Australian Government

Medical Services Advisory Committee

Public Summary Document

Application No. 1196.2 – Repetitive Transcranial Magnetic Stimulation (rTMS) for the treatment of depression

Applicant: Royal Australian and New Zealand College of Psychiatrists

Date of MSAC consideration: MSAC 76th Meeting, 1-2 August 2019

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, visit the MSAC website

1. Purpose of application

A resubmission requesting Medicare Benefit Schedule (MBS) listing of repetitive transcranial magnetic stimulation (rTMS) for treatment of antidepressant medication-resistant major depressive disorder (MDD) was received from the Royal Australian and New Zealand College of Psychiatrists (RANZCP) by the Department of Health.

2. MSAC's advice to the Minister

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness and cost-effectiveness, MSAC supported the new MBS item for initial treatment with rTMS of finite duration for adults diagnosed with antidepressant medication resistant major depressive disorder who have failed to receive satisfactory improvement despite adequate trialling of at least two (2) different classes of antidepressant medicines and who have not received treatment with rTMS previously.

MSAC was of a mind to support an MBS listing for re-treatment with rTMS of finite duration, but considered that further information was required from the RANZCP, particularly regarding the appropriate time period between cessation of the initial treatment course and commencement of a re-treatment course, and the proportion of patients who have responded to initial treatment who are likely to relapse and require re-treatment.

MSAC did not support ongoing maintenance treatment with rTMS due to the limited and weak evidence base.

Consumer summary
The RANZCP applied for public funding of rTMS for adults with major depression who have tried antidepressant medicines or psychological therapy and remain unwell. rTMS is a treatment for depression. It involves placing a magnetic coil on the patient's scalp, which generates electrical pulses in a small area on the surface of the brain. The

Consumer summary
patient is conscious during rTMS treatment. Each treatment lasts about 40 minutes, and patients require between 3 and 5 treatments a week for 4 to 6 weeks. This application is requesting that rTMS is listed on the MBS for use in patients with major depression who have not responded to antidepressant medicines or psychological therapy. To work out if rTMS is safe, effective and cost-effective, rTMS used together with antidepressants was compared with using antidepressants alone. **MSAC's recommendation to the Commonwealth Health Minister** MSAC supported public funding for initial treatment with rTMS. MSAC accepted that some patients will need to have a treatment course with rTMS more than once (retreatment), but will need to get further advice from the RANZCP about how much time there should be between treatments and how many patients might need retreatment. However, MSAC did not support public funding for rTMS when it is used for maintenance treatment (continuously for a long time) because there is not currently enough evidence to show whether maintenance treatment is safe and effective.

3. Summary of consideration and rationale for MSAC's advice

MSAC recalled that advice on funding of rTMS for treatment of major treatment-resistant depression (Application 1196.1) was previously deferred to request further evaluation of the clinical evidence provided in two reports: the European Network for Health Technology Assessment (EUnetHTA 2017) Report and the 2016 Ontario Health Technology Assessment Series Report (HQO 2016). MSAC also requested that a "frame of reference" approach be used for the economic evaluation and MBS costings, comparing rTMS plus antidepressants with antidepressants alone.

MSAC noted that the application is seeking two new MBS items:

- initial prescription and mapping session (done by a TMS-trained psychiatrist)
- rTMS treatment (performed by a nurse or allied health professional).

If the patient is under the care of a TMS-trained psychiatrist, assessment of the patient's eligibility for rTMS and other third-line interventions would be done as part of normal clinical practice. If the patient is not already under the care of a TMS-trained psychiatrist, an additional consultation and referral to a TMS-trained psychiatrist would be required. MSAC noted that prescription/mapping and delivery of the patient's first rTMS treatment session are likely to occur on the same day, and co-claiming of these two item numbers should be permitted. However, co-claiming of the prescription/mapping item with psychiatry consultation items should not be permitted.

MSAC noted that the description of treating personnel in the MBS item descriptor for rTMS treatment delivery should be tightened to "nurse or allied health professional" (i.e. remove the broad term "health care professional").

MSAC has previously accepted that there is a clinical need and place for rTMS retreatment, but noted that there was insufficient evidence to support retreatment. No additional evidence was presented in the resubmission. MSAC noted that the updated economic evaluation did not allow retreatment with rTMS in the base case analysis, but the proposed MBS item descriptors do not explicitly preclude retreatment with rTMS.

Due to the chronic nature of major depression, MSAC considered that retreatment with rTMS should not be excluded completely. However, MSAC considered that further treatment courses should be limited to those who responded to the initial course, and a minimum treatment interval should be stipulated to preclude use of rTMS as ongoing maintenance treatment. MSAC suggested an appropriate minimum interval may be 6-12 months, but considered that further advice on an appropriate minimum interval should be sought from the RANZCP.

MSAC noted the applicant's advice that the average number of therapy sessions required for a complete treatment cycle is 28, but the applicant suggests a limit of 35 sessions. MSAC considered that the disparity may encourage overservicing, unnecessarily increasing costs to the MBS. MSAC suggested that the initial course should be limited to a maximum of 20 sessions, and the remaining 15 sessions should only be provided to patients who have responded but not achieved full symptom remission. This is in line with Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 clinical guidelines for the management of adults with major depressive disorder.

