experiencing depression.	**Thank you for your comment**

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4	Consultee 4: Specialist Adviser	**1.1**	The main recommendation states that patients should understand the possibility that they may derive little or no benefit from the procedure. This statement is clearly true, but arguably unnecessary, as it would apply universally to all medical, surgical and psychological treatments, not just for depression, but in fact for any other medical or psychiatric condition. By stating it however, the Committee seems to imply that rTMS is more likely to fail than other treatments, which is obviously not the case. Indeed, most other treatments can also do harm, whereas rTMS has been repeatedly shown to be very safe. I believe that by informing depressed patients that antidepressants (failure rate of Citalopram at 72%) and /or ECT (failure rate of 40-50%) / rTMS (failure rate similar to ECT) may not help them, they will simply not attempt the treatment. Many such patients believe that there is no hope in the first place, and as a result become suicidal. One of the fundamental basics of treatment in depression and indeed in many other conditions is instillation of hope.	**Thank you for your comment** The Committee based the recommendation on evidence from published literature on the safety and efficacy of rTMS, as well as specialist advice received from specialist advisers that had been ratified by relevant specialist societies. Although there were large numbers of patients in published studies, the Committee encountered difficulties assessing the effect size of rTMS. This lead to the recommendation that patients are properly informed about alternative treatment options. The considerations made by the Committee are outlined in section 6.1 References to consent were removed from section 1.1 and placed in a separate recommendation that states: “During the consent process clinicians should, in particular, inform patients about the other treatment options available and make sure that patients understand the possibility the procedure may not give them benefit.”

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5	Consultee 6: Specialist Society - Royal College of Psychiatrists	**1.1**	We agree there is a strong enough signal in the research literature to allow TMS to be given within the NHS as outlined within Section 1.1. However we feel an additional point should be added to 1.1 that TMS is not the treatment of choice for psychotic depression, severe retarded depression or severe treatment resistant depression. Furthermore we consider a further caveat should be added to 1.1 which should state that patients should be monitored throughout and considered for other treatments in the light of non-response and/or worsening	**Thank you for your comment** A Committee comment was added to section 6 stating: “The Committee was advised that the procedure may not be appropriate for treating some kinds of depression and that patient selection is therefore most important”
6	Consultee 6 Specialist Society - Royal College of Psychiatrists	**1.2**	We strongly support further research on TMS. We do not believe that there is sufficient data on the type of TMS delivery, the nature of the pulse administered, the length of the treatment course or the nature of the patients to whom is should be offered to make definitive recommendations within the NHS. We support further studies and would recommend larger more pragmatic RCTs (ie the type supported by either the EME or the HTA). In the meantime we urge that data on all TMS in the UK is audited and published. We would like to see Section 1.2 changed from an "encourages" to a "recommends" and expanded to encourage the capture and publication of all data (including negative trials) and NHS data. .	**Thank you for your comment** The research recommendation was amended to stat: “NICE encourages publication of further evidence on patient selection, **details of the precise type and regime of stimulation used**, the use of maintenance treatment and long-term outcomes.”

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7	Consultee 6 Specialist Society - Royal College of Psychiatrists	**1.2**	Pages 9 -10 The document may usefully address areas of particular need for further research that may shape future development and implementation of rTMS for the treatment of depression Suggested areas for consideration include research into; 1) the application of rTMS for management of depressive comorbidity in both physical and psychiatric illness; 2) areas to further refine the application and implementation of rTMS treatment, including context of when and when rMS is delivered.	**Thank you for your comment** Please refer to the response to comment 6

