



Australian Government

Medical Services Advisory Committee

Public Summary Document

Application No. 1196.3 – Repetitive Transcranial Magnetic Stimulation (rTMS) for the treatment of depression – Resubmission

Applicant: Royal Australian and New Zealand College of Psychiatrists

Date of MSAC consideration: MSAC 77th Meeting, 28-29 November 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 (third) requesting Medicare Benefit Schedule (MBS) listing of rTMS for retreatment of antidepressant medication-resistant major depressive disorder (MDD) following relapse after an initial course was received from the Royal Australian and New Zealand College of Psychiatrists (RANZCP) by the Department of Health.

This was based on the request of MSAC for the applicant to provide further information on retreatment of repetitive transcranial magnetic stimulation (rTMS) of finite duration:

- Duration between cessation of initial course of treatment and commencement of a retreatment course;
- Proportion of patients who responded to initial course who are likely to relapse and require re-treatment; and
- Duration of retreatment course and frequency of administration (see 4. Background).

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 creation of a new MBS item for rTMS for the retreatment of adults with antidepressant medication-resistant MDD following relapse in people who were in remission or response after an initial course of rTMS treatment. MSAC considered the new MBS item for retreatment should be for a single course only, to start no sooner than four months after the end of the initial course, and with a maximum of 15 sessions.

MSAC recalled it had previously supported MBS funding for initial treatment with rTMS of up to 35 sessions for adults diagnosed with antidepressant medication-resistant MDD who have failed to receive satisfactory improvement despite adequate trialling of at least two different classes of antidepressant medicines and who have not received treatment with rTMS previously. MSAC had previously not supported ongoing maintenance treatment with rTMS due to the limited and weak evidence base (Application 1196.2).

Consumer summary

The Royal Australian and New Zealand College of Psychiatrists (RANZCP) applied for public funding through the Medical Benefits Scheme (MBS) for rTMS (repetitive transcranial magnetic stimulation) 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 patient is conscious during rTMS treatment. Each treatment lasts about 40 minutes, and each course of treatment is made up of between three and five treatments a week for four to six weeks.

MSAC had already supported public funding for initial treatment with rTMS. MSAC had not supported public funding for ongoing treatment. This application was to consider funding for more than one treatment course (retreatment).

MSAC's advice to the Commonwealth Minister for Health

MSAC supported public funding for a single course of retreatment with rTMS in patients who responded to the initial course and have relapsed (become unwell again). There must be at least four months between the end of the initial treatment course and the start of the retreatment course. The retreatment course can be no more than 15 sessions in total.

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

MSAC recalled that, at its August 2019 meeting, it had supported initial treatment with rTMS and had not supported maintenance treatment (Application 1196.2). Also at that meeting, MSAC was of a mind to support retreatment, but considered that further information was required from the Royal Australian and New Zealand College of Psychiatrists (RANZCP), particularly regarding the appropriate time period between stopping the initial treatment course and starting a retreatment course, the proportion of patients who have responded to initial treatment who are likely to relapse and require retreatment, and the duration of the retreatment course and frequency of administration.

Regarding the time period between initial treatment and retreatment, the applicant provided seven studies on rTMS retreatment in patients experiencing relapse. The time to retreatment averaged between four and 10 months. In one double-blind randomised controlled trial with 99 patients (Janicak et al. 2010), 84.2% of retreatment episodes resulted in patient benefit; 15.2% of patients experienced a second relapse, and 5.1% of patients experienced a third relapse. Partial responders were more likely to require retreatment than full responders. In the pre-MSAC response, the applicant requested that the interval between initial treatment and retreatment be three months; however, MSAC considered that average interval of 4 months was appropriate, but noted the highest likelihood of relapse was within 3–9 months.

Regarding the proportion of patients who are likely to relapse and require retreatment, MSAC accepted the data from one study (Dunner et al. 2014) in which 29.5% of patients relapsed after a full remission to initial treatment. MSAC noted the relapse rate increased to 37.5% if response criteria were also included. However, MSAC recalled that it had previously considered this to be a limited and weak evidence base.

Regarding the duration of the retreatment course and frequency of administration, MSAC observed the number of sessions required for a retreatment course was consistently lower (around 15 sessions) than for initial treatment (around 30 to 35 sessions).

In the pre-MSAC response, the applicant:

- requested the same number of sessions in a retreatment course as in the initial course. However, MSAC considered that a maximum of 15 sessions was appropriate for retreatment, as supported by the included studies; and
- requested that the number of retreatment courses available should be unlimited. However, MSAC considered that retreatment should be limited to one course, at least initially, given the low quality of evidence supporting retreatment and the small proportion of patients who experience second or subsequent relapses. MSAC therefore accepted the Department's base-case MBS item descriptor for retreatment, but not the Department-proposed alternative scenarios including two or three retreatment courses.

