



Australian Government

Medical Services Advisory Committee

Public Summary Document

Application No. 1196.1– Repetitive Transcranial Magnetic Stimulation (rTMS) for the treatment of depression

Applicant: Royal Australian and New Zealand College of Psychiatrists

Date of MSAC consideration: MSAC 73rd Meeting, 26-27 July 2018

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 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 and 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 deferred its advice to request further evaluation of the evidence provided in:

- [EUnetHTA Report - Repetitive Transcranial Magnetic Stimulation for Treatment-Resistant Major Depression – March 2017](#)
- [Ontario Health Technology Assessment Series - Repetitive Transcranial Magnetic Stimulation for Treatment Resistant Depression: A Systematic Review and Meta-Analysis of Randomized Controlled Trials – March 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.

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

MSAC recalled that an application for listing of rTMS was first made to MSAC in 2007 (Application 1101) but funding was not supported because, although rTMS was found to be safe and less invasive than electroconvulsive therapy (ECT), there was insufficient evidence to support public funding. In a resubmission in 2014 (Application 1196), rTMS was found to be 'at least as equivalent, or more effective, than antidepressants, depending on the agent', MSAC again did not support funding due to uncertain effectiveness in the target population (patients with treatment-resistant depression) and uncertain cost-effectiveness. MSAC considered that any resubmission should include a clearer definition of the patient population and of the clinical setting for treatment, as well as evidence comparing rTMS against contemporary antidepressants in treatment-resistant patients and further consideration of the treatment costs of antidepressants.

MSAC noted that the resubmission was for rTMS for the treatment of adults with antidepressant medication-resistant MDD after unsuccessful trialling of at least two different antidepressant medications (unless contraindicated or intolerant). Proposed treatment consists of daily sessions (5 days a week) for 4–6 weeks (20–30 sessions of 45 minutes each). Although the mechanism of action of rTMS on depression is unclear, MSAC acknowledged the clinical and social burden of major depressive disorder and the difficulties faced in the diagnosis and treatment of this condition.

MSAC noted that in the RANZCP clinical practice guidelines for mood disorders, rTMS is positioned at step 2 of therapy (i.e. if psychosocial and formulation-based approaches fail). If rTMS does not work, step 3 is ECT. ECT is therefore not a direct comparator for rTMS. ECT is a more invasive procedure and intended for use in acute presentations. MSAC noted modifications to the RANZCP clinical practice guidelines for mood disorders occurred between 2015 and 2018. In 2015, the guidelines stated that rTMS could be trialled in patients with treatment-resistant depression but that it was more expensive and no more effective. In 2018, the guidelines recommended that patients could be treated with rTMS after they had failed one or more trials of standard antidepressant medications and psychological therapies.

MSAC noted that third-line antidepressant medication is an appropriate comparator for rTMS. 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. MSAC suggested that the descriptor should also reinforce that psychotherapy must have also been previously trialled.

MSAC considered that the extent of clinical benefit of rTMS over the comparator in the requested population may be similar to the extent of benefit of switching to other pharmacological antidepressant agents. This means that an MBS fee might be justified that is similar to these alternatives on a cost per patient for the same duration of episodic treatment (possibly around 3 months, rather than continuous treatment). This 'frame of reference' approach anticipates that these antidepressants might be continued alongside rTMS (rather than be replaced), which would affect any cost offset claims. This option would also need to consider any differential out-of-pocket consequences.

MSAC considered that the fee of \$385 proposed by the applicant for the treatment prescription session needs further justification. The critique suggested a fee of \$234.77 would be more appropriate based on input costs and charges by the Black Dog Institute and other providers. The Black Dog Institute offers treatment on a fee-for-service basis: fees are \$160 per session, and \$200 for the initial dosing (mapping) session.

MSAC questioned the assumption that all treatments will be performed in the outpatient setting and noted the high out-of-pocket costs for patients. MSAC noted the resubmission assumed that all services would be conducted in the outpatient setting, although currently only private inpatients have access to rTMS. MSAC considered that this could result in inequity and cost-shifting. MSAC expressed concern that procedures that could be done in the outpatient setting are being done in hospitals and may potentially be driving up costs with patients are being admitted to private hospitals for up to 3 weeks using private health insurance with high out-of-pocket costs. MSAC noted that Medibank is running a pilot private outpatient program.

MSAC noted the new data presented in the resubmission was a systematic review and meta-analysis by Gaynes (2014) and a network meta-analysis (NMA) by Papadimitropoulou (2017).

MSAC noted that there are no major safety concerns related to use of rTMS. The NMA showed a higher rate of withdrawal from treatment for rTMS vs placebo, but it did not compare rTMS with antidepressants in terms of withdrawals due to adverse events.

MSAC acknowledged that performing direct comparisons of rTMS and antidepressants in randomised controlled trials would be ethically challenging. The resubmission claim of superior effectiveness relative to third-line antidepressants was based on the NMA. However, MSAC noted that the NMA is only of medium quality; it provides point estimates of particular interventions (rTMS and antidepressants vs sham) with credible intervals, but does not provide pairwise comparisons of rTMS and antidepressants. The applicant's pre-MSAC response provided a summary of key pairwise comparisons of rTMS against selected antidepressants (derived from the NMA) but MSAC considered that, because of the wide confidence intervals, these data were not convincing.