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8	Consultee 5: NHS professional	**1**	Patient selection: In our experience, a number of patients older than 60 seek TMS as a treatment option. Unlike ECT, which is widely used to treat depression in the elderly (age >60), the experience with TMS in this age group is limited. To date most TMS studies have arbitrarily excluded patients in this age group. We reviewed this practice in our recent work (Sabesan et al., 2015). While a change in dose and duration parameters may be required in older patients, there is no evidence to support the continuous exclusion of this group of patients from TMS trials. Availability within the NHS: We note from the SAQ document that some of the commentators were unaware of the availability of TMS within the NHS. In addition to our unit in Nottingham, we now have TMS clinics in Grimsby (since 2012) and Northampton (since 2014), with more services being planned in other parts of England.	**Thank you for your comment** Sabesan (2015) is a narrative review and would not normally be included in the overview With regard to comments about availability of rTMS in the UK, IPAC recognises that this is the opinion of a specialist adviser. Questionnaire responses cannot be changed but are explicitly noted to be the opinion of the SA and not of IPAC

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9	Consultee 5: NHS professional	**1**	Expertise required: There is no formal accreditation system in the UK to train nurses or doctors on the administration of TMS. At present, TMS clinics that are currently operating in the NHS are offering peer-to-peer training support, with a view of developing a competency framework with the support of the ECT committee of the Royal College of Psychiatrists. This will greatly enhance the speed of diffusion of this treatment.	**Thank you for your comment**

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10	Consultee 6 Specialist Society - Royal College of Psychiatrists	**2.1**	Section 2.1 – A similar comment is made regarding this section. While it does state that depression impairs people's quality of life, it does much more than this. We would like changes to Section 2.1 last sentence which implies that ECT or tDCS are equivalent options for severe depression. ECT has a very strong evidence base in this situation whereas tDCS has effectively none.	**Thank you for your comment** **Section 2 is meant to provide a brief description of the indication and potential treatment options** The section was amended to state: "Depression is a common disorder **which can have a debilitating effect on a person's life**. It is characterised by persistent sadness, loss of interest or pleasure, feelings of guilt or low self-worth, disturbed sleep, appetite and libido, tiredness and poor concentration. It is also often accompanied by feelings of hopelessness, suicidal thoughts **and can lead to suicide.** Depression can last from weeks to years, and can be recurrent. It can substantially impair an individual's ability to function at work or cope with daily life. Treatments for depression include a range of psychological therapies, and antidepressant medications. **In severe depression which has not responded to other treatments electroconvulsive therapy is sometimes used."**

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11	Consultee 5: NHS professional	**2.1**	Consultation document: Section 2.1: The statement “In severe depression, electroconvulsive therapy or transcranial direct current stimulation are sometimes used” is somewhat misleading as it places ECT and transcranial direct current stimulation (tDCS) in equal position. While we are encouraged by the growing interest in tDCS as a treatment option for depression, trial evidence to support its clinical use at present is very limited.	**Thank you for your comment** Please refer to the response to comment 10.

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12	Consultee 6 Specialist Society - Royal College of Psychiatrists	**3.1**	Section 3.1 states that rTMS is usually considered for patients who have failed to respond to antidepressants. This should be extended to state “failed to respond, or not tolerated” antidepressants. Poor tolerability is likely to be a more important reason for using rTMS than non-response.	**Thank you for your comment** Section 1.3 was changed to: “Treatment is usually considered for patients with depression that has not responded to antidepressant medication or **patients for whom antidepressants are not suitable**”

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13	Consultee 5: NHS professional	**3.2**	Consultation document: Section 3.2: The statement "Conventional rTMS uses continuous pulses of electromagnetic energy whereas theta- burst rTMS uses intermittent pulses" is not entirely accurate. Conventional rTMS is a repetition of individual pulses at a preset interval ('train of pulses'); theta-burst is a repetition of short bursts of pulses at a preset interval ('train of bursts') (Huang et al., 2005). Theta-burst can also be used in a continuous or intermittent fashion, and RCT evidence supporting both forms of use in depression are now available (please see below). There are also other differences between the two methods in the user experience: TBS protocols typically require shorter duration of administration and lower magnetic dose than conventional rTMS and allow the patient to have short breaks within a treatment session reducing discomfort (see Chung et al., 2015 for an overview). The above comments are made on the behalf of [redacted] Neuromodulation Network – a partnership of 2 NHS based TMS clinics in England [redacted] Neuromodulation Unit ([redacted]), a NHS-funded TMS clinic supported by [redacted] Healthcare NHS Trust & the University of [redacted], and the TMS clinic at [redacted] Healthcare NHS Foundation Trust ([redacted])] [redacted] & other members of the [redacted]; Healthcare NHS Foundation Trust.	**Thank you for your comment** Section 3.2 was amended to state: "Conventional rTMS is a repetition of individual pulses at a pre-set interval (train of pulses) whereas theta-burst rTMS is a repetition of short bursts of pulses at a pre-set interval (train of bursts)"**.**