MSAC considered that separate MBS item descriptors and fees were required for patient assessment and prescription for initial treatment and retreatment. A single MBS item was required for rTMS treatment delivery, whether this was initial treatment or retreatment. MSAC agreed with the Department's proposed base-case MBS item descriptor for initial assessment and prescription of a single course retreatment with rTMS (see Table 1). However, MSAC recommended the applicant work with the Department on developing criteria to define relapse, including potential validated tools that may be appropriate, to be included in the explanatory notes for the MBS item for retreatment.

MSAC noted that retreatment accounted for approximately 15% of the total annual financial impact of listing rTMS, adding ~\$12 million in Year 5 (compared with the Critique's respecified financial estimates for rTMS in Application 1196.2, which did not include retreatment).

MSAC acknowledged the importance of rTMS being provided by appropriately trained personnel. It was noted that, if this were specified in the item descriptor, it would be a legislative requirement for the Department of Human Services to maintain a register of trained people, which is likely to significantly delay implementation while this register is developed. MSAC advised instead that the requirement for training should be included in the explanatory notes to the item, ensuring that the onus is on the prescribing psychiatrist to ensure the staff providing the treatment are appropriately trained. MSAC recommended the Department write to the RANZCP to ensure safeguards around the training requirements are incorporated into the explanatory notes to avoid delays in implementation, and the college has mechanisms to ensure people administering rTMS have the appropriate training.

MSAC noted that no other changes had been made from the previous resubmission.

MSAC considered the impact on the Extended Medicare Safety Net (EMSN), given that rTMS is provided in an outpatient setting, and patients can potentially receive a large number of services and significant out-of-pocket costs. MSAC considered that an EMSN cap (set at 80% of the MBS fee) for all rTMS services will be consistent with other 'procedural' MBS items to minimise fee inflation and protect patients from high out-of-pocket costs.

4. Background

Previously, MSAC assessed rTMS under Application 1101 in 2007. The first application (MSAC 1196) was considered by MSAC at its November 2014 meeting; the first resubmission (1196.1) was considered at the July 2018 meeting, and the second resubmission (1196.2) was considered at the August 2019 meeting.

Application 1196.2

In summary, 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 (Application No. 1196.2 PSD, p.1).

Application 1196.1

In summary, 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 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 (Application No. 1196.1 PSD, pp.1-2).

Application 1196

In summary, 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.

MSAC considered that any reapplication should include:

- better definition of the patient population;
- better definition of the clinical setting for this treatment;
- evidence comparing rTMS against contemporary alternative antidepressants in this patient population; and
- further consideration of the treatment costs of anti-depressants (Application No. 1196 PSD, p1).

Further information on these applications is available on the [MSAC website](#).

5. Prerequisites to implementation of any funding advice

This was unchanged. Refer to Application 1196.1 PSD 2018, pp5-6 for details of three rTMS items listed on the Australian Register of Therapeutic Goods (ARTG).

6. Proposal for public funding

Department proposed MBS item descriptor for rTMS retreatment.

The Department proposed a separate MBS item descriptor for retreatment with rTMS in those who have relapsed after remission or satisfactory clinical response (according to a validated clinical assessment tool for antidepressant medication-resistant MDD) to an initial course of treatment. In brief, this was based on the applicant's updated evidence pack (see Table 6):

- The applicant stated across the majority of studies the time to retreatment with rTMS averaged between 4-10 months;
- The applicant indicated that the relapse rate in those classified as full remitters after initial response was 29.5%, increasing to 37.5% when including remission and response criteria (Dunner et al. 2014);
- The applicant indicated there was around 15 sessions for a retreatment course following initial course of treatment (much lower than ~30-35 provided in initial therapy); and
- *The Department observed that in those who relapsed after initial course of treatment and received retreatment with rTMS in Janicak et al. 2010, 15/99 (15.2%) and 5/99 (5.1%) experienced a second or third period of symptom re-emergence (i.e. second and third relapse, respectively).*

Based on the applicant's updated evidence pack of retreatment with rTMS, the Department proposed two MBS item descriptors for MSAC consideration:

1. **Base-case:** MBS item descriptor XXXXX (Table 3), permitting only one course of retreatment with rTMS in those who relapsed after initial remission or satisfactory clinical response (according to a validated clinical assessment tool for antidepressant medication-resistant MDD) to initial course of treatment. This assumption was based on the majority of studies only provided data for one retreatment course in the applicant's updated evidence pack.
2. **Alternative scenarios:** MBS item descriptor YYYYYY (Table 4) and ZZZZZ (Table 5) permitting up to two and three courses of retreatment with rTMS, respectively, in those who relapsed after initial remission or satisfactory clinical response (according to a validated clinical assessment tool for antidepressant medication-resistant MDD) to initial course of treatment and subsequent courses of retreatment with rTMS. This assumption was based on the data on second and third relapse provided in Janicak et al. 2010 included in applicant's updated evidence pack.