MSAC noted that the NMA used credibility intervals rather than confidence intervals. rTMS exceeded the minimal clinically important difference compared with sham or baseline depressive symptoms, and there was a trend favouring rTMS over third-line antidepressants in terms of response and remission rates. However, because the credibility intervals were wide and overlapped, MSAC considered the data insufficient to claim that rTMS is superior. MSAC noted that ESC's reanalysis of the data using 83% confidence intervals showed significance for rTMS compared to selected antidepressants ($p < 0.05$). ESC recommended the resubmission reanalyse the NMA data to test noninferiority and superiority with selective serotonin reuptake inhibitors (SSRI) and serotonin and norepinephrine reuptake inhibitors (SNRI) as the comparator.

MSAC noted there was other available evidence which could be informative on the relative effectiveness of rTMS that was not presented in the resubmission, including the EUnetHA (European Network for Health Technology Assessment) report *Repetitive transcranial magnetic stimulation for treatment-resistant major depression 2017* and the Ontario Health Technology Assessment Series - *Repetitive Transcranial Magnetic Stimulation for Treatment Resistant Depression: A Systematic Review and Meta-Analysis of Randomized Controlled Trials* – March 2016.

MSAC noted that there is insufficient evidence to determine the effectiveness of rTMS for maintenance treatment (in patients who respond) or retreatment (in patients who do not respond or relapse). MSAC acknowledged updated data provided by the resubmission claiming that relapse treatment, retreatment and maintenance treatment are effective. The applicant claimed a relapse rate of 29.5% based on the pivotal Neurostar trial (O'Reardon, 2007), and used relapse rates from Richieri (2013) to update the economic model, which

raised the incremental cost-effectiveness ratio (ICER) from about \$6500 to \$28,000. With respect to maintenance therapy, the resubmission presented data from a review of 20 studies by Rachid (2018) that showed less relapse at 20 weeks after maintenance TMS compared with no additional TMS. The applicant's pre-MSAC response also provided data showing successful reintroduction of rTMS after relapse (Philip 2016; Fitzgerald 2006). However, MSAC noted that there was no exploration or measure of heterogeneity in terms of the rTMS treatment used (low frequency, high frequency, bilateral, or newer techniques such as synchronised rTMS, pulsed rTMS, deep rTMS or rTMS with priming stimulation) or whether rTMS was used alone or in addition to antidepressants.

MSAC suggested it would be desirable to collect more complete patient outcome data to inform its decision, but acknowledged that collecting this information systematically is challenging.

MSAC noted that in the review and meta-analysis by Gaynes, the average number of rTMS sessions provided was 12.75 (10–30 sessions over 2–6 weeks). MSAC therefore questioned whether the 20 to 30 sessions requested in the resubmission was excessive.

In terms of the economic model structure, MSAC noted that the time horizon for the model was 3 years but the data input was at 6 months. The longer time horizon would allow more time for benefits to accrue (e.g. quality of life [QoL] improvement, hospitalisation costs avoided). MSAC noted that the critique considered a shorter horizon to be more appropriate, given the limited study follow-up. MSAC also noted the uncertainty in the model about maintenance treatment, which may extend beyond 3 years. MSAC noted that the cycle length (i.e. the time that nonresponders or patients who relapse spend in that state and receive only maintenance antidepressants) was increased from 2 months (in the previous submission) to 3 months to match cost data.

MSAC considered that there were the following limitations in the economic model inputs:

- Baseline remission and response rates were derived using a population that did not match the proposed target population, and in which the trial had small numbers of participants. MSAC acknowledged the applicant's response that this would create a bias against rTMS, 'given that treatment outcomes for earlier lines of therapy have been shown to be more favourable'.
- There was no direct comparison of the relative efficacy of rTMS versus third-line antidepressants. A naive indirect comparison was done instead using point estimates of remission and response rates. MSAC noted that the critique considered that this led to significantly higher remission and response rates being modelled, which was not appropriate. In addition, improved QoL and cost offsets might not be realised, and underestimating the relative cost and overestimating the relative efficacy would substantially underestimate the ICER.
- There is considerable uncertainty regarding cost offsets in the model because they rely on significantly larger remission and response rates compared to antidepressants.

MSAC noted other factors in the model that may underestimate the cost, including:

- the cost of determining patients' suitability for rTMS was not included for those found not to be suitable for treatment (MSAC acknowledged the applicant's response that this would apply to less than 5% of patients)
- the increase in the cycle length increases the time between treatments, which will likely underestimate the cost of maintenance
- once treatment options are exhausted, patients remain in the no response/relapse state at no risk of hospitalisation (and no associated cost), which may not be reasonable

- uncertainty regarding the 10.4% probability of hospitalisations and cost offsets
- ECT in the model inappropriately includes a cost for consultation.

MSAC noted that the ICER is most sensitive to efficacy parameters. If there is no difference in effectiveness (and QoL and cost offsets are not realised), the ICER increases from \$6,489 to \$351,132. The impact of the probability and cost of hospitalisation is moderate: the ICER increases to \$26,961. Increasing the probability of maintenance from the assumed 10% to 50% has a moderate impact, increasing the ICER to \$20,192. Reducing the cost of hospitalisation by 50% has a moderate impact; the ICER increases to \$18,160. The model was not sensitive to utility parameters.