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14	Consultee 6 Specialist Society - Royal College of Psychiatrists	**3.2**	Section 3.2 refers to rTMS being given daily for 2-6 weeks. This should be corrected to read five days a week, rather than daily, since this is the design of most trials and clinical services.	**Thank you for your comment** The Committee chose not to change section 3.2 Section 3.2 aims to provide a brief description of the procedure technique and provide examples of possible treatment regimens.
15	Consultee 4: Specialist Adviser	**4.1**	Treatment resistance is therefore a key concept when the effectiveness of rTMS is being assessed. If monotherapy with rTMS is considered as a proxy for non-resistance, it is interesting that the study by Slotema et al (2010) showed a very large effect size for monotherapy rTMS compared to sham (0.96).	**Thank you for your comment**
16	Consultee 5: NHS professional	**4**	Efficacy: We would like to highlight that the effect sizes of treatment response for rTMS has been steadily improving over time. This is in part due to optimisation of dose, frequency and duration of treatment over the years, providing a NNT of 5 when compared to sham treatment (Gross et al., 2007; Furukawa, 2014).	**Thank you for your comment** Gross (2007) is a systematic review that was included in the previous guidance. Larger, more recent systematic reviews are included in table 2 of the current overview. The study was added to appendix A. Furukawa (2014) is an editorial comment would not normally be included in the overview. A Committee comment was added to section 6 to highlight that: “The Committee was informed that the technology is evolving”

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17	Consultee 6 Specialist Society - Royal College of Psychiatrists	**4.3**	Page 5 Section 4.3. The text describing this systematic review is made confusing through its attempt to integrate both changes in HDRS scores and CGI-I scores as outcomes. The text implies that the assessed outcome was the CGI-I, but this was a secondary outcome. HDRS was the primary outcome. The confusion is then compounded by an incomplete description of CGI-I. Simply stating lower scores represent greater improvement is incorrect. The CGI-I is anchored by a score of 4 meaning no change. Scores above this value denote a worsened condition compare to baseline, and scores below increasingly positive outcomes. Removal of the reference to the CGI-I data may usefully enhance the clarity of this section.	**Thank you for your comment** Authors of the Lepping (2014) study stated that the clinical relevance of findings in the rTMS literature was assessed by translating HDRS data into CGI-I scores. The study was included in table 2 because it was the only study identified that took this approach to assessing the efficacy of rTMS. Section 4.3 reports mean percentage changes in HDRS scores (primary outcome measure) in the main parts of the sentences with CGI-equivalents (secondary outcome measure) stated in brackets. Section 4.3 was amended to state: In a systematic review of 63 studies including 3236 patients treated by rTMS (n=2330), sham stimulation (n=806) or electroconvulsive therapy (ECT; n=100), percentage changes in HDRS scores (lower scores indicate less depression) were pooled and converted to Clinical Global Impression Improvement scale (CGI I) scores. **CGI-I scores range from 1 to 7: a score of 4 means no change, scores less than 4 indicate improvements in depression and scores more than 4 indicate worsening depression.**

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18	Consultee 6 Specialist Society - Royal College of Psychiatrists	**6.0**	Section 6 emphasises that patients should be informed about alternative treatments. However, it is important for the document to make a more definitive statement about rTMS versus ECT, since this is, and will be, the question that clinicians most commonly ask. The evidence presented in the review (i.e. Sections 4.3 and 4.5) suggest that rTMS is NOT as effective as ECT. Patient preference is not dealt with in the document and will also be a significant consideration in assessing the merit of TMS relative to ECT	**Thank you for your comment** Although studies included in the overview made comparisons with ECT, IPAC does not consider comparative effectiveness and does not place procedures in the care pathway.