MSAC noted that the proposed MBS item descriptors have been modified in the resubmission to specifically exclude maintenance treatment with rTMS. MSAC considers this appropriate because of the lack of evidence for comparative safety and clinical effectiveness of rTMS for this use.

MSAC noted that both the EUnetHTA 2017 and HQO 2016 reports showed positive results for rTMS. MSAC considered this sufficient evidence for the clinical effectiveness of initial treatment with rTMS.

MSAC noted that the resubmission provided no new clinical evidence for the effectiveness of rTMS for retreatment, after either successful or failed rTMS treatment. MSAC noted some evidence suggesting that those who respond to rTMS will probably respond to a further course of treatment if a relapse occurs, with a similar level of benefit. No studies have included patients who failed to respond to the initial course. The duration of therapeutic benefit is also uncertain, and there is no evidence regarding a suitable interval between treatments.

MSAC noted that the additional evidence on maintenance rTMS provided in the resubmission is still limited and weak. Observational studies assessing rTMS maintenance treatment suggest some benefit compared with no maintenance treatment or maintenance treatment with antidepressants alone. However, the one published randomised trial (Benadhira et al., 2017) that compared maintenance rTMS with sham rTMS was insufficiently powered to detect statistically significant differences between rTMS and sham arms at any timepoint.

MSAC noted that the efficacy results for rTMS from the EUnetHTA 2017 report are now applied in the economic modelling (instead of Papadimitropoulou, 2017), which produces a more conservative economic model. However, the studies included in the Papadimitropoulou 2017 review are more applicable to the population sought for MBS listing in terms of duration of rTMS therapy and level of treatment resistance.

MSAC noted that some issues remain with model inputs for remission and response rates, and the incremental cost-effectiveness ratio (ICER) is highly sensitive to changes in these estimates. MSAC also noted that a sensitivity analysis allowing retreatment with antidepressants, but not rTMS, produced an ICER more than 35% higher than the base case analysis.

MSAC noted that the resubmission did not address some issues with the structure of the model, including the:

- appropriateness of the chosen cycle length (3 months, which has implications for the interval between treatment cycles)
- high level of uncertainty regarding the probability of hospitalisation and therefore the cost offsets related to hospitalisation.

The uncertainty regarding the cost of adverse events associated with rTMS has also not been addressed. MSAC noted that the economic model was not appropriately structured or populated to specifically assess the cost-effectiveness of retreatment with rTMS. Given the short time horizon of the model (3 years), the full benefits of retreatment may not be realised. MSAC noted that the estimated ICER in the resubmission is much higher than that in Application 1196.1 ($37,734 vs $6,489 per quality-adjusted life year [QALY]). MSAC also noted that the resubmission did not consider that rTMS may be associated with an additional consultation, over antidepressant treatment alone, if the patient requires a referral to another psychiatrist for rTMS treatment. A sensitivity analysis showed that the ICER is moderately sensitive to this additional cost (10% increase in the ICER).

MSAC noted that despite structural and input issues with the model, the respecified base case and sensitivity analyses in the Critique show that rTMS largely remains cost-effective (ICER less than $50,000/QALY).

MSAC considered that the financial implications are likely underestimated, because:

- repeat rTMS use may occur
- additional consults may be co-claimed
- cost offsets are overestimated.

MSAC acknowledged the risk of uptake being higher than predicted because of the ease of rTMS administration, the low risk of side effects and the vulnerability of the patient population.

MSAC noted the issue of inequity of access for rural and remote patients who may not have access to specialist psychiatrists and treatment centres. MSAC also noted the importance of ensuring personnel delivering rTMS are appropriately trained.

MSAC noted that rTMS maintenance treatment is commonly mentioned in consumer discussions on the Beyond Blue website. Some consumers say long-term maintenance is the only thing that helped them; other consumers had results after 5–10 sessions. Consumers mention the tedium of the treatment and the disruption caused by the need for multiple sessions each week. MSAC also noted consumer criticism that having to receive treatment in hospital because rTMS is not on the MBS is occupying a bed unnecessarily.

4. Background

Previously, MSAC assessed rTMS under Application 1101 in 2007. Application 1196 was considered by MSAC at its November 2014 meeting and the previous resubmission (1196.1) was considered at the July 2018 meeting.

At the July 2018 meeting, the MSAC deferred its advice on MBS funding for rTMS for the treatment of depression. MSAC accepted that there was a clinical need and place for rTMS in the initial treatment, retreatment of relapse of major treatment-resistant depression, but

considered that the evidence presented was limited and weak. MSAC did not accept that there was a place for maintenance treatment with rTMS.

MSAC requested further evaluation from evidence provided in EUnetHTA Report, March 2017 (herein referred to as EUnetHTA 2017; and the Ontario Health Technology Assessment Series, March 2016 (herein referred to as HQO 2016). MSAC also requested that the proposed MBS item descriptors (to exclude maintenance), MBS fees, economic evaluation and MBS costings be reconsidered using a 'frame of reference' approach based on the extent of clinical benefit of rTMS being similar to the clinical benefit of switching to other pharmacological antidepressant agents on a cost per patient for the same duration of episodic treatment [Public Summary Document (PSD) Application No. 1196.1 2018, p2].