MSAC noted that the cost of rTMS to the MBS would increase from just under \$11.4 million in the first year to over \$53.7 million by year 5. However, MSAC considered that the uptake used to calculate costs is likely to be an underestimate because:

- the resubmission used a referral rate based on the privately funded setting, which underestimates the full extent of utilisation if rTMS becomes accessible to non-privately insured patients
- the referral rate used is from 2013 and may have increased since then with the availability of new clinics
- the budget impact analysis assumes an uptake of 10%; MSAC acknowledged the suggestion in the critique that uptake may be considerably higher than this
- the resubmission assumed only those eligible for rTMS are assessed for suitability; MSAC noted that the number who take up assessment is likely to differ from the number who are eligible.

MSAC considered that the financial/budgetary impact was underestimated because:

- the model allows for three rounds of rTMS treatment but the financial costings only include two
- the model includes maintenance for 3 years but the financial costs include only 1 year
- the cost offsets applied in all 5 years of the financial costings may not be realised if efficacy gain is not realised.

4. Background

MSAC considered Application 1196 at its November 2014 meeting. MSAC did not support public funding because of uncertain effectiveness and cost-effectiveness due to insufficient comparative data in treatment-resistant patients against current antidepressant treatments and uncertain costs.

Further information is available from the Public Summary Document (PSD) on the MSAC website at www.msac.gov.au.

5. Prerequisites to implementation of any funding advice

Items on the ARTG that are relevant to this application are shown in Table 1.

Table 1 Relevant rTMS devices for the treatment of depression currently listed on the ARTG

ARTG no.	Date of listing	Product description	Product category	Sponsor	Intended purpose
148142	5/12/2007	Psycho-cognitive electromagnetic stimulator	Medical Device Class IIa	Sonoray Pty Ltd	Treatment of Major Depressive Disorder in adult patients who have failed to achieve satisfactory improvement from two prior antidepressant medications, at or above the minimal effective dose and duration in the current episode.
225208	02/07/2014	Magnetic neural stimulation system, stationary	Medical Device Class IIa	Medilink Pty Limited	The device is a magnetic stimulator intended for non-invasive stimulation of neuromuscular tissue, by inducing small currents in the tissue using a brief pulse of electromagnetic energy and is intended for adults and children above the age of 2 years.
269712	11/02/2016	Psycho-cognitive electromagnetic stimulator	Medical Device Class IIa	AI Medical International Pty Ltd	This device produces a magnetic field which stimulates the cortical and peripheral nerves when applied to the skin. The stimulator is indicated for the treatment of Major Depressive Disorder in adult patients who have failed to receive satisfactory improvement from antidepressant medications.

Source: Therapeutic Goods Administration, accessed 05/01/2018 [Link to TGA.gov.au](http://www.tga.gov.au)

6. Proposal for public funding

The resubmission proposed two MBS items for the prescription and treatment of rTMS as outlined in Table 2 and Table 3.

Table 2 Proposed MBS item descriptor, first rTMS session in a course of treatment

Category 3 – THERAPEUTIC PROCEDURES
<p>MBS #####</p> <p>REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION (rTMS) treatment prescription by a psychiatrist</p> <p>The patient to whom the service is provided must:</p> <ul style="list-style-type: none"> • 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 antidepressant medications, unless contraindicated or intolerant. <p>The service is prescribed by a psychiatrist with appropriate training in rTMS</p> <p>Fee: \$385</p> <p>Note: 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.</p> <p>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.</p>

Table 3 Proposed MBS item descriptor, subsequent rTMS session in a course of treatment

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: \$185 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.

7. Summary of Public Consultation Feedback/Consumer Issues

Fifteen responses were received to the public consultation (one research psychologist; three researchers; one professional body; and ten consumers).

Professional body feedback noted that rTMS is currently used in private settings; if it were listed on the MBS it would facilitate equitable access for individuals who currently are not able to access such treatments. It was also noted that countries such as Canada, the United States, Israel and a number of European countries have recognised the efficacy of rTMS, resulting in clinical approval and adoption of the technique. The feedback stated that there is a pressing need for new treatment options for patients with treatment resistant depression, particularly as these patients are typically highly disabled and place a substantial demand on families, private and public health care systems.

Consumer feedback noted that rTMS was the first treatment which alleviated all symptoms in a non-invasive way without any side effects. It was claimed that rTMS will improve patient’s self-esteem and confidence, allow them to have a better standard of living, including work and relationships as well as relieving stress on family/carers/partners. Consumers also considered there would be less need for visits to the local GP and psychologists. Listing rTMS would increase availability to people experiencing financial hardship as well as increasing access in rural communities.

Consumer representatives noted access and equity concerns, exacerbated by the frequency and intensity of the treatment regimen for rTMS with resultant impact on quality of life, productivity and therefore potentially income. Consumers may find psychotherapy options preferable, but these options were not presented and compared making the information incomplete in terms of assessing cost and preference from a consumer perspective. Patient preferences should be considered to achieve a true perspective of the patient population.

Consumers may be impacted by compounding travel costs, out of pocket costs and loss of productivity. This impact would be compounded if a course of treatment needs to be repeated. The proportion of patients who would need this is unclear making it impossible to determine longer term impact.