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19	Consultee 4: Specialist Adviser	**6.1**	At the end of the document, the Committee recommends that : â€œpatients are properly informed about alternative treatment options, about the risk that they may derive little or no benefit from rTMS and about the possible need for repeated treatments.â€• Once again, the possibility of not improving with treatment would apply universally, while the need for maintenance following the resolution of the acute phase would also apply to any treatment for depression and is therefore not specific to rTMS. The study by Janicak (2010), included in this review, showed that the effects of this treatment are quite durable. Furthermore, the term risk implies danger and again carries the same risks to depressed patients as pointed out above.	**Thank you for your comment** The Committee based the recommendation on evidence from published literature on the safety and efficacy of rTMS, as well as specialist advice received from specialist advisers that had been ratified by relevant specialist societies. Although there were large numbers of patients in published studies, the Committee encountered difficulties assessing the effect size of rTMS. This lead to the recommendation that patients are properly informed about alternative treatment options. The considerations made by the Committee are outlined in section 6.1 References to consent were removed from section 1.1 and placed in a separate recommendation that states: “During the consent process clinicians should, in particular, inform patients about the other treatment options available and make sure that patients understand the possibility the procedure may not give them benefit.”

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20	Consultee 4: Specialist Adviser	**6.1**	The review states that the clinical response is variable, which once again would apply to most, if not all, treatments. In fact, some large meta-analyses included in the review showed very substantial effect sizes (i.e. Zhang, 2015: Risk ratio: 3.29), despite the fact that some patients in these RCTs had treatment-resistant depression and would therefore be relatively unlikely to respond to a new intervention. Treatment resistance increases consistently and very substantially after each treatment failure. The results of these studies should, in my view, be explained in the context of the extremely limited alternatives available to these patients.	**Thank you for your comment** The procedure description (section 3.1) highlights that “treatment is usually considered for patients with depression that has not responded to antidepressant medication”
21	Consultee 4: Specialist Adviser	**Overview**	In the study by Ren et al (2014), included in this appraisal, there are two key issues that are not conveyed accurately in the Overview document (page 11) and the Consultation document (page 6), in my view: The Overview states, rather confusingly, that overall ECT was superior to rTMS, both in terms of effectiveness and side-effects, but then adds that rTMS was more effective in psychotic patients. In fact, the study found that rTMS was as effective as ECT in depressed patients without psychosis. It also found that rTMS, unlike ECT, did not induce cognitive side-effects. The Consultation document does not include these important points.	**Thank you for your comment** The overview was amended to state: “Authors state that high-frequency rTMS was as effective as ECT in patients without psychosis: response rates were 52.5% in the rTMS group and 51.4% in the ECT group. No numerators or denominators were reported” The Committee chose not to add this statement to the section 4.5

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22	Consultee 4: Specialist Adviser	**Overview**	The second issue is that using drop-out figures as a proxy for acceptability (in the Overview document) was obviously misleading. In my capacity as both ECT and rTMS practitioner, I can categorically state that rTMS is far more acceptable and tolerable than ECT. The former is virtually side-effect free, very safe, stigma-free, and does not require anaesthesia. Some of my patients have had both treatments and would undoubtedly confirm this. Furthermore, the type of patient requiring ECT is generally more severely ill, with potential risk to life due to lack of hydration/ nutrition, and/or psychosis, and therefore unlikely to drop out of treatment.	**Thank you for your comment** The consultee is referring to Study 4 (Ren, 2014) in table 2 of the overview. The study analysis section highlights to the reader that 'acceptability was assessed by using trial discontinuation rates as a proxy measure'. IPAC considered commentary from patients in addition to published literature. Patient commentary was positive and described significant benefits to quality of life. This is noted in section 6.2.