5. Prerequisites to implementation of any funding advice

Refer to Application 1196.1 PSD 2018, pp5-6 for details of three rTMS items listed on the ARTG.

6. Proposal for public funding

The resubmission presented updated item descriptors for rTMS in response to MSAC comments for Application 1196.1 (changes highlighted in green and Critiques edit's in red). Specifically, separate MBS item descriptors for the treatment prescribing session and the treatment delivery session are presented in Table 1 and Table 2, respectively. The current resubmission also proposed updated fees (highlighted in blue).

If co-claiming was suitable, the Critique stated that the assessment and prescribing item should be Category 3 – Therapeutic Procedures (rather than Category 1 – Professional Attendances).

The Critique also raised the issue to MSAC whether the mapping procedure should be restricted to psychiatrists as suggested by the College, or whether other appropriately trained health professionals may be eligible to do it.

The Critique also commented that the proposed items do not explicitly preclude retreatment with rTMS.

Table 1 Proposed MBS item descriptor, patient assessment and prescribing of rTMS

Category 3 – THERAPEUTIC PROCEDURES ~~or Category 1 – PROFESSIONAL ATTENDANCES*~~
MBS ##### REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION (rTMS) treatment prescription by a psychiatrist The patient to whom the service is provided must: • be an adult (≥18 years) diagnosed with a major depressive episode (MDE) • have failed to receive satisfactory improvement despite the adequate trialling of at least two (2) different classes of antidepressant medications, unless contraindicated ~~or intolerant.~~ • have undertaken psychological therapy unless inappropriate The service is prescribed by a psychiatrist with appropriate training in rTMS Fee: $186.40 (from $385 in Application 1196.1) Note: 1. The trialling of each antidepressant medication must have been at the recommended therapeutic dose for a minimum of three (3) weeks. Where appropriate, the treatment must have been titrated to the maximum tolerated therapeutic dose. The patient's adherence to antidepressant treatment must have been formally assessed. This item enables a psychiatrist to prescribe rTMS, ~~to determine if the patient is eligible to have the treatment,~~ to do the "mapping" procedure whereby the location of the motor cortex on the patients scalp is determined (enabling measurement forward to the dorsolateral prefrontal cortex), to assess the patients resting motor threshold to determine treatment intensity and to prescribe the dose of rTMS as a proportion of the motor threshold. This item is not to be used when it is determined that the patient is ineligible to have the treatment

~~Red~~ Green text indicates changes made to the proposed wording since MSAC Application 1196.1
Blue indicates the previous proposed fees from Application 1196.1
* A Category 1 listing was suggested as an alternative in the Critique of MSAC Application 1196.1 (Table 2)

Table 2 Proposed MBS item descriptor, rTMS treatment delivery

Category 3 – THERAPEUTIC PROCEDURES
MBS ##### REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION treatment provided by a health care professional, nurse or allied health professional. Patient must have previously received, or been eligible for, MBS-subsidised access to REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION (rTMS) treatment prescription by a psychiatrist (MBS #####) during the current course of treatment. The service is performed by personnel with appropriate training in rTMS. Fee: $160 (from $185 in Application 1196.1) This item enables a nurse or allied health professional to provide rTMS treatment to a patient, under medical supervision. The rTMS treatment must be prescribed by a psychiatrist (as described in MBS item #####) and be given in a setting where appropriate medical assistance is available if required. This item number is not be used for the use of TMS as maintenance therapy for the prevention of relapse of depression

~~Red~~ Green text indicates changes made to the proposed wording since MSAC Application 1196.1
Blue indicates the previous proposed fees from Application 1196.1

The summary of the changes to proposed MBS item descriptors are provided in Table 3 (and highlighted in Table 1 and Table 2).

Table 3 Summary of changes to proposed MBS item descriptors

Suggested changes to item descriptors during evaluation of MSAC Application 1196.1	Proposed item descriptor in current resubmission
"MSAC agreed with PASC that the definition of 'adequate' trialling of antidepressants in the item descriptor should mean two full courses of antidepressants from two different classes; it does not include treatment where a patient was intolerant and did not complete the course" (PSD, p.2).	The descriptor now specifies the requirement that two full courses of antidepressant medications from two different classes are to be trialled, with intolerance to a particular antidepressant within a class not constituting an adequate trial.
"MSAC suggested that the descriptor should also reinforce that psychotherapy must have also been previously trialled" (PSD, p.2)	Wording included in the descriptor which states that the patient must have previously trialled psychotherapy, unless inappropriate.
MSAC requested that the proposed MBS item descriptors be updated to exclude maintenance treatment (PSD, p.1).	The current resubmission presents further evidence to support the use of rTMS as maintenance treatment. Nevertheless, the suggestion by MSAC to exclude maintenance TMS treatment from the item descriptor has been accepted.
"Although the [first] item number is proposed to cover the assessment of whether a patient is suitable for rTMS or not, it should be explicit that the item is unable to be claimed if the patient is deemed ineligible for treatment" (Critique, p.30)	The requirement that the item number is not to be used when it is determined that the patient is ineligible to have the treatment has been included within the descriptor.
"ESC queried whether a limit to the number of treatments should be specified" (PSD, p.16).	The Applicant suggests a limit of 35 sessions for acute treatment would be reasonable and clinically appropriate, as stated in the Applicants response to the ESC report for MSAC Application 1196.1. Whether this needs to be specified in the descriptor itself will be left to the discretion of the MSAC.