8. Proposed intervention’s place in clinical management

rTMS is a non-invasive, non-systemic therapeutic device/treatment in which magnetic resonance imaging (MRI)-strength, pulsed, magnetic fields, generated by passing brief

current pulses through a coil placed on the head, are used to stimulate nerve cells in the region of the brain involved in mood regulation and depression.

Despite treatment advances over recent years and an armamentarium of pharmacological interventions for MDD, treatment resistance has continued to be a significant and disabling problem in the clinical management of major depression, with many patients failing to yield adequate clinical improvements. When used as an antidepressant therapy, rTMS therapy produces a clinical benefit without the systemic side effects typical with oral medications and has no adverse effects on cognition.

rTMS is a new intervention and is not currently listed on the MBS.

The clinical treatment algorithm for the management of patients with treatment-resistant depression including rTMS is presented in Figure 1 which indicates the use of rTMS following a failure to respond to two or more antidepressant medication strategies.

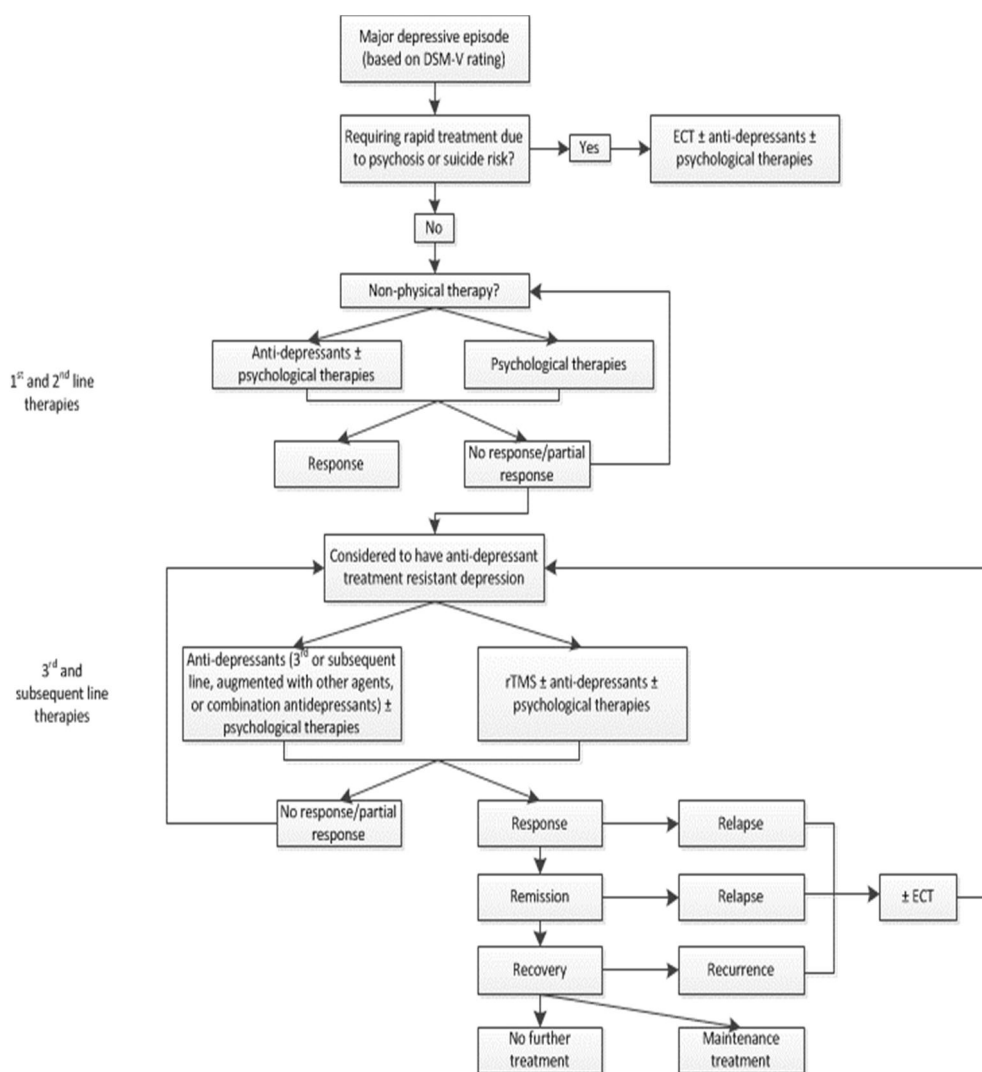


Figure 1 Clinical decision pathway for rTMS treatment

9. Comparator

The main comparator to rTMS considered in this resubmission is third line antidepressant therapy.

10. Comparative safety

As a non-systemic therapy, rTMS avoids the adverse effects that can be associated with antidepressant medications (e.g., weight gain, dry mouth, constipation, nausea, reduced libido, agitation, insomnia, diarrhoea, dizziness, fatigue, abnormal ejaculation, sweating, impotence, anxiety, weakness, and tremor) and the potentially serious adverse effects that can result from atypical antipsychotics (e.g., tardive dyskinesia, hyperglycaemia, weight gain, metabolic syndrome, blood dyscrasias, neuroleptic malignant syndrome, cognitive and motor impairment, coma and death).

The most clinically relevant side effect associated with rTMS is seizure, which was estimated to occur in less than 0.1% of patients according to the rTMS four-year post-market safety surveillance report.

The resubmission stated that the evidence for safety for rTMS and the clinical claim of superior safety compared with third line antidepressants remain applicable.