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23	Consultee 4: Specialist Adviser	**Overview**	Some studies included in the various meta-analyses in the review (i.e. Lepping, 2014; Zhang, 2015; Ren et al, 2014) used low dose rTMS modalities, below the current standard of 120% of the motor threshold, and some patients were treated for only 5 sessions, far below the recommended standard of 15 to 30 sessions. The study by Fitzgerald (2006) used frequencies between 1 and 2 Hz and 900 to 1800 pulses per session, when the more widely accepted standard antidepressant protocol is 10 Hz and 3000 pulses, in other words, twice to three times as much energy, delivered much faster. This standard protocol was in fact used in the study by Janicak (2010), also included in the review, which obtained very high response rates.	**Thank you for your comment** The overview aims to provide an outline of the safety and efficacy of various rTMS modalities that have been used to treat patients with depression. Only 1 of the included systematic reviews (Ren, 2014) stratified outcome measures according to stimulus intensity: frequencies of less than 1 Hz were classified as low-frequency whereas frequencies above 1 Hz her classified as high-frequency.

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24	Consultee 4: Specialist Adviser	**Overview**	The appraisal is mainly based on the results of meta-analyses and RCTs, but it also includes a case series and a case report. The Committee may want to consider our own prospective cohort evaluation data, which I submitted to NICE some time ago and has now been published: Euba R et al. Treatment-resistant depression: experience of the first repetitive transcranial magnetic stimulation clinic in the UK. Future Neurology Vol. 10, No. 3, Pages 211-215 , DOI 10.2217/fnl.15.8 I would suggest that the Committee includes the issue of rTMS in the treatment of perinatal depression and depression in pregnancy in its review. After all, NICE has already recommended rTMS for the treatment of migraine in pregnancy, so NICE has already accepted that this treatment is safe in pregnancy. Given that it is also effective in depression, and given the lack of safe alternatives for the treatment of depression in pregnancy and nursing mothers, I believe that this would be a logical recommendation. Antidepressant medications have teratogenic and other risks in pregnancy and reach the infant through breast milk in lactating mothers. ECT is much more invasive and carries significant cognitive effects affecting the ability of the mother to care and nurture the baby unsupported, as well as anaesthesia-related risks to the foetus.	**Thank you for your comment** Table 2 is meant to provide a brief outline of the safety and efficacy of rTMS and usually comprises 8 to 10 studies. The literature search identified over 150 studies that were published after NICE's initial evaluation of rTMS in 2007. Due to high amount of studies identified, the IP team decided to include studies with large sample sizes (assessed over 100 patients), good methodological study designs (such as systematic reviews and randomised controlled trials), or reported rare adverse events in table 2. The case series of 120 patients (Janicak, 2010) and the case report (Conca, 2000) were included to highlight the occurrence of adverse events that were not identified in other studies in table 2. The study that the consultee is referring to (Euba, 2015) was not found in the initial literature search or the update search. The study is a case series of 62 patients with unipolar or bipolar depression who received rTMS for a mean of 4.3 weeks. Agitation was the only adverse event reported in the study. The study was added appendix A The literature searches did not identify any studies that evaluated the safety or efficacy of rTMS in the treatment of perinatal depression and depression in pregnancy.

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25	Consultee 5: NHS professional	**Overview**	IP346/2- Literature Review: The IP overview has captured most of the trials reported within the search period, but we list some notable omissions below. We note that Bakker et al., (2015) – a nonrandomized comparative study on theta-burst TMS has been included while 2 other studies with a superior methodology (RCT), Li et al., (2014) and Plewnia et al., (2014) have been left out of the appraisal. We also wish to highlight a comprehensive systematic review prepared by the Evidence-based Practice Center, University of North Carolina (RTI-UNC) for the Agency for Healthcare Research and Quality U.S. Department of Health and Human Services. A limited summary of this review was published later (Gaynes et al., 2014), and has already been included in Appendix A of the overview document. Unlike other studies listed in table 2, this review specifically sought the effect of TMS on 2 distinct categories of patients. Tier 1 studies included patients who specifically had two or more prior treatment failures with medications. Tier 2 studies included patients with one or more prior treatment failures. Both the magnitude of treatment effect (risk ratio) and rates of remission associated with TMS were lower in tier 2 than in tier 1 studies, indicating that the evidence base is more robust for patients who fail at least 2 antidepressant trials.	**Thank you for your comment** The overview does not aim to provide a comprehensive list of potentially relevant studies. Instead, it provides a brief outline of studies that demonstrate the safety and efficacy of rTMS. • Li (2014) was not found in the initial literature search or the update search. It is a randomised controlled trial of 60 patients treated by 1 of 3 modalities of theta-burst rTMS or sham stimulation (4 groups of 15 patients). This study was added to appendix A. • Plewnia (2014) was not found in the initial literature search or the update search. It is a randomised controlled trial of 32 patients treated by theta-burst rTMS plus conventional rTMS or sham stimulation. Upon review of the study, only 9 patients in the theta-burst rTMS group and 11 patients in the sham stimulation group completed the 6 week assessment period. The study wasadded to appendix A. • Gaynes (2014) is already in appendix A of the overview

