MSAC application no 1196

Repetitive Transcranial Magnetic Stimulation (rTMS)

June 2014

Assessment Report – Repetitive Transcranial Magnetic Stimulation

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This report is a contracted technical report for use by the Medical Services Advisory Committee (MSAC) to inform its deliberations. MSAC is an independent committee which has been established to provide advice to the Minister for Health and Ageing on the strength of evidence available on new and existing medical technologies and procedures in terms of their safety, effectiveness and cost effectiveness. This advice will help to inform government decisions about which medical services should attract funding under Medicare.

MSAC's advice does not necessarily reflect the views of all individuals who participated in the MSAC evaluation.

This report was prepared for MSAC by Cherrie Galletly, Patrick Clarke, Paul Fitzgerald, Shane Gill, Colleen Loo, Bill Lyndon, Tom Paterson from the RANZCP and Louisa Gordon, Kim-Huong Nguyen, Emilie Bettington from Griffith University with the assistance of Health Expert Standing Panel member Perminder Sachev. The report was commissioned by the Department of Health on behalf of MSAC.

This report should be referenced as follows:

Cherrie Galletly, Patrick Clarke, Paul Fitzgerald, Shane Gill, Colleen Loo, Bill Lyndon, Tom Paterson *Gordon L, Nguyen K, Bettington E. (2013). Repetitive Transcranial Magnetic Stimulation. MSAC Application 1196, Assessment Report. Commonwealth of Australia, Canberra, ACT.*

Contents

Tables

Figures

Executive summary

The procedure

Repetitive Transcranial Magnetic Stimulation (rTMS) is a non-invasive procedure intended to stimulate the dorsolateral prefrontal region of the cerebral cortex. It does this with a targeted application of a powerful (1.5T) but brief magnetic field. rTMS is proposed as treatment for adult patients with moderate to severe treatment-resistant depression. Therapy usually occurs three to five times per week over a four to six week period.

Medical Services Advisory Committee – role and approach

The Medical Services Advisory Committee (MSAC) was established by the Australian Government to strengthen the role of evidence in health financing decisions in Australia. MSAC advises the Minister for Health on the evidence relating to the safety, effectiveness and cost-effectiveness of new and existing medical technologies and procedures, and under what circumstances public funding should be supported.

A rigorous assessment of evidence is thus the basis of decision making when funding is sought under Medicare. In this report, a team from the Royal Australian and New Zealand College of Psychiatrists (RANZCP) have provided a review of the clinical evidence for rTMS and a team from Griffith University was engaged to conduct an economic evaluation and financial analysis.

Research question: What is the safety, effectiveness, and cost-effectiveness of rTMS compared to third-line antidepressants or electroconvulsive therapy (ECT) for patients with treatment-resistant depression?

Assessment of rTMS

Purpose of application

An application to MSAC was submitted in February 2012 by the RANZCP. RTMS currently receives no public reimbursement and the costs are not reimbursed by private health insurance. It is currently available in a small number of hospitals as an inpatient procedure with estimated 10-15 magnetic stimulator devices available throughout Australia. The proposed intervention is rTMS for the treatment of major depression (currently determined by DSM-5 rating). Specifically patients will only be eligible for rTMS after they have failed two trials of different classes of antidepressants at adequate dose, duration and compliance.

Background

An MSAC assessment of rTMS for major depression was performed in 2007 (MSAC 1101) where it was compared to ECT. The application was rejected due to insufficient evidence of effectiveness. MSAC found evidence that rTMS was safe and less invasive than ECT.

Prerequisites to implementation of any funding advice

RTMS has been TGA approved for at least one device. The ARTG item 148142 for the magnetic stimulator manufactured by MagVenture and sponsored by Sonoray Pty Ltd. The purpose aligns to the intended use of the rTMS in this application.

Proposal for public funding

The application of rTMS proposes two new MBS items; one for initial mapping requiring psychiatrist expertise and the remaining procedures to be undertaken by a physician, nurse or allied health professional in an outpatient clinic under medical supervision. It is proposed that rTMS treatment would be provided predominantly in a public or private hospital outpatient clinic. The psychiatrist would need to have specific training in rTMS.

The proposed MBS items include:

Category 3 – Therapeutic procedures
MBS xxxxx REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION treatment prescription by a psychiatrist Fee: $350 This item enables a psychiatrist to prescribe rTMS; to determine if the patient meets diagnostic criteria for major depressive disorder and is eligible to have the treatment; to undertake the 'mapping' procedure whereby the location of the motor cortex on the patients scalp is determined (enabling measurement forward to the treatment site over the dorsolateral prefrontal cortex); and to prescribe the dose of rTMS as a proportion of the motor threshold. The psychiatrist would require training and experience in rTMS.

Category 3 – Therapeutic procedures
MBS xxxxx REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION treatment provided by a nurse or allied health professional. Fee: $150 This item enables a nurse or allied health professional, trained in the administration of rTMS, to provide rTMS treatment to a patient, under medical supervision, within an approved hospital*. The rTMS treatment must be prescribed by psychiatrist (as described above) and be given in a setting where immediate medical assistance is available if required. An approved hospital item number must be provided. *We propose an approved hospital to be one already approved for other neurostimulation services, most commonly ECT.

The proposed listing of rTMS limits use to adults with major depression (DSM-5 rating) with treatment-resistance. Antidepressant medication resistance is defined as depression that has not remitted after at least two trials with antidepressants from different pharmacologic classes with adequate dose, duration and compliance. Patients must also be 18 years of age or older and satisfy the following safety requirements: no metal plates or other implants in the skull; no risk of epileptic seizures; not withdrawing from drugs or alcohol, or have a primary diagnosis of drug or alcohol dependence; and not be pregnant or planning on becoming pregnant during the treatment course.

PASC has advised that the restriction of rTMS to approved hospitals is unnecessary and rTMS could be provided in a day clinic. This is because of the high safety record of rTMS. Facilities providing rTMS would be credentialed by the Australian Council of Healthcare Standards. Wording of the MBS descriptor needs to be altered in this case.

Consumer Impact Statement

No consumer feedback was received from the consultation Protocol and/or PASC about the impact on consumers. Given that rTMS is non-invasive and avoids the serious side effects associated with ECT (i.e., impaired cognition, seizures), consumers are likely to be highly accepting of this technology. This is confirmed in large trials presented in this report where less than 5% discontinued treatment. Furthermore, the procedure takes between 45-60 minutes and patients can be expected to continue with their daily activities with otherwise minimal interruption.

Proposed intervention's place in clinical management

RTMS is intended to be used in place of two current (alternative) interventions; third-line antidepressants or ECT. RTMS may also be used in conjunction with antidepressants. It will also be performed with or without any concurrent psychological therapies such as cognitive behavioural therapies. The clinical management algorithm is clear in the proposed place in clinical treatment. The clinical evidence addressed the requirements of the agreed Protocol.

Comparator to the proposed intervention

The main comparator is antidepressant therapy but PASC has advised that ECT should also be a comparator in this assessment. ECT is used as a comparator in the literature and is another form of neurostimulation therapy. ECT is currently listed on the MBS as item 14224 and 20104 (see Table 4 of Protocol 1196). However, ECT may not be a suitable comparator because it primarily targets a different population than proposed here for rTMS. ECT is often used for serious acute episodes, where the patient may be suicidal or psychotic, requiring a rapid response whereas rTMS is indicated for less acute, non-psychotic patients. Therefore, the potential replacement of rTMS for ECT is expected to small. However both rTMS and ECT can be offered for patients with treatment-resistant depression.