Source: Table 5 of the Resubmission

7. Summary of Public Consultation Feedback/Consumer Issues

This was unchanged. Refer to Application 1196.1 PSD 2018, p7.

8. Proposed intervention's place in clinical management

This was unchanged. Refer to Application 1196.1 PSD 2018, pp7-8.

9. Comparator

Consistent with the previous resubmission, the main comparator to rTMS considered in the current resubmission is third line antidepressant therapy.

10. Comparative safety

No new evidence was presented specifically assessing comparative safety of rTMS + antidepressants *vs.* antidepressants alone. Therefore, the previous evidence for safety and the clinical claim of superior safety compared with third line antidepressants remains. MSAC noted that there are no major safety concerns related to use of rTMS [Application 1196.1 PSD 2018, p3].

11. Comparative effectiveness

As requested, the current resubmission presented clinical evidence from EUnetHTA 2017 and the HQO 2016 Report. In addition, the applicant further identified a more recent systematic review and meta-analysis of rTMS versus sham, conducted by several of the authors of HQO 2016 (Sehatzadeh 2019) (Table 4).

Primary evidence
The authors in the HQO 2016 report commented that the weighted mean difference (WMD) in reduced depression scores on the Hamilton Rating Scale for Depression (HAM-D) (WMD of 2.31, 95% CI: 1.19–3.43, $p < 0.001$) did not meet the pre-specified criteria for clinical significance (specified a priori as 3.5 points). However, the Critique highlighted the PBAC accepted minimal clinically important difference (MCID) of 1.5 (based on Coleman 2012) for the purposes of the purposes of a cost-minimisation analysis between two active antidepressant medications was appropriate as a conservative cut-off for showing no difference. Therefore, the Critique reasoned that the 3.5 points as per specified a prior by the HQO 2016 report may therefore be more appropriate.

Included is results from the Critique's additional meta-analysis based on the systematic review by Sehatzadeh et al. (2019), which assessed unilateral or bilateral high frequency **rTMS + antidepressants** versus **sham + antidepressants** were included if the participants in the study had failed to respond to at least two different antidepressants. The Critique stated that the most applicable results on which base effectiveness of rTMS would therefore be the systematic review which presents data on rTMS + antidepressants vs sham + antidepressants (Sehatzadeh 2019).

Table 4 Summary of systematic reviews and HTA reports (abridged version)

	HTA reports requested to be reviewed by MSAC		Updated HQO review
	HQO 2016	**EUnetHTA 2017**	**Sehatzadeh 2019**
Selection criteria			
Trial design	RCTs of rTMS vs ECT * or sham	RCTs of rTMS vs ECT * or sham	RCTs of rTMS vs sham *Critique confirmed majority of studies (and all of those since 2011) provided rTMS alongside antidepressants*
Population	Adult patients (≥18 years) with unipolar depression only or proportion of bipolar patients ≤20%	Adult patients (>18 yrs) with unipolar MDD or proportion of bipolar patients ≤20%	Adult patients (≥18 years) with unipolar depression only or proportion of bipolar patients ≤20%
rTMS specifications	HF unilateral (≥5 Hz) to the left DLPFC; at least 10 sessions per patient	HF unilateral (≥5 Hz) to the left DLPFC as monotherapy or add-on therapy	HF unilateral (≥5 Hz) to the left DLPFC or sequential bilateral LF to the right DLPFC, complied with rTMS safety guidelines, one session per day, at least 10 sessions per patient
Definition of TRD	≥80% of patients resistant to treatment in each study	As per HQO 2016. *See note ŧ*	≥80% of patients resistant to treatment in each study
Included studies	23 RCTs (2 were not included in meta-analyses)	25 RCTs (2 additional primary studies included (Solvason 2014 and Kang 2016	23 RCTs (of which 19 are unilateral rTMS versus sham)
Results	Response RR=1.72 (95% CI 1.13, 2.62, p =0.011) Remission RR=2.20 (95% C:1.44, 3.38, p <0.001) WMD in depression scores=2.31 (95% CI: 1.19, 3.43)[a]	Response RR=1.82 (95% CI 1.18, 2.82, p=0.0068). Remission RR=2.16 (95% CI 1.42, 3.29, p=0.0003) WMD in depression scores =as per HQO 2016	Response RR=2.00 (95% CI 1.26, 3.19) Remission RR= 2.33 (95% CI 1.52, 3.58) WMD in depression scores =3.36 (95% CI: 1.85–4.88) *Critique's meta analysis* *Response RR= 2.30 (95%CI 1.29, 4.12)* *Remission RR=3.68 (95%CI 1.85, 7.32)* *WMD = 4.16 (95% CI 2.08, 6.24)*

Source: Compiled using Table 3 of the Resubmission and Table 1 of the Critique

Abbreviations: CI, confidence interval; CrI, credible intervals; DLPFC, dorsolateral prefrontal cortex; HQO, Health Quality Ontario; HTA, health technology assessment; MDD, major depressive disorder; NMA, network meta-analysis; RCT, randomised controlled trial; RR = rate ratio/relative risk; rTMS, repetitive transcranial magnetic stimulation; SMD, standardised mean difference; SR, systematic review; WMD, weighted mean difference

* Trials comparing rTMS with ECT are not relevant to the submission and are not discussed in the table

ŧ The initial scope of the report specified the identification of trials where patients had a 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. However, due to the identification of the HQO report in Phase 1 of the search, which included nine RCTs with a less strict inclusion criteria where the study population was defined as having failed at least one antidepressant medication, the scope of the EUnetHTA review was subsequently altered (EUnetHTA 2017, p.25).