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26	Consultee 5: NHS professional	**Overview**	Funding sources: [redacted]. Potential conflicts of interest: [redacted] is employed by the University of [redacted]. [redacted] is employed by [redacted] Healthcare NHS Foundation Trust that funds the TMS clinic ([redacted]). [redacted] has received travel support (2014) to speak at a meeting organized by [redacted], a company that manufactures TMS devices. Chung, S., Hoy, K., Fitzgerald, P.B., 2015. Theta-burst stimulation: a new form of TMS treatment for depression? Depress Anxiety 32, 182–192. doi:10.1002/da.22335 Furukawa, T.A., 2014. How can we make the results of trials and their meta-analyses using continuous outcomes clinically interpretable? Acta Psychiatr Scand 130, 321–323. doi:10.1111/acps.12278 Gaynes, B.N., Lloyd, S.W., Lux, L., Gartlehner, G., Hansen, R.A., Brode, S., Jonas, D.E., Swinson Evans, T., Viswanathan, M., Lohr, K.N., 2014. Repetitive transcranial magnetic stimulation for treatment-resistant depression: a systematic review and meta-analysis. J Clin Psychiatry 75, 477–489; quiz 489. doi:10.4088/JCP.13r08815	**Thank you for your comment** • Chung (2015) is a review and would not normally be included in the overview. • Furukawa (2014) is an editorial comment would not normally be included in the overview. • Gaynes (2014) is already in appendix A of the overview

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27	Consultee 5: NHS professional	**Overview**	**Comment 26 continued** Gross, M., Nakamura, L., Pascual-Leone, A., Fregni, F., 2007. Has repetitive transcranial magnetic stimulation (rTMS) treatment for depression improved? A systematic review and meta-analysis comparing the recent vs. the earlier rTMS studies. Acta Psychiatr Scand 116, 165–173. doi:10.1111/j.1600-0447.2007.01049.x Huang, Y.-Z., Edwards, M.J., Rounis, E., Bhatia, K.P., Rothwell, J.C., 2005. Theta Burst Stimulation of the Human Motor Cortex. Neuron 45, 201–206. doi:10.1016/j.neuron.2004.12.033 Plewnia, C., Pasqualetti, P., Große, S., Schlipf, S., Wasserka, B., Zwissler, B., Fallgatter, A., 2014. Treatment of major depression with bilateral theta burst stimulation: A randomized controlled pilot trial. Journal of Affective Disorders 156, 219–223. doi:10.1016/j.jad.2013.12.025 Sabesan, P., Lankappa, S., Khalifa, N., Krishnan, V., Gandhi, R., & Palaniyappan, L. (2015). Transcranial magnetic stimulation for geriatric depression: Promises and pitfalls. World journal of psychiatry, 5(2), 170.	**Thank you for your comment** • Gross (2007) is a systematic review that was included in the previous guidance. The study was added to appendix A. • Hung (2005) is a proof of principle study which demonstrated the effects of theta-burst rTMS on the motor cortex. It would not normally be included in the overview • Plewnia (2014) was not found in the initial literature search or the update search. It is a randomised controlled trial of 32 patients treated by theta-burst rTMS or sham stimulation. Upon review of the study, only 9 patients in the theta-burst rTMS group and 11 patients in the sham stimulation group completed the 6 week assessment period. The study was added to appendix A. • Sabesan (2015) is a narrative review and would not normally be included in the overview