Comparative safety

The primary sources of evidence for safety are US-based, randomised controlled, open-label extension trials and post-market reviews. There is no direct comparative evidence of safety outcomes from trial evidence for rTMS compared with either antidepressants or ECT. The available evidence shows for all three treatments, there are different toxicity profiles (Table ES.1). Comparatively, rTMS has the least serious effects of all three options.

Table ES.1: Summary of common adverse events for rTMS, antidepressants and ECT

Treatment	Common adverse events
rTMS	Pain at site during stimulation, headaches, eye pain, muscle twitching,
Antidepressant therapies:	
SSRI	Nausea, agitation, sleep disturbance, sexual dysfunction, headaches
SNRI	Nausea, anxiety, fatigue, sexual dysfunction, headaches
RIMA	Headaches, nausea or heartburn, dizziness, increased sweating
TCA	Sedation, sleepiness, dry mouth, constipation, low blood pressure, falls
NaSSA	Sedation, dizziness, increased appetite, and weight gain
NARI	Dry mouth, constipation, agitation, dizziness, headache, sexual difficulties, difficulty urinating increased heart rate, increased sweating
MAOI	Drowsiness, lethargy, insomnia, headache, dizziness, nausea or heartburn, dry mouth, blurred vision, constipation, increased sweating, muscle tremor, loss of appetite
ECT	Cognitive problems, retrograde and anterograde amnesia, post-ictal delirium, falls, headaches, myalgia, cardiovascular, pulmonary and dental complications

Source: MSAC 1101, 2007
ECT = electro convulsive therapy; MAOI=Monoamine Oxidase Inhibitors; TCA= Tricyclic Anti-depressants; SSRI= Selective Serotonin Reuptake Inhibitors; NARI= Noradrenaline Reuptake Inhibitors; SNRI= Serotonin and Noradrenaline Reuptake Inhibitors; RIMA=Reversible Inhibitors of Monoamine Oxidase– A; rTMS = repetitive Transcranial Magnetic Stimulation; NaSSA=Noradrenaline Serotonin Specific Anti-depressants

The strength of the evidence for the NeuroStar trial and post-market review trials indicates that rTMS is safe with few harmful effects (e.g. 7 seizures reported for 14,000 patients undergoing over 300,000 treatments since 2008). The sham trials consistently support this. There were no seizures or deaths and an absence of suicidal ideation during acute treatment in the NeuroStar trials. The most notable adverse events in the NeuroStar TMS trials were application site discomfort (11%), site pain (36%), muscle twitching (21%) but these were considered mild and transient.

Comparative effectiveness

For the primary comparator of antidepressants, no direct head-to-head trial was identified that compared rTMS and antidepressants. The trials used in this report are listed in Table ES.2 below.

Table ES.2: Summary of studies/reports included in the assessment of effectiveness and safety of rTMS

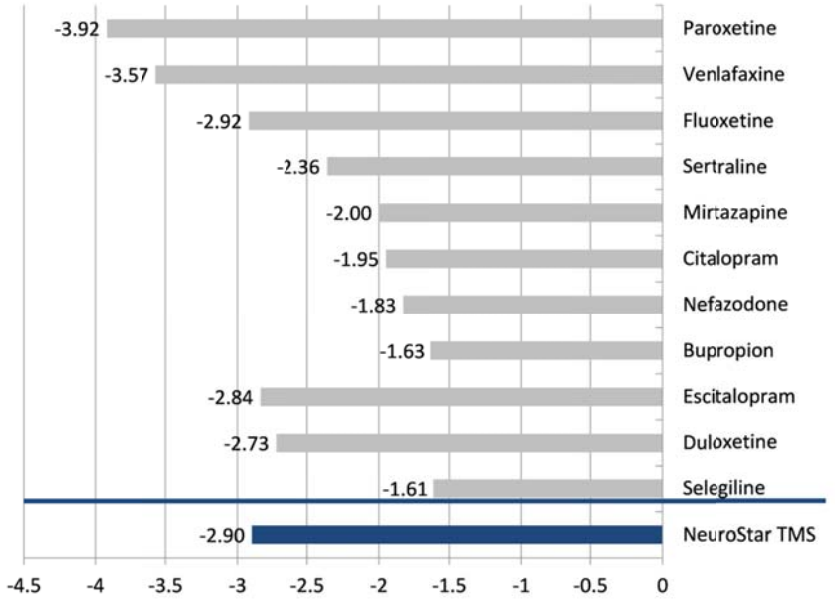
Study	Comparison groups	Study design	Assessed:
NeuroStar TMS 2007	rTMS vs sham	RCT (multicentre)	Efficacy and safety
OPT-TMS 2010	rTMS vs sham	RCT (multicentre)	Efficacy and safety
15 x meta-analyses 2001-2013	rTMS vs sham	Meta-analysis	Efficacy
Avery 2008, Demitrack 2009	rTMS vs sham	Open label (multicentre)	Efficacy
OPT-TMS (McDonald 2011)	rTMS vs sham	Open label (multicentre)	Efficacy
Carpenter 2012, Janicak (2013)	rTMS vs sham	Observational, naturalistic	Efficacy
Mantovani 2012	rTMS vs sham (long term)	Open label (multicentre)	Efficacy
Janicak 2010	rTMS vs sham (long term)	Open label (multicentre)	Efficacy
Neuronetics 2013 (data on file)	rTMS vs sham (long term)	Observational, naturalistic	Efficacy
STAR*D	Antidepressant vs placebo	RCT	Efficacy
Bonneh-Barkay 2014	rTMS vs sham	Conf abstract (pooled analysis) Open label studies	Efficacy
Turner 2008, Shelton 2005, Corya 2006, Thase 2007, Berman 2007, Marcus 2008	Antidepressant vs placebo	RCTs[1]	Efficacy

Study	Comparison groups	Study design	Assessed:
Janicak 2007	rTMS vs ECT	Meta-analysis (open-label studies)	Efficacy
Berlim 2013	rTMS vs ECT	Meta-analysis (open-label studies)	Efficacy

[1] Used in a pooled analysis with NeuroStar TMS data in a comparison of treatment vs placebo/sham.

A comparison of antidepressants and rTMS each with placebo as a common comparator is presented in Figure ES.1. This shows the reduction in HAMD17 score indicates rTMS treatment is equal or superior to known studies reporting improved depression levels for common antidepressants. These studies do not involve treatment-resistant populations.

Figure ES.1: Treatment effects in randomised controlled trials - Change from baseline in HAM-D17 total score (mean difference active vs. placebo)



NOTE: Data in figure from the following sources: Khan, et al. (2000, 2001, and 2007); Detke, et al. (2002a, 2002b); Goldstein, et al. (2002, 2004); Perahia, et al. (2006); Feiger, et al. (2006); Bodkin, et al. (2002). Each antidepressant medication shown represents the average of all available registration studies.

HAMD = Hamilton depression rating score; TMS = Transcranial Magnetic Stimulation

Evidence for rTMS efficacy versus ECT is determined by two meta-analyses where ECT was found to be more effective in the overall sample, but this difference was much less when considering only non-psychotic depression, the patient sample for which rTMS is proposed.