[a] Prespecified criteria for clinical significance on the Hamilton Rating Scale for Depression (HAM-D)[2] was specified a priori as 3.5 points

Supportive evidence: rTMS as maintenance treatment

The current resubmission presented results from two reviews (Rachid et al.; 2018 and Senova et al. 2018) comprising 11 unique studies assessing rTMS maintenance treatment in TRD. The studies were largely non-randomised and non-comparative with heterogeneity in terms of duration and protocol for maintenance, rTMS intensity and frequency parameters and the adjunctive use of antidepressant medication. The Critique stated that the updated evidence is still limited and weak. Observational studies assessing rTMS maintenance treatment are consistent that there appears to be some benefit compared to no maintenance treatment or maintenance treatment with antidepressants alone. However, there is currently only one randomised trial published comparing maintenance rTMS with sham rTMS, which was

insufficiently powered to report statistically significant differences between rTMS and sham arms after correcting for multiple analyses.

Clinical Claim

The clinical claim was unchanged; rTMS plus antidepressants is superior to antidepressants alone.

12. Economic evaluation

The current resubmission presented a cost-utility analysis of rTMS + antidepressants *vs*. third-line antidepressants in TRD, over a three year time horizon. The Critique stated that the structure of the microsimulation model is generally unchanged from the previous submission, however the model no longer allows for rTMS retreatment nor maintenance. The Critique stated that previous issues, including model structure issues (e.g. patients in the no response/relapse health state are not at risk of hospitalisation) were not addressed in current resubmission.

The treatment effect of rTMS was now based on relative risk (RR)s for remission (2.16) and response (1.82) reported in the EUnetHTA report (2017), and for antidepressants continues to be estimated from the STAR-D study (now the rates of response and remission observed in patients treated with mirtazapine and nortriptyline in Step 3 of the STAR-D study). However, the Critique highlighted patients may have received prior bupropion or buspirone use in combination with citalopram (Step 2); therefore the applicability concerns noted previously remain [MSAC Application 1196 PSD, November 2014].

Furthermore, the Critique stated that the remission and response rates from the STAR-D study were defined based on changes in the Quick Inventory of Depressive Symptomatology–Self-Report (QIDS-SR) score. A recent analysis (Kirsch et al. 2018) of the outcomes from the STAR-D study observed that remission and response rates were substantially inflated on the QIDS-SR relative to scores based on the Hamilton Rating Scale of Depression (HAM-D). Therefore the modelled baseline remission and response rates may be an overestimate.

The current resubmission's base-case incremental cost-effectiveness of rTMS (plus antidepressant) compared to antidepressant alone is presented below in Table 5.

Table 5 Incremental cost-effectiveness

Treatment arm	rTMS	AD	Incremental
Cost	$21,663.24	$20,732.36	$930.88
QALYs	1.7269	1.7022	0.0247
ICER			$37,734

Source: Table 10 of the Resubmission
Abbreviations: AD, anti-depressants; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year; rTMS, repetitive transcranial magnetic stimulation

The Critique respecified the base case ICER using:

- the treatment effect of rTMS based on the most applicable data (i.e. *Critique's* additional meta-analyses based on Sehatzadeh et al. 2019), and
- baseline remission and response rates on antidepressants based on Blumberger et al. 2016 (largest study included in meta-analysis by Sehatzadeh et al. 2019 (Table 6).

Table 6 Respecified base case assuming RRs from Sehatzadeh et al. (2019), with varying baseline remission and response rates.

	Inc. cost	Inc. QALYs	ICER
Base case (EUnetHTA RRs and STAR-D baseline remission and response rates, 10.7% and 15.6%)	***$931***	***0.0247***	***$37,734***
Sehatzadeh et al (2019) RRs, assuming baseline remission and response rates from STAR-D (10.7% and 15.6%)	*-$625*	*0.0558*	*Dominant [a]*
Sehatzadeh et al (2019) RRs, assuming baseline remission and response rates from Blumberger et al. (2016) (2.4% and 4.9%)[b]	*$1,583*	*0.0134*	*$118,135*
Sehatzadeh et al (2019) RRs, assuming the weighted average baseline remission and response rates (4.2% and 11.5%)[c]	*$814*	*0.0243*	*$33,495*
Sehatzadeh et al (2019) RRs, assuming the average baseline remission and response rates, weighted by the random effects meta-analysis weights (6.3% and 21.3%)[d]	*-$387*	*0.0409*	*Dominant [a]*

Source: SBA Critique Table 3
ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year; RR = relative risk.
[a] A dominant ICER indicates that the intervention (i.e. rTMS + AD) is less costly and is associated with more QALYs than the comparator.
[b] Blumberger et al. (2016) was the largest and among the most recent studies included in the meta-analysis conducted by Sehatzadeh et al. (2019). This study was also conducted in a comparable setting (Canada).
[c] Average remission and response rates were estimated from the studies in the meta-analysis conducted during the Critique, weighted by patient numbers in each of the included studies.
[d] Average remission and response rates were estimated from the studies in the meta-analysis conducted during the Critique, weighted by the random effects weights as reported in SBA Critique Figure 2 and SBA Critique Figure 1 respectively.