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28	Consultee 6: Specialist Society - Royal College of Psychiatrists	**Other: Lay description**	The wording of the first box on the first page underplays the potentially devastating impact of depression, presenting it more like a mild, almost trivial condition. It would be more accurate to state that it is associated with significant morbidity and mortality.	**Thank you for your comment** The lay description was changed to state: "Depression can have **a debilitating effect on a person's life, causing** low mood or sadness **which can lead to suicide."**
29	Consultee 1: Private Sector Professional	**Other: Specialist advice**	2. We fully support the points made by Dr [redacted], in particular that TMS is an established procedure and no longer new, it is used worldwide in the USA, Canada, Europe and Australia but not in the U.K. The recommendation will redress this imbalance. The literature cited by Dr [redacted] on efficacy and safety, and in the consultation and interventional procedure overview, all provide very strong support for the recommendation.	**Thank you for your comment** The Committee is pleased to have received the views of individuals and/or organisations that perform rTMS

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30	Consultee 1: Private Sector Professional	**Other: Specialist advice**	3. We strongly disagree with the points on efficacy, safety and trajectory made by Dr [redacted] and Dr [redacted]. In particular the following points; TMS is not only available privately but at [redacted] in [redacted], [redacted] Institute of Mental Health and [redacted] NHS. Our experience with TMS and significant effectiveness reported in the literature refutes their point of uncertain efficacy and safety. Although the effect size is modest, for those patients where it is effective, the impact on their quality of life is huge. The trajectory issue of acceptability to attend on a regular basis has, in our experience, never been a problem.	**Thank you for your comment** IPAC recognises that this is the opinion of a specialist adviser. Questionnaire responses cannot be changed but are explicitly noted to be the opinion of the SA and not of IPAC
31	Consultee 5: NHS professional	**General**	IP346/2 -General comments: Using the term 'severe depression': This in our view may unnecessarily restrict the utility of this treatment. Most RCTs have considered patients at several stages of treatment-resistant depression, but not necessarily in 'severe' depression as defined by the current classificatory systems such as ICD-10.	**Thank you for your comment** The previous guidance (IPG 242) was titled: Transcranial magnetic stimulation for severe depression. The word 'severe' had been removed from the title of the new guidance. Furthermore, the guidance considered evidence from studies that assessed rTMS in patients who had various stages of depression, including treatment resistant depression.

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32	Consultee 3: Patient	**General**	A Patient's Perspective on Theta-burst rTMS My History I was abused by my parents, sexually and mentally throughout my childhood. I have been depressed with anxiety since the age of approximately 4. I encountered further abuse on several occasions since. I have had two 'breakdowns' one at age 21 and at age 43. I am now 46. I had counselling for many years, Gestalt, Humanistic and CBT. I have been treated with a variety of drugs in a variety of combinations, including: nortriptyline, sertraline, quetiapine, venlafaxine, mirtazepine, diazepam, propanolol, amitriptyline, lithium, liothyronine, phenelzine, tryptophan, agomelatin, pregabalin, tranylcypromine, lamotrigine, bupropion, citalopram, fluoxetine. As a result of the medication, my weight, blood pressure, cholesterol and digestive system have been significantly affected, which consequently I take medication to combat.	**Thank you for your comment** The Committee is pleased to have received the views of patients who have received rTMS Section 6.2 states: “The Committee noted that commentary from patients was positive and described significant benefits to their quality of life, including the advantages, for some patients, of being able to stop the use of oral antidepressant medications.”

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
33	Consultee 3: Patient	**General**	**Comment 32 continued** I believed my only hope was to have deep brain stimulation (DBS) / cingulotomy,. To qualify I had to have tried ECT, so I had 8 bilateral ECT treatments, further to which I lost a substantial amount of memories of people, places, skills, work etc. The cingulotomy was arranged with Dr [redacted] (Consultant in Clinical Psychopharmacology and Neurostimulation) and Mr [redacted] ([redacted] Professor & Consultant Neurosurgeon) but the new 'Specialist Depression Service' (Dr [redacted]) in [redacted] would not refer me. At this point my suicidality peaked, as I simply could not face the rest of my life like this – pharmacology doesn't offer a life worth living in the long term, based on the results / side-effect trade-off.	**Thank you for your comment** Please refer to the response to comment 31.