Economic evaluation

A cost-utility analysis was undertaken using a Markov microsimulation model with three-year duration and two-monthly cycles. This provided a structure where sufficient time could elapse to capture the treatment consequences of remission, relapse, maintenance, hospitalisations and re-treatment with rTMS or an alternative. The model inputs were based on reviews of the literature, Australian cost estimates and Health Expert Standing Panel (HESP) advice where assumptions were necessary. In the model, the total cost for one course of rTMS treatment was $4,595 compared with $8,490 for ECT and $505 for antidepressants. The key results of the cost-utility analyses are presented in Table ES.3 below.

Table ES.3: Key economic evaluation findings (3 year duration)

Strategy	Mean Costs	Mean QALYs	ΔCost	ΔQALY	ICER
rTMS	$29,670	1.250	referent	referent	referent
Antidepressants	$31,330	1.180	-$1,660	0.070	rTMS dominant
ECT	$31,260	1.280	-$1,591	-0.030	$75,844

ECT = Electroconvulsive therapy; rTMS = repetitive Transcranial Magnetic Stimulation; QALY = quality-adjusted life years; ICER = incremental cost effectiveness ratio

The economic model predicted that rTMS is cost-effective compared with a strategy of antidepressants but not cost-effective compared with ECT. Compared with ECT, rTMS produced fewer costs but also slightly fewer QALYs. Further details of the sensitivity analyses are provided in this report. In 50,000 iterations, there was a 70.5% likelihood that rTMS was cost-effective against antidepressants and 38.8% against ECT at the willingness-to-pay threshold of $50,000 per QALY.

Financial / budgetary impacts

A summary of the overall expected uptake and costs of rTMS is provided in Table ES.4.

Table ES.4: Summary of financial estimates for rTMS funding

	2015	2016	2017	2018	2019
Expected number of rTMS patients	2,012	2,233	2,460	2,695	2,935
Total number of rTMS treatments per year	82,777	91,870	101,236	110,872	120,757
Cost of rTMS to MBS	$13,586,786	$15,079,417	$16,616,702	$18,198,329	$19,820,809
Total cost saving to the PBS (reduced antidepressant use)	-$295,481	-$327,942	-$361,374	-$395,771	-$431,056
Total cost saving to MBS (reduced ECT use)	-$284,104	-$314,239	-$322,758	-$351,951	-$364,742
Total Net MBS cost	$13,302,682	$14,765,178	$16,293,945	$17,846,378	$19,456,067
Overall Net Cost to the health budget	$13,007,201	$14,437,236	$15,932,570	$17,450,607	$19,025,011

The financial estimates above take into account the numbers of patients requiring reintroduction and maintenance and a small upwards adjustment for increased uptake if more magnetic stimulators are made available in Australia. The listing of rTMS therapy is expected to have a net cost to the MBS of approximately $13.303 million in Year 1, increasing to $19.456 million in Year 5. Over the next 5 years, rTMS treatment and psychiatrist consults would cost the MBS approximately $81.664 million, after cost-offsets are taken into account. In sensitivity analyses, the net costs to the health budget are strongly influenced by the uncertainty around the expected number of rTMS patients. In the base case, of those who have failed two adequate antidepressants, 0.56% are estimated to receive rTMS but if this increases to 1.5%, the net Government cost in the first year increases substantially to $35.318 million.

Conclusions

The main reasons to support rTMS for the proposed MBS population are the superior safety profile of rTMS over both antidepressants and ECT and the equivalent to superior effectiveness to antidepressants.

The main sources of uncertainty in this application are the lack of direct evidence of a benefit of rTMS over ECT or antidepressants and the reliance of comparing outcomes

indirectly. The common sources of bias with the available evidence are the subjective nature of the outcomes, the inconsistency with choice of outcome measures in the trials and unclear methodology around blinding. Further research is necessary to directly assess rTMS with antidepressant and non-psychotic patients receiving ECT. The biological mechanism of why rTMS works is also not fully understood.

The expected use of rTMS in Australia is unknown due to the 10-15 machines that currently exist but the potential for rapid uptake of this non-invasive, safe and acceptable antidepressant treatment for patients. ECT remains a useful approach for severely ill patients but the availability of rTMS provides another treatment for ongoing or maintenance therapy for these patients. Information on the likely numbers of patients for rTMS retreatment or maintenance is largely unknown and assumptions were necessary for these parameters in the economic model and financial estimates. Further evidence is needed on these issues around clinical practice.

Introduction

The Medical Services Advisory Committee (MSAC) has reviewed the use of repetitive transcranial magnetic stimulation, which is a therapeutic procedure for treatment resistant depression. MSAC evaluates new and existing health technologies and procedures for which funding is sought under the Medicare Benefits Scheme in terms of their safety, effectiveness and cost-effectiveness, while taking into account other issues such as access and equity. MSAC adopts an evidence-based approach to its assessments, based on reviews of the scientific literature and other information sources, including clinical expertise.

MSAC is a multidisciplinary expert body, comprising members drawn from such disciplines as diagnostic imaging, pathology, surgery, internal medicine and general practice, clinical epidemiology, health economics, consumer health and health administration.

This report summarises the assessment of current evidence for repetitive transcranial magnetic stimulation being proposed for third-line therapy for treatment-resistant depression.

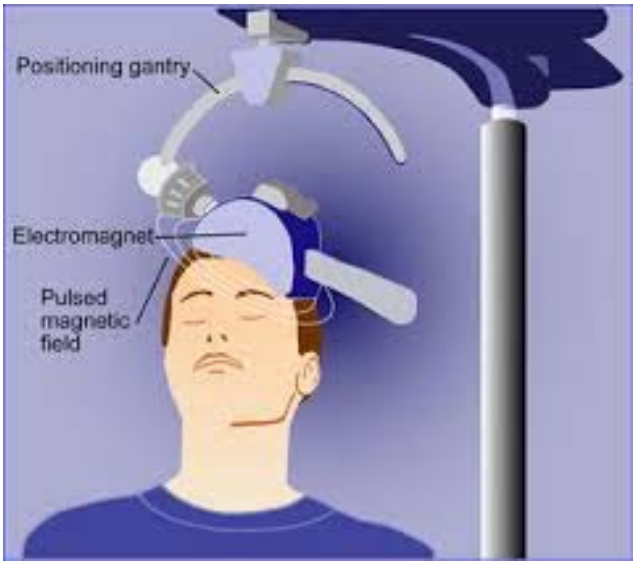
Background

Proposed technology: rTMS

Transcranial Magnetic Stimulation (TMS) therapy is a non-invasive, non-systemic therapeutic device/treatment that uses magnetic resonance imaging (MRI)-strength, pulsed, magnetic fields to induce an electric current in a localized region of the cerebral cortex. During TMS treatment, the patient is conscious and there is no requirement for anaesthetic or muscle relaxants. The therapeutic magnetic strength is set by adjusting the amount of magnetic energy until the motor threshold is reached (i.e., when the patient's fingers or hands start to twitch). Treatment lasts approximately 40 minutes. Sessions are normally performed three to five times a week over a period of four to six weeks.

When used as an antidepressant therapy, TMS therapy produces a clinical benefit without the systemic side effects typical with oral medications and has no adverse effects on cognition (Janicak, et al., 2008; Guse, et al., 2010). TMS is not for use in patients with metal items such as cochlear implants and implanted electrodes in close proximity to the electromagnetic coil during treatment. Patients who are at risk for epileptic seizures, are withdrawing from drugs or alcohol or who have drug or alcohol dependence should also not be referred to TMS.