The Critique stated that the ICER is highly sensitive to changes in these estimates (an increase in the ICER of up to 900% was observed when values from alternate sources were tested). The Critique stated that given that the Australian studies included in the meta-analysis could not provide information on both remission and response rates in an Australian population, MSAC may wish to consider what baseline remission and response rates would be most applicable, and whether the base case requires further respecification.

13. Financial/budgetary impacts

Consistent with previous resubmission, an epidemiological approach was used to estimate the financial implications to the MBS. The Critique stated that the current resubmission has not presented the financial implications to the MBS; this is presented in Table 7.

Table 7 Resubmission base net financial implications to the MBS

	Year 1	Year 2	Year 3	Year 4	Year 5
Cost of rTMS to the MBS	*$45,076,623*	*$72,241,023*	*$86,936,156*	*$87,129,717*	*$75,378,870*
Change in use of other MBS items	*−$2,240,507*	*−$5,831,204*	*−$10,152,315*	*−$14,483,046*	*−$18,229,708*
Net implications to the MBS	***$42,836,116***	***$66,409,818***	***$76,783,842***	***$72,646,671***	***$57,149,161***

Note: These have not corrected for the minor errors identified

However, the Critique stated the costs offsets to the MBS are likely to have been substantially overestimated, as total hospital costs associated with ECT treatment have been assumed to offset MBS costs, and that cost offsets have been assumed to accrue in all years subsequent to rTMS treatment. A respecified analysis has been presented to attempt to account for these limitations (Table 8), sensitivity analyses exploring further key uncertainties have been presented around the respecified base case.

Table 8 Respecified net financial implications to the MBS

	Year 1	***Year 2***	***Year 3***	***Year 4***	***Year 5***
Population with TRD (less prior patients)	112,488	103,015	86,779	66,902	47,027
Uptake rate of rTMS	10.00%	17.50%	25.00%	32.50%	40.00%
Patients starting rTMS	11,249	18,028	21,695	21,743	18,811
Resubmission base net to the MBS	***$42,836,116***	***$66,409,818***	***$76,783,842***	***$72,646,671***	***$57,149,161***
1. Estimating MBS costs as a proportion of ECT cost offsets [a]	*$44,706,939*	*$71,278,874*	*$85,261,024*	*$84,740,015*	*$72,370,968*
2. Assuming cost offsets apply for three years (as per the model time horizon)	*$42,836,116*	*$66,409,818*	*$76,783,842*	*$74,887,178*	*$62,980,366*
Respecified net implications to the MBS (i.e. multivariate analysis #1 and #2)	***$44,706,939***	***$71,278,874***	***$85,261,024***	***$85,109,698***	***$73,333,116***
Assuming maximum uptake of 60%[b]	*$44,706,939*	*$91,749,890*	*$112,416,162*	*$101,895,560*	*$71,359,525*
Assuming all prescription rTMS items are claimed with item 306	*$46,489,199*	*$74,135,171*	*$88,698,344*	*$88,554,671*	*$76,313,479*

Source: compiled from Table 12 of Critique and SBA Critique Table 5

Note: These have not corrected for the minor errors as identified in Table 12.

[a] In the economic model, ECT treatment was comprised of 10 sessions at $907 (based on AR-DRG U40Z). MBS items associated with ECT are item 14224 ($70.35) and item 20104 ($79.20). Thus the component of ECT therapy costs attributed to the MBS is approximately 16.5%.

[b] While the proportion that uptake increases from Years 1 to 5, the pool of patients eligible for rTMS decreases as the number of patients eligible who had not previously received rTMS decreases. Thus the implications to the MBS are observed to peak in Year 3.