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
34	Consultee 3: Patient	**General**	**Comment 32 continued** The Treatment My psychiatrist then told me about the research trial on theta-burst rTMS and rTMS that was taking place in [redacted]. I had heard of TMS previously, but nothing I read made me think it would be likely to work. However I felt that at this point, I had nothing to lose. I received theta-burst rTMS via the trial. The first treatment in October 2014. involved locating the corresponding point on my skull with that from the MRI, testing for the right 'dose' and then treatment. The pulses felt like a tapping sting initially, but then once I got used to it, felt like a finger tapping. So no pain or discomfort. I had another MRI at the end of the treatment. I truly did not believe it could help, but having committed to the trial, I had four treatments a week for four weeks. Personally I didn't really feel anything had changed.	**Thank you for your comment** Please refer to the response to comment 31.

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
35	Consultee 3: Patient	**General**	**Comment 32 continued** The Outcome So Far In December 2014 I woke up to a multitude of 'voices', visual clips, feelings, from a variety of times in my life. Like my brain was running different episodes of my life all at once, with corresponding narrative (mine) to match each. Like someone had their hands inside my skull, fiddling with my brain. This lasted for 2 days, then over the next five days slowly eased. The improvement then began and increased over the next two weeks. Absolutely nothing has given me anywhere near the improvement in my mood this has. I noticed colour with some interest and caught myself smiling. If I had to put a figure on it, I would say around a 25% improvement. I could do things without the full weight of anxiety. I could manage sometimes half a day without thinking 'I can't do this'. I could actually laugh, not pretend laugh. These things alone are a gigantic gift. I had no side effects. As you can imagine, it made sense to me that further treatment could give me 50%, 75% or even 100% improvement perhaps. It should then be possible to come off some or all of my drugs and be free from their side-effects.	**Thank you for your comment** Please refer to the response to comment 31.

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
36	Consultee 3: Patients	**General**	**Comment 32 continued** I was therefore dismayed to realise this really wouldn't be possible as theta-burst rTMS has not been licensed. I was offered four 'rescue' sessions of rTMS, but I don't think I saw any benefit from this. I am living proof that theta-burst rTMS works and surely I cannot be so extraordinary to be the only one? Having been so desperately ill for virtually my entire life, yet being finally granted some relief, (with the possibility of further relief) I ask you to give serious consideration to licensing this treatment. If you would like to discuss this with me personally, please feel free to get in touch.	**Thank you for your comment** Please refer to the response to comment 31.

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
37	Consultee 7: NHS professional on behalf of a patient	**General**	Please accept apologies for sending this mail after closing date for NICE consultation for rTMS for depression. Unfortunately one of my patient who had rTMS treatment sent his response this morning hence the delay. I would be grateful if you could kindly add his response to consultation. Many thanks for your help. “I have experienced depression and anxiety since childhood. I did not experience any side effects from the rTMS treatment other than minor facial twitching sometimes at the start of treatment sessions, but it was usually possible to stop this facial muscle activation by adjusting the angle of the magnet / stimulating device. I tolerated the treatment without difficulty. Prior to treatment I had been experiencing insomnia and poor quality sleep for a number of years. These sleep issues improved significantly after treatment. I have noticed significant mood improvements. My ability to concentrate and focus has improved. Anxiety levels and panic attacks have reduced. My libido also improved noticeably during and after treatment. The treatment has had a significant positive impact on my quality of life”	**Thank you for your comment** Please refer to the response to comment 31.
38	Consultee 4 Specialist Adviser	**NOTE**	NOTE : I use rTMS in the private sector, but I am also an NHS Consultant Psychiatrist and would welcome the use of rTMS in the NHS.	**Thank you for your comment**