Figure 1: Illustration of rTMS



(Source: nimh.nih.gov)

TMS therapy can be provided with a number of commercially available TMS stimulators. One of those, the NeuroStar TMS Therapy System manufactured by Neuronetics Inc, received FDA clearance in the US in October of 2008. There is no evidence, or practical reason, why therapy responses vary between standard TMS devices. As such, information in this document will be drawn from a large range of studies conducted investigating the safety and efficacy of TMS in general. It will also draw on information utilised in the evaluation of the NeuroStar TMS Therapy System including data from the clinical program supporting original device approval.

Clinical need

Whilst there are a range of treatments available for patients who initially present with depression including medication and psychotherapy treatments, many patients do not respond to these initial treatment interventions. Treatment resistance is a common and disabling problem in the clinical management of major depression. For example, it is estimated that 20% to 40% of patients do not benefit from or are unable to tolerate standard treatments even after repeated treatment attempts (Kessler, et al., 2003).

In addition, even with successful acute treatment outcomes, the long term durability of response among treatment-resistant patients is poor. For instance, the large, National Institute of Mental Health (NIMH)-sponsored Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study reported that 40.1% of patients who achieved remission after failing one adequate antidepressant course experienced relapse (mean time 4.1 months) over 12 months of follow-up (Rush, et al., 2006).

Burden of treatment resistant depression

Treatment resistant depression (TRD) also incurs a significant burden to the healthcare system at large. Major depression is a chronic and debilitating disease:

- Major depression ranks among the leading cause of disability worldwide;
- The 12-month prevalence of depression in Australia is 4.2% in adult males and 12% females;
- Fewer than half of depressed people seek help from health services in the previous 12 months;
- Estimated costs of the health sector and loss of productivity considered to be in excess of $3 billion dollars annually; and
- Patients with TRD are twice as likely to be hospitalised, costs are very high among patients with MDD (MSAC 1101 Assessment report, 2007)

Proposed MBS listing

It is proposed that rTMS treatment would be provided predominantly in a public or private hospital outpatient clinic. It would be initially prescribed by a psychiatrist following the conduct of an adequate assessment. The psychiatrist would also perform a procedure to localize the appropriate site for stimulation and dose relevant to the patient's motor threshold. The rTMS treatment would then be delivered by a physician, nurse or allied health professional. An individual treatment session takes approximately 40 minutes. Most patients would undergo a course of treatment between 20 and 30 treatments over a four- to six-week period of time. Some patients would require repeated courses of treatment during depressive relapses.

The proposed MBS items will allow rTMS prescription and treatment. The first item number would be utilized by a psychiatrist assessing a patient for, prescribing and initiating an rTMS treatment course. The second item number would be utilized to fund a physician, nurse or allied health professional to provide the actual rTMS treatment under medical supervision.

The two MBS items proposed include:

Category 3 – Therapeutic procedures
MBS xxxxx REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION treatment prescription by a psychiatrist Fee: $350 This item enables a psychiatrist to prescribe rTMS; to determine if the patient meets diagnostic criteria for major depressive disorder and is eligible to have the treatment; to undertake the 'mapping' procedure whereby the location of the motor cortex on the patients scalp is determined (enabling measurement forward to the treatment site over the dorsolateral prefrontal cortex); and to prescribe the dose of rTMS as a proportion of the motor threshold. The psychiatrist would require training and experience in rTMS.

Category 3 – Therapeutic procedures
MBS xxxxx REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION treatment provided by a nurse or allied health professional. Fee: $150 This item enables a nurse or allied health professional, trained in the administration of rTMS, to provide rTMS treatment to a patient, under medical supervision, within an approved hospital*. The rTMS treatment must be prescribed by psychiatrist (as described above) and be given in a setting where immediate medical assistance is available if required. An approved hospital item number must be provided. *We propose an approved hospital to be one already approved for other neurostimulation services, most commonly ECT.

Marketing status of rTMS

Magnetic stimulator devices are classed as Class IIa devices. Of the 10 listings of magnetic stimulator devices in Australia on the Australian Register of Therapeutic Goods, four devices potentially pertain to rTMS (Table 1). It is estimated there are currently 10-15 private hospital or clinics currently using rTMS (HESP advice).

Table 1: Magnetic stimulators registered in Australia for rTMS

Sponsor	ARTG ID	Approved:	Intended purpose:
Sonoray Pty Ltd	148142	05/12/2007	To stimulate the 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.
Medtel Pty Ltd	136823	23/03/2007	This device produces a magnetic field which stimulates the cortical and peripheral nerves when applied to the skin. Used for diagnostic and therapeutic purposes
Symbiotic Devices Pty Ltd	216897	04/11/2013	Produces a magnetic field which stimulates the cortical and peripheral nerves when applied to the skin. Used for diagnostic and therapeutic purposes
Olympus Australia Pty Ltd	163160	06/07/2009	A stimulator that applies an electrical signal to stimulate tissue or nerves.

Source: http://www.tga.gov.au/industry/artg.htm#.U4VSR_mSzAI

Issues raised in the Protocol

Breadth of indication

The decision analytic protocol (Protocol) requests clarification as to whether the applicant's wish to broaden the indicated population to include those who failed at least two different treatments, one of which may be a psychological therapy. The use of rTMS should be defined as applying to patients who have failed to respond to two different classes of antidepressant medication, despite adequate dose, duration and compliance.

Primary and secondary comparators

In the original application antidepressant medication was proposed as the sole comparator. PASC has determined that ECT and psychotherapy should be considered as comparators. Available information addressing these two additional comparators is provided in this response. Due to a lack of evidence of rTMS versus psychotherapy, the assessment provides evidence on the two comparators ECT and antidepressant medication predominantly.

Use of intervention in circumstances of depression relapse

The Protocol requested information on how many cycles of rTMS will be contemplated if a patient responses to treatment but then relapses. This is likely to be predominately determined by the duration of remission of symptoms achieved with each cycle of rTMS treatment. If the duration of treatment is clinically meaningful (for example six months to several years) as is the case in the treatment of many patients with rTMS, it is anticipated rTMS treatment is provided for all or most subsequent relapse episodes. If patients achieve successful clinical response, but the duration of this response is limited, other treatment strategies would be adopted to try to achieve a greater duration of clinical benefit, including potentially augmentation with different medications or psychological treatment strategies.