11. Comparative effectiveness

To assess the effectiveness of rTMS from the new evidence identified, the resubmission presented the results of the Mas of rTMS versus sham as reported by Gaynes 2014 and Papadimitropoulou 2017. The comparative analyses of rTMS against the proposed comparator in this resubmission (third-line antidepressant medication) as reported in the NMA by Papadimitropoulou 2017 are also presented.

Both reviews reported on three main outcomes; severity of depressive symptoms, response rates and remission rates. The resubmission stated that the overall results of the Mas (shown in Table 4) demonstrated that:

- rTMS resulted in a significant and clinically meaningful decrease in depressive severity of approximately four points according to the HAM-D and MADRS rating scales compared with sham; Gaynes 2014: MD in HAM-D score: -4.53 and Papadimitropoulou 2017 (6 weeks): MD in MADRS score: -3.6.
- Patients receiving rTMS were significantly more likely to achieve a response, defined as a $\geq 50\%$ improvement from baseline according to HAM-D or MADRS scores, compared with the sham control group; Gaynes 2014: RR=3.38 and Papadimitropoulou 2017 (6 weeks): OR=8.01.
- Patients receiving rTMS were significantly more likely to achieve remission, (definitions variable according to rating scale), compared with the sham control group; Gaynes 2014: RR=5.07 and Papadimitropoulou 2017 (6 weeks): OR=8.58.

Table 4 Summary of results from the included SR/Mas

Outcome details	Gaynes 2014	Papadimitropoulou 2017
Change in depressive rating scale scores (HAM-D/MADRS) ¹ MD (95%CI/95%CrI ³)	1-6 weeks: -4.53 (-6.11,-2.96)	2 weeks: -4.2 (-6.4, -1.8) 4 weeks: -5.8 (-8.6, -2.9) 6 weeks: -3.6 (-7.6, 0.3)
Response rates RR/OR ² (95%CI/95%CrI ³)	2-6 weeks: 3.38 (2.24, 5.10)	2 weeks: 2.9 (1.5, 6.0) 4 weeks: 2.7 (NR) 6 weeks: 8.01 (1.16, 56.98)
Remission rates RR/OR ² (95%CI/95%CrI ³)	2-6 weeks: 5.07 (2.50, 10.30)	2 weeks: 3.5 (1.5, 9.8) 4 weeks: 9.51 (NR) 6 weeks: 8.58 (1.15, 112.55)

Abbreviations: CI, confidence interval; CrI, credible interval; HAM-D, Hamilton Depression Scale; MADRS, Montgomery-Asberg Depression Rating Scale; MD, mean difference; NR, not reported; OR, odds ratio; RR, relative risk

Therefore, on the basis of the evidence presented in the previous application and further supported by the identification of new relevant data, the resubmission suggested that rTMS has superior efficacy relative to third-line antidepressant medication.

Clinical Claim

The resubmission's clinical claim for rTMS compared to third-line antidepressant medications is one of superior efficacy and superior safety. The resubmission stated this is consistent with the findings of the Assessment Report (Application 1196) considered by MSAC in November 2014.

Importantly, the claim of superior efficacy in this resubmission is further supported by new data and analyses not available for MSAC Application 1196. Specifically, this resubmission identified two systematic reviews/meta-analyses of rTMS in patients who had failed two or more antidepressant treatment regimens (Papadimitropoulou 2017 and Gaynes 2014). The results from these meta-analyses are therefore considered highly applicable and relevant to this resubmission in terms of the patient population proposed for rTMS listing on the MBS.

12. Economic evaluation

The resubmission stated that the economic model presented is essentially the same economic model as for Application 1196. The economic model presented a cost-utility analysis with a time horizon of 3 years.

The total and incremental per patient costs and QALYs, along with the ICER, as calculated for the intervention and comparator in the model, are shown in Table 5 for the base-case analysis. The incremental cost per QALY gained for rTMS over third line antidepressant treatment was \$6,489.

Table 5 Incremental cost-effectiveness

Treatment arm	TMS	AD	Incremental
Cost	\$19,272.31	\$18,051.38	\$1,220.93
QALYs	1.83	1.64	0.19
ICER			\$6,489

The modelled results were most sensitive to the odds ratios used for the probabilities of remission and response with rTMS, along with the probability and costs of an inpatient hospitalisation during acute treatment. The model horizon is also a key model parameter.

13. Financial/budgetary impacts

An epidemiological approach was presented to examine the estimated size of patient population potentially eligible for rTMS for treatment-resistant depression on the MBS. The resubmission estimated the prevalence of depression is 4.1% of the Australian population. Of which, 13.6% are expected to meet the definition of treatment resistant depression (failure of two prior treatments).

The estimated net financial implications to the MBS resulting from the proposed listing of rTMS for treatment resistant depression (TRD) are shown in Table 6. Overall, the listing of rTMS is expected to result in a net budget impact of approximately \$6 million in year 1, with savings of approximately \$24 million projected by year 5 as a result of cost-offsets.