Department-proposed base case

Table 1 Base case MBS item descriptor, patient assessment and prescribing of up to 1 rTMS retreatment course

Category 3 – THERAPEUTIC PROCEDURES or Category 1 — PROFESSIONAL ATTENDANCES*
MBS XXXXX REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION (rTMS) treatment prescription by a psychiatrist
The patient to whom the service is provided must: <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 classes of antidepressant medications, unless contraindicated or intolerant.• have undertaken psychological therapy unless inappropriate; and• been eligible for and received rTMS therapy and relapsed after either initial remission, or satisfactory clinical response, as assessed by a validated MDD tool after and no sooner than 4 months after completion of initial course
The service is prescribed by a psychiatrist with appropriate training in rTMS
Fee: \$186.40 (from \$385 in Application 1196.1)
Note: <ol style="list-style-type: none">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 restricted to once per patient.
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)

Note highlighted includes Department revisions for Application 1196.3

Department-proposed alternative descriptors

Table 2 Alternative MBS item descriptor, patient assessment and prescribing of up to 2 rTMS retreatment courses

Category 3 – THERAPEUTIC PROCEDURES or Category 1 – PROFESSIONAL ATTENDANCES*
MBS YYYYY REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION (rTMS) treatment prescription by a psychiatrist
The patient to whom the service is provided must: <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 classes of antidepressant medications, unless contraindicated or intolerant.• have undertaken psychological therapy unless inappropriate; and• been eligible for and received rTMS therapy and relapsed after remission or satisfactory clinical response as assessed by a validated MDD tool after and no sooner than 4 months after completion of initial course
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 restricted to twice per patient.
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)

Note highlighted includes Department revisions for Application 1196.3

Table 3 Alternative MBS item descriptor, patient assessment and prescribing of up to 3 rTMS retreatment courses

Category 3 – THERAPEUTIC PROCEDURES or Category 1 – PROFESSIONAL ATTENDANCES*
MBS ZZZZ REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION (rTMS) treatment prescription by a psychiatrist
The patient to whom the service is provided must: <ul style="list-style-type: none">• be an adult (≥18 years) diagnosed with an episode of a major depressive disorder (MDD)• 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; and• been eligible for and received rTMS therapy and relapsed after remission or satisfactory clinical response as assessed by a validated MDD tool after and no sooner than 4 months after completion of initial course
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 restricted to thrice per patient.
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)

Note highlighted includes Department revisions for Application 1196.3

Explanatory notes

The Department considered that an explanatory note indicating the definition of relapse could be added to the proposed MBS item descriptors for retreatment with rTMS in those who have relapsed after remission or satisfactory clinical response to initial course of treatment and/or subsequent courses of retreatment with rTMS (~~strike through~~ represents edit from applicant):

The definition of relapse as provided in the pivotal studies: recurrence of full Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria for two consecutive weeks, ~~or failure to achieve symptom improvement despite six weeks of rTMS retreatment (Janicak et al. 2010); Quick Inventory of Depressive Symptoms Self report 16 Item version (QIDS-SR) score ≥11 (Dunner et al. 2014); and Hamilton Depression Rating Scale six item (HAMD-6) score >7 (Pridmore et al. 2019).~~

In the pre-MSAC response, the applicant stated it would be reasonable to require documentation of the criteria used for the definition of relapse or to provide criteria that would need to be met. The applicants are willing to work with the department to refine these criteria.

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 resubmission is third line antidepressant therapy.

10. Clinical evidence

Time period between initial treatment course and retreatment

The applicant stated that there is limited evidence on rTMS retreatment in patients experiencing relapse, providing seven studies (Demirtas-Tatlidede 2008, Fitzgerald 2006, Janicak 2010, Dunner 2014 were included in previous MSAC1196 iterations; and Philip 2016, Pridmore 2019, and Kelly 2016 were included as new evidence to MSAC; see Table 4 below).

The applicant indicated that from these studies, the time to repeat treatment (i.e. retreatment) averaged between 4-10 months. However, the applicant stated that the duration until retreatment was fairly consistently dependent on the degree of initial response achieved by patients. The applicant highlighted that a typical course of TMS treatment is typically considered around 30 sessions (plus or minus a short taper) and a longer duration of treatment is typically associated with greater clinical response. The applicant noted that retreatment in the included studies is likely to have occurred relatively early due to the inclusion of patients in a research protocol and subsequent early detection of signs of relapse.

Pre-MSAC response

The applicant suggested that the retreatment course to be limited to a minimum gap of three months with no maximum gap.