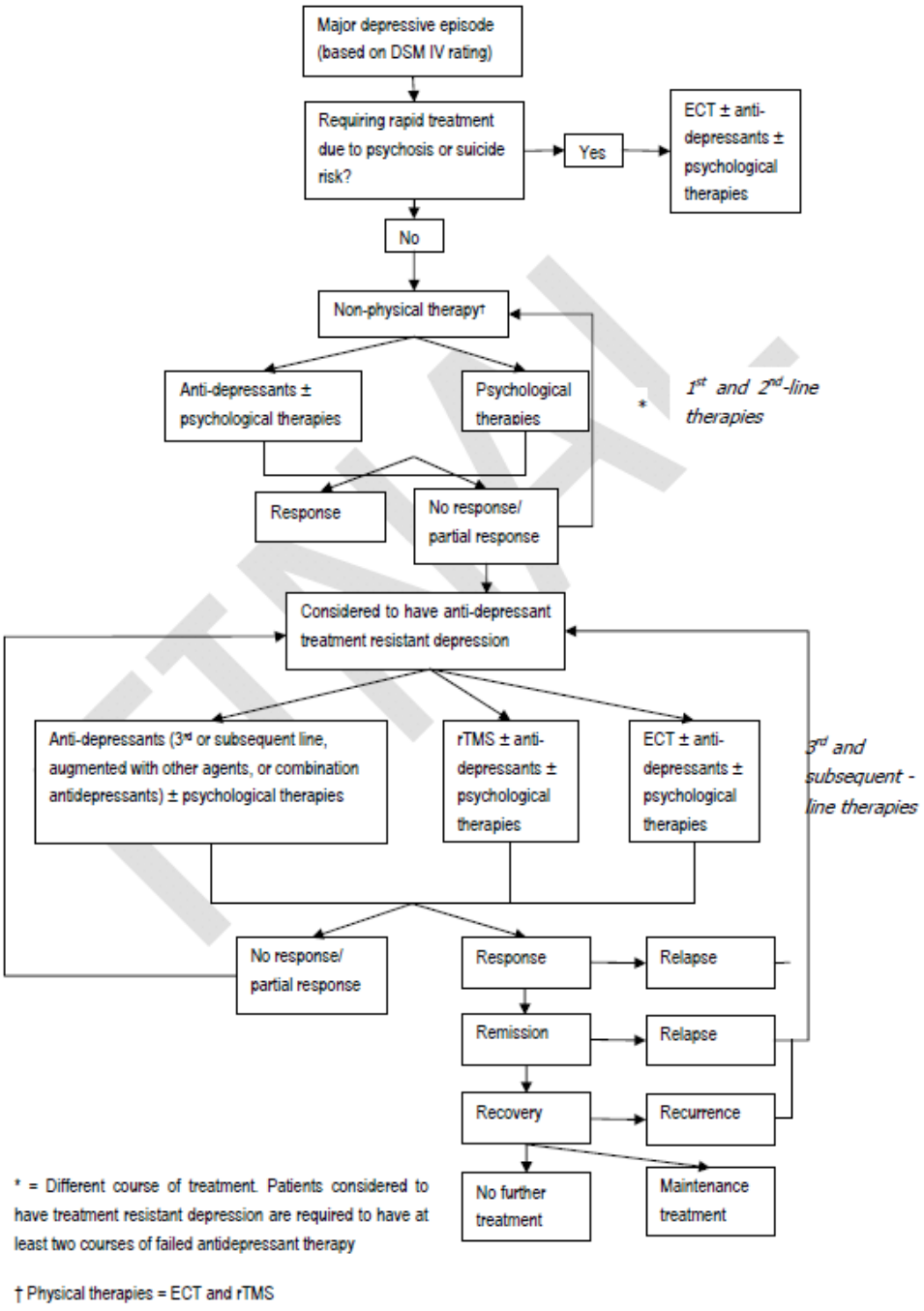
Approach to assessment

Objective

The objective of this assessment is to undertake a structured evaluation of the clinical need, safety, effectiveness and cost-effectiveness of rTMS for patients with treatment-resistant depression.

Clinical decision pathway

Figure 2: Clinical decision pathway for rTMS treatment



After a person has demonstrated that they have TRD they can be referred to an rTMS psychiatrist. The rTMS psychiatrist will assess the patient for suitability for rTMS and ascertain that they do not have any ferrous metal in their head, a history of epilepsy or existing comorbidities. If they are found to be suitable they undergo "mapping" to determine the threshold of the rTMS stimulus. After the mapping, the patient can commence a course of rTMS. This algorithm indicates the use of TMS following a failure to respond to two or more antidepressant medication strategies.

Comparators

Several potential comparators for TMS treatment are identified in the Protocol. Antidepressant medication was proposed as the most appropriate comparator in the initial application to MSAC. The Protocol identifies both ECT and psychotherapy as other potential comparators.

Antidepressant medication: the main comparator

Antidepressant medications are commonly used in the treatment of depression. However, there is a substantial body of evidence that indicates that if patients have failed to respond to one or two trials of medication, response rates to a third line antidepressant treatment are very low. In clinical practice, patients will commonly cycle through multiple courses of antidepressant therapy including adjuvant treatment such as antipsychotics and mood stabilisers in an attempt to achieve clinical response. The use of third line antidepressant medication is the most appropriate comparator for rTMS treatment.

Electroconvulsive therapy

ECT treatment is typically utilised for patients with depression where a rapid clinical response is required, commonly related to the presence of psychotic symptoms or high suicide risk. It is also used in patients with treatment resistant depression, although many patients with treatment resistant depression may not be offered ECT if their symptoms are not considered of sufficient severity to justify this treatment due to the risks and side effects associated with it. Often patients will not accept a recommendation of ECT due to fear of the treatment itself, or concern about memory impairment.

There is likely to be only a small overlap in use between rTMS and ECT because patients with very severe episodes of depression, where patients are suicidal or psychotic, will not be appropriate for rTMS.

Psychotherapy

Psychotherapies, especially cognitive behavioural therapy (CBT) and interpersonal psychotherapy (IPT) are commonly used treatments for depression. They are most typically used as first line interventions, often preceding or concurrently utilised with antidepressant medications. There is some research suggesting that psychotherapy may have some value in treatment-resistant depression.

Position statements and guidelines

The American Psychiatric Association's 2010 Practice Guidelines for the Treatment of Patients with Major Depressive Disorder state that "For patients whose symptoms have not responded adequately to medication…transcranial magnetic stimulation could also be considered…"

The Royal Australian and New Zealand College of Psychiatrists (RANZCP) current position statement on the use of rTMS treatment in depression also emphasises the use of this treatment in patients with treatment resistant depression, stating that "Those with treatment- resistant depression who respond to rTMS treatment (of the order of 50% of patients) will subsequently experience a lower burden of disease both subjectively and functionally. Over the past several years*, the evidence for efficacy has been compelling for this population group*, with a shift towards consistently positive findings following refined treatment parameters."

The World Federation of Societies of Biological Psychiatry Guidelines on Brain Stimulation Treatments in Psychiatry (2010) also support the use of rTMS in patients with treatment-resistant depression, stating that "For the acute management of patients with moderately treatment-resistant depression there is sufficient class I evidence of acute efficacy for TMS in depression in medication-free unipolar depressed patients. The large body of evidence from single site small sample trials suggests that it may also be useful clinically in moderately treatment-resistant patients, either alone or used adjunctively with medications. We thus recommend that psychiatrists consider using TMS in non-psychotic adults with major depression. Typically patients will have tried and failed at least one attempt at medication therapy, although this is not required. There are only limited data about using it in a maintenance fashion after acute response."

Comprehensive technology reviews also provide support that rTMS is an evidence-based treatment option for patients who have failed to benefit from initial acute phase treatment of major depression. In 2011, the US federally-funded Effective Health Care Program of the Agency for Healthcare Research and Quality (AHRQ), published a Comparative Effectiveness Review (Number 33), entitled, "Non-pharmacologic interventions for treatment-resistant depression in adults". Overall, the AHRQ Panel concluded that there is a "substantial and well-replicated body of evidence from randomized, sham-controlled clinical trials that provide a *high strength of evidence* that TMS produces significantly greater decreases in depression severity, response rate and remission rate when compared to a sham treatment condition in the majority of peer-reviewed published clinical trials."

Differences between the rTMS and antidepressants

Indications

There are no major differences in indications for rTMS treatment and antidepressant medication or psychotherapy. As described above, ECT is typically used in more severely depressed patients where there is an urgent need for clinical response related to psychosis or suicidality.

Contraindications

The major contraindications for rTMS are a history of a seizure disorder or the presence of ferrous metal in the skull or brain, or the presence of a magnetically programmable medical device such as a pacemaker. The major contraindications for antidepressant medication are related to tolerability or side-effects with specific individual medications. The major contraindications for engagement in psychotherapy relate to the suitability and capacity of patients to actually engage in individual forms of psychotherapy: this is typically an under recognised but important reason why a substantial proportion of individuals cannot adequately benefit from different forms of psychotherapy.