Table 6 Estimated cost of rTMS to the MBS in the first five years of listing

Variable	Year 1 (2019)	Year 2 (2020)	Year 3 (2021)	Year 4 (2022)	Year 5 (2023)
Australian population, aged above 18	19,853,831	20,173,593	20,492,073	20,813,398	21,139,340
Estimated prevalence of TRD MDD each year (4.1%*13.6%)	110,705	112,488	114,264	116,056	117,873
Expected uptake	1.85%	3.89%	5.93%	7.96%	10.00%
Patients who will start rTMS (first time)	2,052	4,296	6,396	8,227	9,690
Total number of MBS treatments per year ^a					
Initial MBS items	2,523	5,282	7,864	10,115	11,914
Subsequent MBS items	64,663	135,372	201,531	259,227	305,326
Total cost to the MBS					
Initial MBS items	\$825,721	\$1,728,648	\$2,573,477	\$3,310,231	\$3,898,887
Subsequent MBS items	\$10,168,254	\$21,287,261	\$31,690,826	\$40,763,504	\$48,012,457
All MBS items	\$10,993,974	\$23,015,909	\$34,264,303	\$44,073,734	\$51,911,344
Total savings due to rTMS across all health budgets (private and public) ^b	-\$5,068,908	-\$15,680,677	-\$31,478,657	-\$51,799,398	-\$75,733,765
Net impact of rTMS on total health care expenditure	\$5,925,067	\$7,335,232	\$2,785,646	-\$7,725,663	-\$23,822,420
MBS	\$9,676,131	\$18,939,159	\$26,080,305	\$30,606,637	\$32,221,656
PBS	-\$93,415	-\$288,978	-\$580,118	-\$954,608	-\$1,395,693
Public hospital	-\$1,924,794	-\$5,954,354	-\$11,953,251	-\$19,669,555	-\$28,758,046
Private hospital	-\$1,283,196	-\$3,969,569	-\$7,968,834	-\$13,113,037	-\$19,172,031
Patient	-\$449,660	-\$1,391,025	-\$2,792,457	-\$4,595,100	-\$6,718,306

Abbreviations: MBS, Medicare Benefits Schedule; rTMS, repetitive transcranial magnetic stimulation

^a This figure is not exactly equal to the number immediately preceding it because it includes patients being re-treated with rTMS

^b Expected savings per patient are based on results from the economic model, undiscounted and annualised. For example, the economic model estimates cost offsets of approximately \$7500 per patient over three years. Therefore, the 2052 patients initiating rTMS in Year 1 will accrue savings of \$2500 in each year thereafter of this analysis. As will the 4296 patients initiating rTMS in Year 2, and so on. These costs are further disaggregated by the respective budget holders (e.g.: private health insurers accrue the cost of private hospital admission for depressive episodes in privately insured patients, public hospitals for uninsured patients).

14. Key issues from ESC for MSAC

Key Issues from ESC to MSAC

ESC Key ISSUES	ESC ADVICE
Strength of evidence	Key piece of new information (NMA) still does not directly compare rTMS vs 3 rd line antidepressants. The naïve indirect comparison of rTMS and 3 rd line antidepressants through placebo showed no statistical significant difference. <ul style="list-style-type: none"> • ESC noted the NMA would be more convincing if an SSRI was used as the comparator • Suggest report measures of heterogeneity. Analysis of heterogeneity would be helpful.
Re-treatment	In the absence of evidence regarding re-treatment with rTMS, consider analogy with medical treatment: the best predictor of future response is past response
Relapse and maintenance	Need for rigorous review of relapse rates, and need for maintenance treatment, but no data on these provided by the applicant. Unjustified use of relapse rate of 29.5% from an uncertain source, versus 65% from the US STAR*D trial,
Comparators	Comparators – 3 rd line antidepressant Selection: should this be failure of 2 anti-depressants or 2 classes of antidepressants (6 classes available) How to categorise intolerance of medication (probably shouldn't count as a trial of the medication)
Relative efficacy – ICER potentially substantial under estimate	The submission used the point estimate difference in efficacy in the calculation of the ICER ignoring statistical significance. At 5% significance claim of superiority in efficacy for rTMS over AD (in remission and response rates) not supported. If no difference in effectiveness ICER increases from \$6,489 to over \$351,000.
Lack of evidence for maintenance and retreatment in non-responders or relapse	No evidence provided to support use of rTMS for either maintenance in patients who respond or re-treatment with rTMS in patients who do not respond or relapse

ESC Discussion

ESC noted that this is a resubmission of MSAC Application 1196 (first presented to ESC in 2007) requesting the reimbursement of rTMS for treatment-resistant depression (TRD), and was considered by MSAC at the November 2014 meeting.

ESC recalled that the proposed population for rTMS listing comprises adults with antidepressant resistant major depressive disorder (MDD; DSM-5 rating) who have not satisfactorily improved despite the adequate trialling of at least two different antidepressant medicines, unless contraindicated or intolerant. The trialling of each antidepressant medicine must have been at the recommended therapeutic dose for a minimum duration of three (3) weeks.

ESC noted that there are at least six classes of antidepressants available, and suggested that the descriptor be modified to specify that two classes of antidepressants should be trialled. ESC also queried whether intolerance to antidepressants constituted a trial, and suggested that intolerance to an antidepressant within a class did not preclude the trialling of a different antidepressant within that class, and that a within-class change of medicine was not considered an adequate trial within the context of the required criteria for the use of rTMS.

ESC noted that in response to comments made by ESC and MSAC in the Public Summary Document (PSD) for MSAC Application 1196, the main comparator to rTMS considered was third line antidepressant therapy.