Proportion of responders likely to relapse and require retreatment

The applicant cited Dunner et al. 2014 (n=257) as the most relevant study, which included 12 month follow-up data from 205 patients. *MSAC noted that Dunner et al. was an observational study and therefore low quality evidence. In addition, it was unclear if the trial population was fully applicable to the proposed MBS population, as patients were not required to have failed to respond to at least 2 antidepressants at study recruitment.*

A total of 78 patients were classified as full remitters after initial therapy – 55 (70.5%) remained well for 12 months indicating a 29.5% relapse rate. The time relapse was 0-3 months (for 6 patients), 3-6 months (for 8 patients), 6-9 months (for 6 patients) and 9-12 months (for 3 patients). The highest likelihood was from between 3-9 months.

The applicant stated that when patients who met remission and response criteria were included there were 120 patients and 75/120 (62.5%) maintained their response over 12 months of follow-up, indicating a potential of 37.5% of responders to relapse and require retreatment. Remission implies a complete or almost complete reduction of symptoms with initial treatment. Patients meeting response criteria have improved to a significant degree but may still remain symptomatic. The applicant stated the data suggests patients with greatest degree of initial improvement are likely to remain well over 12 months.

MSAC noted that the same observational study (Dunner et al. 2014) was used to inform the applicant's current relapse rate for rTMS retreatment (29.5%), and the rTMS relapse rate (36.2%) in previous iterations of MSAC 1196 (1196, 1196.1), which MSAC previously

considered a “limited and weak evidence base” (Application 1196.1 PSD 2018, p1). [See Table 4 below].

Number of sessions required for retreatment and frequency of administration

The applicant stated that the number of sessions appears to be fairly consistently lower than the number of treatments provided during an acute episode of therapy. Across several studies this was around 15 treatments compared to ~ 30-35 provided in the initial acute course of therapy (e.g. 14.3 in Janicak et al. 2010). MSAC noted that the applicant’s assumption of 15 treatments per retreatment course was similar to the previous estimate of 16.2 (also taken from Dunner et al. 2014) [See Table 4 below].

Pre-MSAC response

The applicant suggested the same number of sessions in a retreatment course as in the initial course of treatment with rTMS.

Number of rTMS retreatment courses

The Department observed that there was no limit to number of retreatment courses with rTMS in Janicak et al. 2010, and 15/99 (15.2%) and 5/99 (5.1%) experienced a second or third period of symptom re-emergence, respectively [See Table 4 below].

Pre-MSAC response

The applicant suggested two solutions for the proposed MBS item descriptors:

1. Allow reimbursement of the initial course only once but not restrict the number of repeat treatment courses; or
2. Allow claiming of the initial treatment course once every calendar year with a restricted number of repeat treatment courses then allowed across the rest of the year.

The applicant stated that the most appropriate mechanism to limit over servicing would be to restrict the frequency with which the repeat treatment codes may be claimed.

Definition of retreatment versus maintenance treatment

Pre-MSAC response

The applicant stated repeat treatment (i.e. retreatment with rTMS) refers to the provision of an intensive course of treatment (usually sessions 5 times per week over 2-6 weeks) in a patient with who has experienced a defined relapse of depression (recurrent of significant symptoms after having achieved ‘wellness’ or a substantial benefit from an initial course of rTMS therapy). Maintenance therapy, in contrast, refers to the use of rTMS to try and prevent relapse – i.e. treatment is provided in a patient who is not experiencing relapse, usually in a less intensive manner.

Table 4 Applicant's data on rTMS retreatment and Department overview's comments

Publication name, (Country)	Study design	Patients and characteristics	Follow up	Use of repeat treatment	Duration to repeat treatment data	Duration of repeat treatment	Response to repeat treatment	Other comments	Outcomes, clinical tools used to assess remission, response and relapse	Included as study assessing retreatment in previous MSAC Applications			Meet target MBS population (failed ≥ 2 ADs and rTMS used as add on to ADs)	
										1196	1196.1	1196.2	Failed trials of AD	AD status during trial
Demirtas-Tatlidede et al. 2008 (US)	Prospective OL study	16 patients (14 followed up), no medication, retreatment when evidence of relapse including HAMD>17	4 years	64 total courses,	5 months between courses on average	Mostly of short duration (9 treatments only initially) low dose (pulse number and intensity)	Antidepressant response consistently achieved with each course	3 (of 14) achieved a stable response not requiring further treatment for up to 31 months	Repeated rTMS when patient felt need and HAM-D ≥ 18 and patient remained free of ADs	Yes. Stated to show sustained durability of rTMS following successful acute retreatment (p32)	No	No	≥ 3	No AD
Fitzgerald et al. 2006 (Australia)	Prospective, double-blind or OL study	19 patients (16 initial responders, 6 initial partial responders), mixed other treatments (4 medication free)	3 years	30 total courses	Average 10 months between episodes	Usually no more than 20 treatments, low dose (pulse number and intensity)	Antidepressant response consistently achieved with each course		BDI used to assess response. Clinical response >50% reduction in MADRS scores Partial response 25-50% reduction		Yes (Table 26, p61)	Yes. Study included in SR by Sehatzadeh 2019	≥ 2	Mixed (no AD in 4, add on in 15)