Adverse events

Detailed information on the safety profile of TMS treatment in clinical trials and real-world use will be provided in following sections. The most important adverse event with rTMS treatment is the induction of a seizure: rates of these are extremely low. rTMS treatment is otherwise tolerated extremely well with low treatment discontinuation rates. Antidepressant medications are associated with a wide range of adverse events which include treatment limiting side-effects as well more serious potential complications. Antidepressant medications can also produce significant discontinuation syndrome on medication withdrawal. ECT has significant risks and adverse effects related to both the anaesthetic and the ECT treatment. ECT treatment can result in significant impairment in both short-term and long-term memory with permanent changes seen in a small subset of patients.

Research Questions

The following research questions will be addressed in this report:

1. Is rTMS therapy more effective for patients with major depressive disorder who have previously failed two antidepressant medications at adequate dose and duration compared with either third-line antidepressants or ECT (with or without psychological therapies)?

2. Is rTMS therapy safer for patients with major depressive disorder who have previously failed two antidepressant medications at adequate dose and duration compared with either third-line antidepressants or ECT (with or without psychological therapies)?

3. What is the cost-effectiveness of rTMS compared with antidepressants or ECT?

Summary of the primary elements of the decision analysis (PICO)

The PICO table for the assessment is provided in Table 2.

Table 2: Summary of PICO

Patients	Intervention	Comparators	Outcomes to be assessed
Adults with treatment resistant major depression (two or more failed courses of antidepressants)	Repetitive transcranial magnetic stimulation (rTMS) ± antidepressant medication ± psychological therapy	Antidepressant medication* ± psychological therapy or ECT ± psychological therapy ± antidepressant medication *Where antidepressant medication can be a third class of antidepressant, or augmented with a second agent (eg, lithium, thyroid hormones, pindolol, psychostimulants, atypical antipsychotics, sex hormones, anticonvulsants/mood stabilizers, and dopamine agonists) or combined antidepressant medications	Safety Side effects from rTMS, e.g. seizures, headache, transient scalp pain, facial muscle twitching Side effects of antidepressant medication, e.g. sexual dysfunction, weight gain, insomnia, daytime sleepiness/sedation, treatment emergent anxiety and nervousness, cognitive, memory and attention difficulties Side effects from ECT, e.g. transient or permanent neuropsychological deficits, adverse reaction to anaesthetic agents and neuromuscular blocking agents, alterations in blood pressure, cardiovascular complications, death, dental and oral trauma, pain and discomfort, pulmonary complications, skin burns, stroke. Side effects from psychological therapies, e.g. damage caused by use of psychotherapy when other treatments would have been more effective, the impact of inappropriate therapist behaviour, and the negative effects of prolonged dependency on the therapist. Effectiveness Primary outcomes: meeting diagnostic criteria for depression (remission), severity of depressive symptoms, quality of life, survival Secondary outcomes: suicidal ideation and attempts, symptoms of anxiety, global functioning, social and occupational functioning, treatment refusal or discontinuation, rate of hospital admission Cost-effectiveness Cost, cost per relevant health outcome (eg LYG, QALY)
Questions 1. Is rTMS ± antidepressant medication ± psychological therapy as safe, effective and cost-effective as antidepressant medication ± psychological therapy, or ECT ± antidepressant medication?			

ECT = electroconvulsive therapy; LYG = life-year gained; rTMS = repetitive transcranial magnetic stimulation; QALY = quality adjusted life-year.

Population and problem

The population eligible for rTMS therapy are patients with major depressive disorder who have failed to respond to two adequate medication trials from two different classes of drugs.

Before discussion of the clinical trial results, it is important to understand the research definition of the key inclusion criterion of an "adequate" antidepressant medication trial. An adequate drug trial is defined by the Antidepressant Treatment History Form (ATHF) (Sackeim, 2001), a rigorous and validated methodology for establishing antidepressant treatment resistance in research settings. The ATHF assigns each drug therapy an "antidepressant resistance rating" ranging from 1 to 5 (1 being the lowest and 5 being the highest), based on the dosage and duration of treatment. Generally, drug therapy must last at least four weeks to be considered of an adequate duration by this methodology. An antidepressant resistance rating of 3 or greater indicates an adequate trial, in both duration and dosage. In many instances, patients receive multiple trials of drug therapy, the majority of which do not achieve treatment exposure adequacy as defined by the ATHF, usually because of intolerance to the adverse effects of treatment, or due to general non-adherence to recommended therapy. When rigorously assessed in research studies, a replicated observation has been that, on average, for every four to five treatment trials, only one is able to be administered at an adequate dose for an adequate duration of time.

In other words, without examination of the dose and duration of exposure, some patients may be incorrectly classified as having treatment failure, when in fact they have not yet received an adequate drug trial (termed 'pseudo-resistance'). Both the NeuroStar registration trial and the NIMH-sponsored study, which will be described in the following enrolled patients who met the very stringent research definition of a prior course of *adequate* drug therapy in the current episode of their illness. In the NeuroStar rTMS registration trial, the average patient had received four antidepressant treatment trials, with a range from one to as many as 23 separate treatment attempts in the current episode.

Review of the literature

Literature sources and search strategies

Searches were conducted of MEDLINE, EMBASE, the Cochrane database of systematic reviews and the US based clinical trial registry (15th October 2013). In addition, we have reviewed and included evidence from the following document:

AHRQ Comparative Effectiveness Review (Number 33), entitled, "Non-pharmacologic interventions for treatment-resistant depression in adults".

This was produced by the RTI International-University of North Carolina (RTI-UNC) Evidence-based Practice Center for the Agency for Healthcare Research and Quality, U.S. Department of Health and Human Services. This document provides an independent and comprehensive review of the effectiveness and comparative effectiveness of non-pharmacological interventions for treatment-resistant depression in adults, including TMS treatment as well as ECT and psychotherapy.

Expert advice

An advisory panel was established to provide guidance to the evaluators to ensure that the assessment is clinically relevant and takes into account consumer interests. Membership of the advisory panel is provided at Appendix A.

Results of assessment

Evidence for the effectiveness of rTMS

No direct head-to-head or direct randomised trials comparing TMS treatment to the primary comparator were identified in the literature search or within any other documents.

A summary of the studies used in this assessment is provided in Table .

Table 3: Summary of studies/reports included in the assessment of effectiveness and safety of rTMS

Study	Comparison groups	Study design	Assess
NeuroStar TMS 2007	rTMS vs sham	RCT (multicentre)	Efficacy and safety
OPT-TMS 2010	rTMS vs sham	RCT (multicentre)	Efficacy and safety
15 x meta-analyses 2001-2013	rTMS vs sham	Meta-analysis	Efficacy
Avery 2008, Demitrack 2009	rTMS vs sham	Open label (multicentre)	Efficacy
OPT-TMS (McDonald 2011)	rTMS vs sham	Open label (multicentre)	Efficacy
Carpenter 2012, Janicak (2013)	rTMS vs sham	Observational, naturalistic	Efficacy
Mantovani 2012	rTMS vs sham (long term)	Open label (multicentre)	Efficacy
Janicak 2010	rTMS vs sham (long term)	Open label (multicentre)	Efficacy
Neuronetics 2013 (data on file)	rTMS vs sham (long term)	Observational, naturalistic	Efficacy
STAR*D	Antidepressant vs placebo	RCT	Efficacy
Bonneh-Barkay 2014	rTMS vs sham	Conf abstract (pooled analysis) Open label studies	Efficacy
Turner 2008, Shelton 2005, Corya 2006, Thase 2007, Berman 2007, Marcus 2008	Antidepressant vs placebo	RCTs[1]	Efficacy
Janicak 2007	rTMS vs ECT	Meta-analysis (open-label studies)	Efficacy
Berlim 2013	rTMS vs ECT	Meta-analysis (open-label studies)	Efficacy

[1] Used in a pooled analysis with NeuroStar TMS data in a comparison of treatment vs placebo/sham.