14. Key issues from ESC for MSAC

ESC key issue	ESC advice to MSAC
Adequacy of response to MSAC	Applicant has provided the comparative effectiveness evidence requested from MSAC in response to Application 1196.1. A number of MSAC's previous concerns about the economic evaluation have been addressed.
Comparative effectiveness	HQO 2016 and EUnetHTA 2017 reports, and the results of a recent meta-analysis, confirm that rTMS is effective compared with sham, although long-term effectiveness is unknown.
Retreatment	There was lack of data to support the use of rTMS in retreatment. Specifically, there was substantial uncertainty related to the likelihood of response based on previous response, duration of therapeutic benefit, and the frequency of retreatment. The base case model and financial estimates did not include rTMS retreatment.
Evidence for rTMS maintenance therapy	New evidence remains to be weak as is observational and subject to selection bias and the effects of confounding. RCT evidence is lacking. The base case model and financial estimates did not include rTMS maintenance therapy.
Safety	Evidence for safety of rTMS is unchanged. There are no major safety issues, although the long-term outcomes are still unknown.
Item descriptor	Clarify whether eligibility assessment is included in the fee or should it be excluded in the descriptor. Amend wording to exclude retreatment It is likely that an additional consultation fee will be claimed; should co-claiming be considered?
Model inputs: effectiveness data	Probabilities of response and remission are key drivers of the model, with significant impact on the ICER. Evidence on effectiveness of third-line antidepressants and of rTMS does not strictly match the proposed population.
Model inputs: hospital admission data	High level of uncertainty regarding the probability of hospital admissions and probability of remaining in hospital, which has a moderate to significant impact on the ICER.
Financial/budgetary impact	The financial/budgetary impact has been underestimated. The treatment model being proposed does not fit the MBS funding model. The true financial impact on the health system may be underestimated because there is no direct relationship between the MBS cost (referrer) and cost to medical practices (to employ treatment provider).

ESC Discussion

Application 1196.2 is a resubmission seeking Medicare Benefits Schedule (MBS) listing for repetitive transcranial magnetic stimulation (rTMS) to treat depression after unsuccessful trialing of at least two different classes of antidepressant medications. ESC noted that the current resubmission includes the 'frame of reference' approach previously suggested by MSAC, and accepted by ESC, estimates the incremental cost-effectiveness of rTMS continued alongside antidepressants, compared with antidepressants alone.

ESC agreed with the view of the Royal Australian and New Zealand College of Psychiatrists (RANZCP) that the prescription of rTMS, including the determination of treatment site and parameters (i.e. the mapping session), should be a specialist medical activity undertaken by TMS-trained psychiatrists.

ESC noted that the revised MBS item descriptor for patient assessment and prescribing now includes a note that 'This item is not to be used when it is determined that the patient is ineligible to have the treatment'. ESC considered that this could be further revised to include 'or when prior treatment has been unsuccessful' to exclude use for re-treatment in patients who did not respond to initial treatment.

ESC noted the applicant's request that MSAC reconsider the need to specify such 'strict' requirements for defining treatment resistance. However, ESC considered the descriptor wording has sufficient scope for clinical interpretation and recommends that it does not need to be changed.

ESC noted that the proposed fee for patient assessment and prescribing has been significantly reduced (from $385 to $186.40) to be more in line with fees charged by private providers (e.g. the Black Dog Institute). However, ESC noted that the Black Dog fee of $200 for mapping and prescribing does not include assessment for eligibility; patients are charged separately for the assessment session using MBS consultation item 306, which has a fee of $186.40 (making Black Dog's total charge $386). ESC therefore queried whether the lower fee proposed in the resubmission will include assessment of eligibility.

ESC noted the applicant's pre-ESC response (May 2018) that if a patient is assessed by a non-TMS trained psychiatrist, they would claim MBS item 306 and refer the patient to a TMS-trained doctor who would claim the proposed fee for prescription. If the patient is assessed by a TMS-trained doctor, a separate consultation for eligibility assessment would not be required. However, ESC considered that, if assessment is not included, the most likely scenario would be an additional consultation fee on top of the mapping and prescription item.

ESC queried whether any changes are required to the item descriptor if assessment is not included, and whether co-claiming should be considered. ESC noted that the economic evaluation presented by the submission does not represent these scenarios. However, ESC noted that if an additional consultation fee ($186.40) is included, the impact on the ICER will be moderate (increasing the base case ICER to $41,512). ESC also queried what the impact would be on out-of-pocket costs for patients.

ESC commented that the treatment model being proposed (i.e. initiated by a specialist but provided by healthcare professional not eligible for Medicare) does not fit the MBS funding model. It is unclear how these items will be used in the real world. It is possible that the true financial impact on the health system has been underestimated because there is no direct relationship between the MBS cost (claimed by the referrer) and the cost to hospitals of employing the person providing the treatment.
ESC noted that the proposed fee for rTMS treatment delivery has also been reduced (from $185 to $160 per session), in line with the fee charged by the Black Dog Institute. ESC also noted that, given the need for five treatments per week for 4–6 weeks, this would contribute most of the cost.

ESC noted the Critique's comment that the proposed items do not explicitly exclude the use of rTMS for retreatment, and the applicant's response that they would consider restricting retreatment to patients with prior response or those with sufficient time between treatments (suggesting 1 year as an example). However, ESC noted that there is no clear evidence about

the likelihood of response based on previous response. The duration of therapeutic benefit is also uncertain, and there is no evidence regarding a suitable interval between treatments. Based on these critical uncertainties, ESC advised that the item descriptor should be amended to exclude retreatment with rTMS.

ESC noted consumer comments that there have been reports of seizures associated with rTMS, and that these seem to occur during the procedure rather than after treatment. However, the frequency of seizures, and whether there is any difference between the intervention and sham, is unknown. Consumers have also complained of facial spasms during treatment for which they were not sufficiently prepared. ESC noted that consumer information available from the Black Dog Institute and Beyond Blue do not mention any safety issues.