ESC noted that the evidence regarding the safety of rTMS was unchanged from the November submission. ESC considered that there were no major safety issues for rTMS, although the long term outcomes were unknown.

ESC noted that the evidence to support the submission had been updated by the inclusion of a review by Papadimitropoulou et al (2017) comparing the relative efficacy and tolerability of TRD treatments (rTMS, sham rTMS, electroconvulsive therapy [ECT] and pharmacological interventions) by means of a Bayesian network meta-analysis (NMA) in patients with at least two drug treatment failures. However, ESC noted that there was still no evidence provided that directly compared rTMS to antidepressants.

ESC noted that the NMA reported three main treatment outcomes; severity of depressive symptoms, response rates and remission rates. ESC noted that using the minimum clinically important difference (MCID) approach, an MCID change of 3.8 on the Montgomery Asberg Depression Rating Scale (MADRS) was considered clinically important.

ESC noted that according to the submission claim, rTMS had superior efficacy relative to third-line antidepressants because:

- patients experienced a significant and clinically meaningful decrease in depression severity at 6 weeks of approximately -3.6 points (95% confidence interval [CI] -7.60 to 0.30) according to the MADRS, compared with sham;
- patients receiving rTMS were significantly more likely to achieve a response (odds ratio [OR] = 8.01, 95% CI 1.16 to 56.98) at 6 weeks, defined as a $\geq 50\%$ improvement from baseline according to MADRS scores, compared with the sham control group; and
- patients receiving rTMS were significantly more likely to achieve remission (OR = 8.58, 95% CI 1.15 to 112.55) at 6 weeks (definitions variable according to rating scale), compared with the sham control group.

ESC noted that this claim was disputed by the critique on the basis that the 95% confidence intervals were overlapping and hence did not demonstrate statistically significant superiority of effect. However, ESC raised the issue of whether it was appropriate to determine the statistical significance of the difference between the statistics for the intervention and comparator medicines based on overlapping CIs.

ESC considered that for the selective serotonin reuptake inhibitor (SSRI) fluoxetine, and the serotonin and norepinephrine reuptake inhibitors (SNRI) venlafaxine, a recalculation of the CIs at 83% using a rule of thumb (Austin PC et al 2002) for the change from baseline data (using a standard deviation of 2.2), and also for the response data (by converting the OR to natural logarithm [ln] OR, and using a standard deviation of 1.2) suggested that there may no longer be an overlap between rTMS and the two medicines. ESC suggested that this may provide an approximation that the means calculated for these data may be significantly

different from one another, and that as such rTMS potentially had superior efficacy relative to these two antidepressants, based on these two measures of improvement in depression. However, ESC also noted the considerable uncertainty here and the large implications for the ICER and budget impact.

ESC considered that based on these findings, a re-analysis of the data from the NMA could be undertaken using an SSRI as a comparator (instead of placebo/sham). ESC noted that the submission provided no data on early response to rTMS, the effect of maintenance therapy with rTMS, or repeat therapy with rTMS. ESC noted that one review of mainly case series had been located, but showed no difference in relapse rates for maintenance therapy in small numbers of patients. ESC considered that evidence for a repeat trial of rTMS in patients who were non-responsive to a first trial was needed. ESC noted that in general, an initial response to a given treatment was a good indicator of response to subsequent treatment with the same intervention, and that conversely a lack of response to initial treatment with rTMS might be predictive of a lack of response to subsequent treatment.

ESC noted that no evidence had been presented in the submission for relapse rates and that much of the evidence presented in the submission for the effectiveness of antidepressant medicines was based on the STAR*D trial (Rush AJ et al 2006).

ESC noted that no examination of heterogeneity in the pooled estimates of the NMA had been undertaken, and that as such the possibility that the placebo arms used as the common comparator in the NMA were not comparable could not be ruled out. ESC suggested that an analysis of heterogeneity is required before the findings from the NMA could be accepted.

ESC noted that an updated modelled economic evaluation had been provided based on the updated clinical evidence. ESC noted that a cost-utility analysis (CUA) had been performed based on the claims of superior efficacy of rTMS over third line antidepressant medicines, improved quality of life (QoL) and gains in quality adjusted life years (QALY) from superior efficacy presented with resultant decreased use of health care. ESC considered that the concerns with the efficacy data presented had implications for the economic model.

ESC noted that for the base-case analysis, over the 3-year horizon rTMS treatment was associated with additional costs and QALYs of \$1,221 and 0.16 per patient, respectively, compared to the comparator, equating to an incremental cost-effectiveness ratio (ICER) of ~\$6,500/QALY.

ESC noted that the effect of rTMS compared to third line antidepressants was based on the NMA by Papadimitropoulou et al using a naïve indirect comparison. ESC noted that the economic model incorporated response and remission rates from patients in step three of the STAR*D trial. ESC noted that the model used baseline remission and response rates from STAR*D patients who had not responded to treatment with a single antidepressant and as such did not match the proposed population (patients who had failed two trials of antidepressant medicine).

ESC considered that the higher rates of response and remission in the STAR*D trial would affect the QoL benefits generated, and introduce considerable uncertainty around cost-offsets associated with a reduction in hospitalisations, thereby resulting in a potential underestimation of the ICER. ESC noted that sensitivity analysis showed the ICERs were most sensitive to efficacy parameters (remission and response), and that modifying the inputs to assume equivalent efficacy increased the ICER from ~\$6,500/QALY to ~\$351,000/QALY.