Patient characteristics

Patients receiving NeuroStar rTMS Therapy in clinical practice settings are comparable with the patient population studied in research settings in the NeuroStar rTMS Therapy clinical trials in patient demographics, diagnostic history and level of treatment resistance.

The evidence reviewed in the preceding section reveals several clinical features that help define the patient for whom rTMS represents an appropriate clinical choice for the treatment of their illness. For example, these data show that in both research settings and in clinical practice for nearly all patients this is not their first illness presentation, most having experienced a recurrent course of their disease at the time of presentation to treatment. Second, most patients have already experienced multiple antidepressant medication trials without success, with the majority of these trials having been incomplete, usually due to the emergence of intolerable side effects. Third, and also consistent with these clinical features, the average age of the patient is in the latter part of the fifth decade of their life, about a decade older than the typical age of first onset for major depression. Finally, all patients had clearly documented evidence of some level of

treatment resistance as shown by failure to benefit from one or more prior antidepressant medications.

In short, these clinical descriptors define a patient who has likely experienced treatment success in a prior illness episode, but has now experienced an illness recurrence, and has tried and failed to achieve satisfactory clinical benefit from acute phase treatment with a thorough antidepressant medication in this episode. This has meant, for the average patient, at least four antidepressant medication trials in this illness episode, with at least one medication taken for an adequate dose and duration.

An appropriate patient for whom the attending physician should recommend rTMS therapy would usually have experienced several unsuccessful attempts at antidepressant medication treatment in the current illness episode. Based on clinical trial evidence of safety and effectiveness, TMS therapy would be an appropriate clinical choice in advance of more burdensome interventions such as second generation antipsychotic augmentation. For example, although this category of drugs has been TGA-approved for this use, they nevertheless carry a significant amount of systemic adverse events. In addition, rTMS therapy should also be considered in advance of more complex medication combination or augmentation approaches (e.g. lithium, thyroid hormone) that are not widely approved for use in such patients. Finally, for most patients, the choice of rTMS therapy would also come well in advance of more invasive therapeutic options such as ECT.

Is rTMS effective versus sham?

The acute safety and efficacy of TMS therapy has been studied in two multisite independent Level I trials as well as a series of smaller independent clinical trials.

Trial 1: Neuronetics-sponsored randomised controlled trial (Table)

Results of the NeuroStar registration trial were originally published in 2007 (O'Reardon, et al.), with further analysis and review published by Janicak and colleagues (2008) and Demitrack and Thase (2009). The results of the NeuroStar registration trial will be briefly summarized here to place the results of this initial trial in context with the more recently published literature, reviewed below.

This trial was a randomized and sham-controlled study enrolling depressed patients meeting DSM-IV criteria for MDD, with a moderate level of treatment resistance meeting the following criteria:

(i) Insufficient clinical benefit by rigorous ATHF research criteria of at least one and as many as four antidepressant medication trials administered at an adequate dose and duration in the current illness episode; OR

(ii) Intolerance to four or more trials of less than adequate dose or duration of therapy.

The study consisted of three phases, a one week, no-treatment lead-in, a six week acute treatment phase of daily rTMS given as a monotherapy in medication-free patients, and a three week taper phase during which time all patients were begun on an open-label, single antidepressant medication and followed for six months to examine the durability of the acute effect of rTMS.

Table 4: Overview of NeuroStar registration trial - a randomized controlled clinical trial evaluating the acute safety and effectiveness of the NeuroStar TMS Therapy system in patients with TRD

Trial Type	Patient Population/Study Design	Key Findings
Randomized, Controlled, Multicenter	- Sponsor: Neuronetics, Inc. - Multicenter (23 sites), sham-controlled N=301 patients with MDD, demonstrated treatment resistance from 1 through 4 research-grade antidepressant medication in current episode (ATHF verified) - 6 week acute phase; 4 week exit for non-responders - Primary efficacy outcome: MADRS; Change from baseline at 4 weeks - Key secondary outcomes: HAMD24 change from baseline; Response and remission outcomes (MADRS, HAMD24) at 4 and 6 weeks References: 1. O'Reardon et al, Biol. Psychiatry (2007); 62(11):1208-1216 2. Demitrack, MA and Thase, ME. Psychopharmacology Bulletin (2009); 42(2):5-38.	Primary Outcome: [favours TMS] - ATHF 1 - 4 cohort (N=301): MADRS change from baseline @ week 4 (P=0.057), Effect size = 0.39 - ATHF 1 cohort (N=164): MADRS change from baseline @ 4 weeks (P=0.0006), Effect size = 0.94 Secondary Outcomes: [favours TMS] - ATHF 1 - 4 cohort (N=301): HAMD24 change from baseline @ 4 weeks (P=0.012) HAMD24 change from baseline @ 6 weeks (P=0.015) HAMD24 response rate TMS vs. sham @ 4 weeks: 19.4% vs. 11.6% (P=0.030), @ 6 weeks: 23.9% vs. 15.1% (P=0.042) MADRS response rate TMS vs. sham @ 4 weeks: 18.1% vs. 11.0% (P=0.045), @ 6 weeks: 23.9% vs. 12.3% (P=0.007) HAMD24 remission rate TMS vs. sham @ 6 weeks: 17.4% vs. 8.2% (P=0.012) MADRS remission rate TMS vs. sham @ 6 weeks: 14.2% vs. 5.5% (P=0.011) - ATHF 1 cohort (N=164): HAMD24 change from baseline @ 4 weeks (P=0.0006) HAMD24 change from baseline @ 6 weeks (P=0.0041) HAMD24 response rate TMS vs. sham @ 4 weeks: 21.6% vs. 9.2% (P=0.0047), @ 6 weeks: 25.7% vs. 13.2% (P=0.0139) MADRS response rate TMS vs. sham @ 4 weeks: 25.0% vs. 9.2% (P=0.0083), @ 6 weeks: 25.0% vs. 9.2% (P=0.0026) HAMD24 remission rate TMS vs. sham @ 6 weeks: 15.9% vs. 5.3% (P=0.012) MADRS remission rate TMS vs. sham @ 6 weeks: 17.0% vs. 6.6% (P=0.0112)

ATHF = antidepressant treatment history form; HAMD = Hamilton depression rating scale; MADRS = Montgomery-Asberg depression rating scale; MDD = major depressive disorder; N = number; TMS = Transcranial Magnetic Stimulation; TRD = treatment resistant depression

Results for the overall study population demonstrated clinically meaningful improvement on the primary outcome measure, baseline to endpoint change on the Montgomery-Asberg Depression Rating Scale at four weeks (MADRS, P=0.057, standardized effect size = 0.39). Additionally, several secondary outcome measures demonstrated statistically and clinically significant benefit for NeuroStar rTMS compared with sham. Among these secondary outcomes was a superior outcome on the Hamilton Depression Rating Scale (HAM-D), with both the 17-item and 24-item versions showing baseline to endpoint change in favour of NeuroStar rTMS at 4 weeks (17-Item change: P=0.006, standardized effect size = 0.55; 24-Item change: P=0.012, standardized effect size = 0.48).