ESC noted that the lack of evidence for consumers' opinions on the value of rTMS. RANZCP argues that because rTMS is a non-invasive procedure, people are very likely to opt for it. However, this does not reflect the reality of decision-making capacities among consumers generally or people with major depression specifically.

ESC noted that because psychiatrists are largely metro-based, access will be limited for rural/remote patients. The requirement for 20–30 treatments over a number of weeks will have a significant impact on rural/remote patients. People with major depression may be out of work and therefore unable to afford consultation with a psychiatrist.

ESC noted that out-of-pocket costs will be affected by specialist fees and gaps in private health insurance payments. Follow-up treatments will be an issue; the length of treatment will have a significant impact on both patient outlays and income-earning capacity. However, this might be offset if improved health allows the person to return to work.

ESC noted that both the European Network for Health Technology Assessment (EUnetHTA 2017) report and the Ontario Health Technology Assessment Series (HQO 2016) report showed positive results for rTMS. The EUnetHTA report found that patients were approximately twice as likely to experience response or remission with rTMS as with sham. The HQO report showed a significant reduction in Hamilton Rating Scale for Depression (HAM-D) scores for rTMS compared with sham. However, although the studies in the HQO report all included a sham, ESC had limited confidence in the consistency of shams between studies. ESC also noted that the Critique's meta-analysis (based on the systematic review by Sehatzadeh et al.., 2019) showed very positive results for rTMS compared with sham when antidepressants are used concurrently. ESC agreed with the Critique and considered the most applicable evidence on which to base the effectiveness of rTMS would be Sehatzadeh et al.. 2019 (rTMS + antidepressants vs. sham + antidepressants) (with 2 or more failed trials of antidepressants).

ESC considered that the updated evidence on maintenance rTMS provided in the submission is still limited and weak, and does not warrant reconsidering advice regarding maintenance treatment. Observational studies assessing rTMS maintenance treatment are consistent in showing some benefit compared with no maintenance treatment or maintenance treatment with antidepressants alone. However, these studies have a high risk of selection bias and confounding. The only randomised controlled trial comparing rTMS with sham was insufficiently powered to report statistically significant differences between the rTMS and sham arms. ESC noted the resubmission's item descriptor was updated to exclude maintenance treatment with rTMS.

ESC noted that the updated economic evaluation in the resubmission addresses MSAC's previous concerns regarding the intervention (rTMS + antidepressants to reflect current clinical practice); proposed fees; baseline response/remission rates (related to natural history of depression for the proposed target population); and rTMS effects.

ESC noted that, after rTMS maintenance and re-treatment were removed from the base case, the resulting incremental cost-effectiveness ratio (ICER) ($37,734) is significantly higher than in the previous submission ($6,489) because of more conservative figures and assumptions used in the model. ESC noted that changes to the rTMS cost in the resubmission has minimal effect on the ICER.

ESC noted the sensitivity of the model to effectiveness data (remission and response rates of rTMS vs antidepressants), which has an indirect impact on cost offsets attributable to hospitalisation and electroconvulsive therapy. Changes in baseline remission and response rates change the ICER significantly. ESC noted that the evidence for effectiveness of the comparator (third-line antidepressants) and of rTMS does not strictly match the proposed population (e.g. different stages of anti-depressant resistance, different classes of anti-depressants).

ESC noted that the model inputs for hospitalisation (e.g. probability of hospital admissions: 10.4%) remain based on assumption and consistent with previous MSAC advice, are highly uncertain. Changing these inputs has a moderate to significant impact on the ICER. A three-way sensitivity analysis changing inputs for hospital admission resulted in a 60% increase in the baseline ICER to ~$58,000 (changing probability of admission after treatment failure from 10.4% to 8%, probability of remission if admitted from 35% to 40%, and probability of remaining in hospital from 50% to 10%).

ESC noted that the cycle length of the model is 3 months, but according to 2015–16 data from the Australian Institute of Health and Welfare, the national average number of days per hospitalisation for 'depressive episodes' was only 14.3 days. ESC considered a more reasonable assumption in the model would be that all patients who do not gain remission are discharged to the 'No response/relapse' state at the end of the cycle.

ESC agreed with the Critique that the financial/budgetary impact on the MBS has been underestimated, especially considering that an additional consultation item may be claimed.

15. Other significant factors

Nil.

16. Applicant's comments on MSAC's Public Summary Document

The Applicant, RANZCP, welcomes MSAC approval of repetitive transcranial magnetic stimulation (rTMS) for the initial treatment of antidepressant medication resistant major depressive disorder (MDD) and is committed to working closely with MSAC and the Department of Health to ensure reimbursement for rTMS is available as soon as possible.

RANZCP also appreciates MSAC's acknowledgement of the clinical need for re-treatment with rTMS and accepts that whilst the evidence is not as robust as that for initial acute rTMS therapy, the requirement for re-treatment in patients who have previously responded to rTMS is an important aspect of patient management given the relapsing-remitting nature of antidepressant medication resistant MDD.

RANZCP is willing to provide any further information on these and any other outstanding matters, including maximum session limits, to help inform the decision regarding re-treatment and finalise the MBS item descriptor(s) for rTMS.

17. Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website: visit the MSAC website