ESC also noted that there was additional uncertainty due to the small number of patients (n = 16) in step three of the STAR*D study.

ESC noted that as the submission only provided evidence for initial treatment, this introduced further uncertainty because in the model structure, patients who a) did not respond to treatment with either lithium augmentation or ECT; b), did not respond to rTMS or a third line antidepressant; or c) relapsed following maintenance treatment with either rTMS or a third line antidepressant were all considered to be eligible for three trials of rTMS. ESC queried whether this was clinically appropriate, and considered that it was not justified by the evidence provided.

ESC queried the three year time horizon used in the model, and considered that a shorter time frame may be more appropriate given the limited follow-up of the included studies. ESC noted that the use of a longer time horizon had allowed benefits to accrue in terms of improvements in quality of life and hospitalisation costs avoided, thus favouring rTMS, which may not be appropriate. ESC also queried the length of maintenance treatment and the use of rTMS beyond three years.

ESC noted that the cycle length had been modified from two months to three months to match cost data. However, ESC noted that consequentially patients in the non-response or relapse cycle spend three months receiving only maintenance antidepressants, and queried if it was clinically appropriate to increase the amount of time between treatment cycles. ESC noted that an increase in cycle length (and subsequent increase in time between treatments) was likely to underestimate the cost of maintenance treatment.

ESC also considered that it was important that the severity of depression and the frequency of depressive episodes should be captured in the model due to the increased risk of subsequent events. ESC suggested that a modification of the model structure incorporating these variables would be helpful.

ESC noted that there was the potential for further underestimation of costs due to:

- the zero cost incurred from patients who were not suitable for rTMS, as it was assumed that all patients were suitable;
- the lack of a transition to hospitalisation from the 'no response/relapse' state once treatment options are exhausted (and consequential costs of hospitalisation), which may not be appropriate;
- considerable uncertainty regarding the cost of adverse events; and
- considerable uncertainty regarding the 10.4% probability of hospitalisation in non-responders assumed in the model (only applicable during acute treatment), and hence cost-offsets from hospitalisation.

ESC noted that the cost of rTMS to the MBS ranged from ~\$11.3 million to ~\$53.8 million per year over a five year period. However, ESC considered that the rate of uptake had most likely been underestimated as:

- the submission referral rate was based on the privately funded setting and had failed to consider the extent of anticipated utilisation by non-privately insured patients;
- the 2013 referral rate used may have increased over subsequent years; and
- the submission had assumed only those patients eligible for rTMS would be assessed with the first of the proposed items (psychiatric consultation at initiation of treatment course), and that the number of patients assessed is likely to differ from the number of patients eligible.

ESC noted that the financial costs were also likely to be underestimated as:

- the model allows for three attempts at rTMS, whereas the financial costings were for two;
- the financial costs included maintenance for one year only, whereas the model structure allowed for three years; and
- the cost-offsets applied in all five years of the financial costings may not be realised if the efficacy gain is not realised.

ESC also queried the assumption that all treatments would be conducted in the outpatient setting.

ESC considered that given the high cost estimates, greater certainty as to the effectiveness of the treatment was required.

ESC noted that the MSAC (November 2014) had requested justification of the proposed treatment fee of \$150, given that rTMS would be provided by a nurse or allied health professional. ESC noted that the resubmission had increased the proposed fee to \$185 based on accounting data from a real world practice with four rTMS chairs. ESC considered that this was based on the incorporation of additional overheads, including marketing, and may not be appropriate.

ESC noted the proposed service fee for the first rTMS session of \$385, which was considerably higher than MBS item number 293 (Fee: \$282.95) which is a professional attendance by a consultant psychiatrist of 30 to 45 minutes for a new patient. ESC noted that the fee is almost twice what is being charged currently at the Black Dog Institute (\$385 vs \$200). ESC considered that the proposed fee was not justified.

ESC queried whether a limit to the number of treatments should be specified, given the potentially high cost to the MBS.

ESC noted that the submission had not quantified the financial implications to consumers. ESC noted that for each initial treatment course there were high out-of-pocket costs for consumers, assuming that providers do not bulk bill or charge above the proposed fee.

15. Other significant factors

A key change from the original MSAC submission 1196 is that the clinical management algorithm for MDD has been updated to reflect the use of rTMS as a therapy for treatment resistant depression as an alternative to third line antidepressant medication while ECT is reserved for use as a further downstream option for non-responders.

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

Whilst welcoming the fact MSAC's deferral is an improvement on the rejection of application 1196, RANZCP remain disappointed rTMS as a treatment for depression was not approved by MSAC. Neither of the Ontario HTA and EuNeHTA reports contain evidence comparing rTMS with anti-depressants as previously requested by MSAC, as required to address the DAP and as provided in our application. We do not accept that the evidence supporting the clinical use of rTMS as initial treatment and re-treatment of depression is 'weak' - there is a substantive clinical evidence base demonstrating the superiority of rTMS to placebo treatment and minimal evidence supporting the basis of current practice for these patients. We are concerned that ongoing lack of access to public funding of rTMS therapy is

perpetuating systematic inequity in access to an effective therapy and driving up substantial costs associated with unnecessary private hospital admissions.

17. Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website:
[visit the MSAC website](#)