Publication name, (Country)	Study design	Patients and characteristics	Follow up	Use of repeat treatment	Duration to repeat treatment data	Duration of repeat treatment	Response to repeat treatment	Other comments	Outcomes, clinical tools used to assess remission, response and relapse	Included as study assessing retreatment in previous MSAC Applications			Meet target MBS population (failed ≥ 2 ADs and rTMS used as add on to ADs)	
										1196	1196.1	1196.2	Failed trials of AD	AD status during trial
Janicak et al. 2010 (US)	MC, double-blind RCT. (active vs. sham)	99 partial responders (to a 6 week course of rTMS plus taper period), on antidepressant medication, 70 followed for full 2 years	2 years	38 worsened (38.4%) sufficiently to justify retreatment	Time to reintroduction was 109 +/-5 days	Reintroduction averaged 14.3 sessions (SD=9.3) No limit to number of TMS reintroduction courses, 15 and 5 experienced a 2 nd or 3 rd period of symptom re-emergence	84.2% of re-treatment episodes resulted in benefit	Partial responders more likely to require retreatment than full responders	Retreatment occurred if patients met prespecified criteria for symptom worsening (i.e. change of at least 1 point on CGI scale for 2 weeks. <u>Primary outcome:</u> relapse, defined as recurrence of full DSM-IV criteria for MD for 2 consecutive weeks; or failure to achieve symptom improvement despite 6 weeks or rTMS reintroduction <u>Secondary outcomes</u> Remission <10: MADRS <11 HAMD24 Response $\geq 50\%$ reduction on MADRS or HAMD24 scales	Yes, included in assessment of rTMS efficacy and safety (Table 3, p26)	Yes, included in assessment of rTMS efficacy and safety (Table 19, p40-41)	Yes included under rTMS maintenance studies (Table 4, p15)	1-4 AD trials	Add on

Publication name, (Country)	Study design	Patients and characteristics	Follow up	Use of repeat treatment	Duration to repeat treatment data	Duration of repeat treatment	Response to repeat treatment	Other comments	Outcomes, clinical tools used to assess remission, response and relapse	Included as study assessing retreatment in previous MSAC Applications			Meet target MBS population (failed ≥ 2 ADs and rTMS used as add on to ADs)	
										1196	1196.1	1196.2	Failed trials of AD	AD status during trial
Dunner et al. 2014 (US)	Prospective, MC observational study	257 patients (responders and non responders), 205 followed full 12 months Nonresponder: 77 Partial responder: 59 Responder: 44 Remitter: 76	1 year	93 (36.2%) received repeat treatment Average 16.2 days therapy, much more likely to need further treatment if less initial response	Remitters who relapsed did so spread across the year, highest likelihood between months 3 and 9		There was an overall persistence of long term benefit in initial treatment responders and remitters.	78 initial remitters (QIDS-SR total score <6)–70.5% remained well throughout the 12 months	CGI-S Remission <2 Response <3 Nonresponder ≥ 4 & ≤ 1 or <4 PHQ-9 Remission <5 Response <10 Partial responder decrease $<25\%$ but $<50\%$ Nonresponder decrease $<25\%$ IDS-R Remission <15 Response $\geq 50\%$ reduction Partial responder decrease $<25\%$ but $<50\%$ Non responder decrease $<25\%$ QIDS-SR Remission <6 Relapse ≥ 11	Yes, p34	No	No	Did not require minimum number of AD trials. Prior ADs mean (SD) Nonresponder: 1.8 (1.5) Partial responder : 1.6 (1.5) Responder: 2.1 (1.7) Remitter: 1.6 (1.6)	Add on

Publication name, (Country)	Study design	Patients and characteristics	Follow up	Use of repeat treatment	Duration to repeat treatment data	Duration of repeat treatment	Response to repeat treatment	Other comments	Outcomes, clinical tools used to assess remission, response and relapse	Included as study assessing retreatment in previous MSAC Applications			Meet target MBS population (failed ≥2 ADs and rTMS used as add on to ADs)	
										1196	1196.1	1196.2	Failed trials of AD	AD status during trial
Phillip et al. 2016 (US)	MC, OL RCT (active vs. observation)	49 medication free patients randomised to have one TMS session per month or no treatment, responders most in remission, only 16 followed for full 12 months	1 year	35-39% of the patients did not require repeat treatment	Mean ± SD duration of time from the end of the acute treatment to reintroduction was 91.2 ± 65.8 days for the once per month group and 77.1 ± 51.7 days for the non treatment group	The number of retreatment TMS sessions received was 14.3 ± 17.8 in the one treatment per month group and 16.9 ± 18.9 in the no treatment group.	Reintroduction success rate (defined for each patient as return to the HAMD17 score they reached at the end of acute treatment, or better) was 14/18 (78%) for the once per month group versus 17/27 (63%) for the no treatment group.		Primary objective: sustained response, not requiring TMS reintroduction during maintenance phase <u>HAMD</u> Remission: HAMD17 <8, HAD24<11 <u>CGI-S</u> Remission<3; Response<4 <u>PHQ-9</u> Remission<5 Response<10 <u>IDS-SR</u> Remission<15 Response >50% reduction	No	No	No	1-4 AD trials	No AD
Pridmore et al. 2019 (Australia)	Naturalistic (observational) prospective study	120 hospitalised patients received an initial course and 30 patients a second course of treatment			Mean: 27.5 +/- 16.7 weeks		Same degree of response seen for first and second course of treatment	Based on HAMD6: Initial course: 26 (87%) remitters	<u>HAMD6</u> Remission ≤4 Relapse >7 Partial remission 4 -7 <u>CGI-S</u> Remission >2	No	No	No	Failed ADs (did not specify number of AD trials)	Add on

Publication name, (Country)	Study design	Patients and characteristics	Follow up	Use of repeat treatment	Duration to repeat treatment data	Duration of repeat treatment	Response to repeat treatment	Other comments	Outcomes, clinical tools used to assess remission, response and relapse	Included as study assessing retreatment in previous MSAC Applications			Meet target MBS population (failed ≥ 2 ADs and rTMS used as add on to ADs)	
										1196	1196.1	1196.2	Failed trials of AD	AD status during trial
								Second course: 22 (73%)						
Kelly et al. 2016	Retrospective chart review	16 patients had a second course out of 225 studied				Reintroduction defined as ≥ 3 sessions per week, >2 weeks <3 months (30 sessions)	Average percent change in BDI across induction was similar to that after reintroduction (57.967.7% and 56.569.4%, respectively; paired-samples t test, $p=0.9$) (Figure 1). Ten of 16 (62.5%) patients were responders to the initial rTMS treatment course, and 11 of 16 (68.8%) patients were		BDI Response: $>50\%$ reduction Partial response 25%-50% reduction	No	No	No	≥ 2	Add on

Publication name, (Country)	Study design	Patients and characteristics	Follow up	Use of repeat treatment	Duration to repeat treatment data	Duration of repeat treatment	Response to repeat treatment	Other comments	Outcomes, clinical tools used to assess remission, response and relapse	Included as study assessing retreatment in previous MSAC Applications			Meet target MBS population (failed ≥2 ADs and rTMS used as add on to ADs)	
										1196	1196.1	1196.2	Failed trials of AD	AD status during trial
							responders to reintroduction.							

Source: Table 1, Applicant response and extracted data from publications (Demirtas-Tatlidede 2008, Fitzgerald 2006, Janicak 2010, Dunner 2014, Philip 2016, Pridmore 2019, Kelly 2016)

Abbreviations: AD = antidepressant; BDI = Beck Depression Inventory; CGI-S = Clinician-Reported Clinical Global Impressions-Severity of Illness scale; DSM_IV = Diagnostic and Statistical Manual of Mental Disorders; HAMD = Hamilton Depression Rating Scale; IDS-SR = patient-reported Inventory of Depressive Symptoms-Self Report; MADRS = Montgomery-Ashber; MBS = Medicare Benefits Schedule; MD = major depression; MC = multi centre; OL = open label; PHQ-9 = 9-Item Patient Health Questionnaire; QIDS-SR = Quick Inventory of Depressive Symptoms Self report 16 Item version; RCT = randomised controlled trial; rTMS = repetitive transcranial magnetic stimulation; SD = standard deviation; SR = systematic review

Note italicised includes data added in by the Department from the applicant's evidence pack for Application 1196.3

11. Economic evaluation

Previously, 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 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/quality-adjusted life year [QALY]) (Application No. 1196.2 PSD, p.4).

12. Financial/budgetary impacts

The financial estimates from MSAC 1196.2 using an epidemiological approach were updated by the Department to include the applicant's current proposed values for rTMS retreatment, which were largely similar to previous values used in previous iterations of MSAC 1196 (Table 5).

Table 5 Summary of rTMS retreatment from previous iterations of MSAC 1196 (shaded grey is current application)

	MSAC 1196		MSAC 1196.1		MSAC 1196.2		MSAC 1196.3		Base case
	Value	Source	Value	Source	Value	Source	Value	Source	
Initial course									
Number of sessions	28.3	Carpenter 2012 and Protocol p14	28.3	Unchanged	28.3	Unchanged	28.3	Unchanged	
Total cost	\$4,595	MBS fee: \$150 + \$350 psychiatrist consultation	\$5,620.50	MBS fee: \$185 + \$385 psychiatrist consultation	\$4,714.40	MBS fee: \$160 + \$186.40 psychiatrist consultation	\$4,714.40	Unchanged	
Retreatment									
Retreatment with TMS after initial TMS	36.2%	NeuroNetics for rTMS; Dunner et al. 2014	36.2%	Unchanged	0%	Removed due to lack of evidence ^a .	37.5%	<i>Dunner et al. 2014</i>	
Number of rTMS sessions per course/year	16.2	NeuroNetics data; Dunner et al 2014	16.2	Unchanged	N/A	N/A	15	<i>Assumption-based on Janicak et al. 2010</i>	
Applied in economics	Yes (25-45%)	-	Yes	-	No	N/A	No	-	
Applied in financials	Yes	-	Yes	-	No	N/A	<i>Applied 4 months after initial course of treatment</i>	<i>Assumption, based on average time to retreatment of 4-10 months across included studies in Table 5.</i>	

Source: Extracted from Table 8, pp36-38 of Application 1196.2

Abbreviations: AD = antidepressant; MSAC =Medical Services Advisory Council; NA = not applicable; TMS = repetitive transcranial magnetic stimulation

^a Also removed from AD arm for consistency

Note italicised includes Department calculations based on applicant's evidence pack for Application 1196.3

Base case: one retreatment course

Based on the Department-proposed MBS item descriptor for one course of retreatment with rTMS (base case MBS item descriptor XXXXX; Table 1), the updated financial implications of listing rTMS to the MBS including one rTMS retreatment course only in those who relapse after remission or satisfactory clinical response (according to a validated clinical assessment tool for antidepressant medication-resistant MDD) is summarised in Table 6. Note, these updated values were based on the respecified model provided in the Critique, including the previous sensitivity analysis (1 and 2 below in Table 6).

Table 6 Respecified net financial implications to the MBS (as 1196.2 Critique), updated to include one course of retreatment

	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	11,249	18,028	21,695	21,743	18,811
<i>Non-remitters^a who relapse (37.5%); rTMS retreatment subpopulation</i>	3,248	5,205	6,264	6,278	5,432
Resubmission base net to the MBS					
Starting TMS	\$45,076,623	\$72,241,023	\$86,936,156	\$87,129,717	\$75,378,870
Retreatment (15/patient/year)	\$7,140,730	\$11,443,929	\$13,771,831	\$13,802,494	\$11,941,005
Changes in use of other MBS items	-\$2,240,507	-\$5,831,204	-\$10,152,315	-\$14,483,046	-\$18,229,708
Total base net to the MBS	\$49,976,846	\$77,853,747	\$90,555,673	\$86,449,165	\$69,090,166
<i>1. Estimating MBS costs as a proportion of ECT cost offsets^b</i>	\$51,847,670	\$82,722,802	\$99,032,856	\$98,542,508	\$84,311,973
<i>2. Assuming cost offsets apply for three years (as per the model time horizon)</i>	\$49,976,846	\$77,853,747	\$90,555,673	\$88,689,672	\$74,921,371
Critique's respecified net implications to the MBS (i.e. multivariate analysis #1 and #2)					
<i>Assuming maximum uptake of 60%^c</i>	\$51,847,670	\$106,463,513	\$130,552,333	\$118,442,270	\$83,044,083
<i>Assuming all prescription rTMS items are claimed with item 306</i>	\$54,144,556	\$86,403,855	\$103,462,701	\$103,351,901	\$89,115,064

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

Abbreviations: MBS = Medicare Benefits Schedule; ECT = electroconvulsive therapy; rTMS = repetitive transcranial magnetic stimulation

Note: Critique corrected these for the minor errors

^a 100%- 23% = 77% classified as non-remitters in Critique base case model (adapted from resubmission (1196.2) base case)

^b 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%.

^c 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.

Note italicised includes Department calculations based on applicant's evidence pack for Application 1196.3

Additional sensitivity analyses were performed investigating the impact of using other plausible estimates for retreatment variables from the applicant's updated evidence pack:

1. Higher relapse rate of 38.4% from partial responders from Janicak et al. 2010 (base case = 37.5% relapse rate from remission and response criteria);
2. Lower relapse rate of 29.5% from non-remitters from Dunner et. al 2014 (base case = 37.5% relapse rate from remission and response criteria); and
3. Higher number of rTMS sessions per patient retreatment course of ~24 sessions; using standard deviation from Janicak et al. 2010 (base case = 15 sessions) (Table 7).

Table 7 Sensitivity analysis investigating financial impact of 1 course of retreatment with rTMS

	Year 1	Year 2	Year 3	Year 4	Year 5
Critique's respecified net implications to the MBS (base case)	\$51,847,670	\$82,722,802	\$99,032,856	\$98,912,192	\$85,274,121
<i>Sensitivity analysis</i>					
1. Higher relapse rate of 38.4% (base case =37.5%)	\$52,019,047	\$82,997,457	\$99,363,380	\$99,243,452	\$85,560,705
2. Lower relapse rate of 29.5% (base case =37.5%)	\$50,324,314	\$80,281,431	\$96,094,865	\$95,967,660	\$82,726,707
3. Sessions per retreatment course: 24 (base case = 15)	\$55,823,332	\$89,094,306	\$106,700,439	\$106,596,847	\$91,922,376

Source: Compiled using Critique spreadsheet

Abbreviations: MBS = Medicare Benefits Schedule; ECT = electroconvulsive therapy; rTMS = repetitive transcranial magnetic stimulation

Note italicised includes Department calculations based on applicant's evidence pack for Application 1196.3

Scenario analyses: multiple retreatment courses

Two scenario analyses were performed to investigate the impact on the financial estimates if multiple retreatment courses of rTMS are allowed in the MBS listing (Table 8):

1. an additional second course of retreatment with rTMS (alternative MBS item descriptor YYYYY; Table 2). This was based on 15/99 (15.2%) responders who experienced a second relapse¹ in Janicak et al. 2010. Given the paucity of data, the second-line retreatment regimen and timing of therapy was assumed to be similar to first-line retreatment (e.g. relapse occurring four months after completion of rTMS retreatment 1; and involving 15 sessions/course; retreatment course 2 would apply in same year as initial course of treatment); and
2. an additional third course of retreatment with rTMS (alternative MBS item descriptor ZZZZZ; Table 3). This was based on 5/99 (5.1%) responders who experienced a third relapse in Janicak et al. 2010. Given the paucity of data, the third-line retreatment regimen and timing of therapy was assumed to be similar across all treatment lines (e.g. relapse occurring four months after completion of rTMS retreatment line 2; and involving 15 sessions/course; retreatment course 3 would apply in subsequent year after initial course of treatment).

Table 8 Scenario analyses investigating financial impact of allowing up to 3 courses of retreatment with rTMS

	Year 1	Year 2	Year 3	Year 4	Year 5
Critique's respecified net implications to the MBS (base case = 1 course of rTMS retreatment)^a	\$51,847,670	\$82,722,802	\$99,032,856	\$98,912,192	\$85,274,121
<i>Scenario analyses</i>					
1. Two courses of retreatment with rTMS ^b	\$54,732,813	\$87,346,612	\$104,597,232	\$104,488,957	\$90,098,770
2. Three courses of retreatment with rTMS ^c	\$54,732,813	\$88,308,327	\$106,138,502	\$106,343,749	\$91,957,691 ^d

Source: Compiled using Critique spreadsheet

^a Retreatment course 1 applied in same year as initial course (initial course: months 1-2; retreatment course 1: months 6-7)

^b Retreatment course 2 applied in same year as initial course (initial course: months 1-2; retreatment course 1 months 6-7; retreatment course 2: months 11-12)

^c Retreatment course 3 applied in next year after initial course (initial course: months 1-2; retreatment course 1 months 6-7; retreatment course 2: months 11-12; retreatment course 3: months 15-16)

^d Note, cost of retreatment course 3 (\$1,608,216 in Year 5) is not included in Year 5 estimates as it is applied in Year 6

Note italicised includes Department calculations based on applicant's evidence pack for Application 1196.3

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

The applicants are grateful for the time and effort that MSAC has put into assessing the case for rTMS therapy for depression and welcome the committees recognition that rTMS is an

¹ Based on prespecified criteria for symptom worsening (a change of one point on the CGI-scale for 2 consecutive weeks) in Janicak et al 2010

important new treatment for patients with depression. Unfortunately, the restrictions that MSAC has chosen to place on the capacity of patients to access ongoing treatment with rTMS after an initial successful course of therapy will place major limitations on successful use of this treatment with a marked negative impact on patients. The recommendations of the committee are such that a patient with depression will be able to only access a single course of rTMS and one additional ‘half course’ (15 sessions) in their entire lifetime. As depression is a recurrent illness, implementation of these recommendations will mean that patients who have done extremely well with their initial therapy will effectively be denied access to funded effective treatment for the duration of their lives after this. Other forms of treatment for mental health conditions have not been restricted in such a severe way: patients are able to access as many courses of medication, Medicare supported psychotherapy or electroconvulsive therapy throughout their life as is required to deal with multiple episodes of relapse. Restricting a repeat treatment to 15 sessions will also result in suboptimal outcomes. The data reviewed by the committee suggested that 15 sessions was on average sufficient: this implies directly that at least half of the patients requiring further treatment required longer courses than 15 to adequately respond. The applicants remain committed to working with MSAC and government to maximise availability and efficacy of this important new treatment. We recommend that repeat courses be allowed for patients who have had a demonstrated positive response to the initial course, and that this is not restricted to a maximum number over a person’s lifetime. If some restriction is felt to be necessary, then a maximum number of 30 sessions per patient for each 12 month period following the successful initial course would be more clinically appropriate. These 30 sessions could be flexibly given as either one full course of 30 sessions, or alternatively two half-courses of 15 sessions each, or possibly 3 brief courses of 10 sessions each, or any similar combination, according to the patient’s individual needs.

14. Further information on MSAC

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