Trial 2: NIMH-sponsored randomised controlled trial (the optimization of TMS, 'OPT-TMS', Study) (Table)

In 2010, a second, large (N=190) multisite (4) randomized sham-controlled trial was published that provided additional evidence of the safety and efficacy of rTMS in patients diagnosed with treatment resistant depression (George, et al, 2010). This study was sponsored by the US Federal NIMH. Further details of the trial design and results are summarized in Table . These investigators focused on the primary efficacy endpoint of remission, measured using the 24-item HAM-D. The trial design consisted of a 2 week

no treatment lead-in phase, a 3 week fixed treatment phase and a variable, 3 week treatment extension for clinical improvers. The trial included 190 antidepressant drug free patients with major depressive disorder with a moderate level of treatment resistance meeting the following criteria:

(i) Insufficient clinical benefit by rigorous ATHF research criteria of at least one and as many as four antidepressant medication trials administered at an adequate dose and duration in the current illness episode; or
(ii) Intolerance to three or more trials of less than adequate dose or duration of therapy.

Table 5: Overview of OPT-TMS study - a randomized controlled clinical trial providing additional safety and effectiveness data for the NeuroStar TMS Therapy system in patients with TRD

Trial Type	Patient Population/Study Design	Key Findings
Randomized, Controlled, Multicenter	- Sponsor: National Institute of Mental Health, NIH - Multicenter (4 sites), active sham-controlled - N=190 patients with MDD, demonstrated treatment resistance from 1 through 4 research-grade antidepressant medication in current episode (ATHF verified) - 3 week fixed acute phase; 3 week variable duration extension for responders - Primary efficacy outcome: HAMD24 remission rate (at endpoint) - Key secondary outcomes: MADRS, HAMD24 change from baseline Reference: George, et al, Arch Gen Psychiatry. (2010) 67(5):507-516	Primary Outcome: [favours TMS] HAMD24 Remission rate TMS vs. sham @ endpoint: 14.1% vs. 5.1% (P=0.02), odds ratio = 4.2 (95% CI: 1.32, 13.24) Secondary Outcomes: [favours TMS] HAMD24 change from baseline @ endpoint: (P=0.06), effect size = -0.42 (95% CI: -4.23, 0.10) MADRS change from baseline @ endpoint (P=0.01), effect size = -0.51 (95% CI: -6.10, -0.76)

ATHF = antidepressant treatment history form; CI = confidence interval; HAMD = Hamilton depression rating scale; MADRS = Montgomery-Asberg depression rating scale; MDD = major depressive disorder; N = number; NIH = National Institutes of Health; TMS = Transcranial Magnetic Stimulation; TRD = treatment resistant depression

The authors reported that, for the entire treatment resistant patient population, there was a significant effect of active treatment on the proportion of remitters (15% active rTMS vs. 4% sham control group, P=0.015), representing a 4.2 greater odds of reaching remission with active rTMS compared to sham control. They concluded that "...daily left prefrontal rTMS as monotherapy produced significant and clinically meaningful antidepressant therapeutic effects greater than sham..." (George, et al., 2010)

It is important to note that this study used the NeuroStar rTMS Therapy System, the first rTMS device cleared for commercial use by the FDA, and the same treatment parameters as reported in NeuroStar rTMS Therapy registration study (O'Reardon, et al., 2007; Janicak, et al;., 2008; Demitrack and Thase, 2009). Prior randomized trials have used different protocols; these two randomized studies are the first to use identical protocols using a rTMS device that has been cleared by the FDA for the treatment of depression. The results of the NIMH-sponsored study further validate the results of the NeuroStar rTMS registration study.

Single site trials and meta-analyses supporting the efficacy of TMS in the treatment of depression

The accumulated evidence for the clinical efficacy of rTMS in the treatment of depression is considerable, now spanning more than 30 controlled clinical studies in over 2,000 patients. To date, this aggregate data has been examined in more than ten meta-analyses and two qualitative reviews of rTMS published in the peer-reviewed literature between 2001 and 2013 (see Table for a complete summary of these references). *Overall,*

these reports provide a consistent, comprehensive and replicated literature base that supports the specific use of left-prefrontal, high frequency rTMS in patients with treatment-resistant depression.

As an example of the comprehensiveness of these reports, one of the more recently published meta-analyses (Slotema, et al, 2010) examined data from 34 studies involving 1,383 patients. These authors reported an effect size of 0.55 (95% CI: 0.38, 0.72) for the use of TMS in the treatment of treatment resistant depression.

Table 6: Meta-analyses and qualitative reviews of the efficacy of rTMS vs. Sham

Meta-Analysis	No. studies	No. patients	Effect size (95% CI)	Conclusions
McNamara (2001)	5	81	NNT = 2.3 (1.6, 4.0)	TMS has "demonstrable beneficial effects in major depression"
Holtzheimer (2001)	12	264	0.81 (0.42, 1.20)	"TMS is statistically superior to sham stimulation in the treatment of depression, showing a moderate to large effect size"
Martin (2001) for the Cochrane Collaboration	14	372	-0.35 (-0.04, -0.66)	"The information in this review suggests that there is no strong evidence for benefit from using TMS to treat depression, although the small sample sizes do not exclude the possibility of benefit"
Kozel (2002)	12	230	0.53 (0.24, 0.82)	"…[the data] supports the hypothesis that left prefrontal rTMS is an acute antidepressant treatment with statistically significant effect sizes and measurable clinical improvement"
Burt (2002)	23	432	0.62 (NR)	"A meta-analysis of controlled studies indicates that this [antidepressant] effect is fairly robust from a statistical viewpoint. However, effect sizes are heterogeneous and few studies have shown that rTMS results in substantial rates of response or remission, and the durability of the antidepressant effects is largely unknown"
Aarre (2003)	12	306	Qualitative review of data only	Authors deferred application of formal meta-analysis because the study methods were too diverse, and no large studies were present. Insufficient evidence as of yet to determine the efficacy of rTMS in the treatment of depression.
Couturier (2005)	6	91	WMD = -1.1 (-4.5, 2.3)	"…[data] suggests that rapid-rate rTMS is no different from sham treatment in major depression; however, the power within these studies to detect a difference was generally low. Randomized controlled trials with sufficient power to detect a clinically meaningful difference are required" NOTE*: Hermann (2006) cited the use of inappropriate statistical methodology in the Couturier analysis.*
Loo (2005)	25	745	Qualitative review of data only	"There is fairly consistent statistical evidence for the superiority of rTMS over a sham control, though the degree of clinical improvement is not large. However, this data is derived mainly from two-week comparisons of rTMS versus sham, and evidence suggests greater efficacy with longer treatment courses."
Herrmann (2006)	33	877	0.71 (0.45, 0.97)	"Active TMS was more effective than sham, but variability was too great to take any single study design as paradigmatic."
Gross (2007)	5	274	-0.76 (-0.51, -1.01)	"Our findings showing that the recent TMS trials had larger effect sizes when compared with the earlier rTMS studies give additional support for the antidepressant effects of rTMS."
Lam (2008)	24	899	0.48 (0.28, 0.69)	"…active rTMS is significantly superior to sham in short-term acute treatment of TRD. The risk difference of 17% and the NNT of 6 are of clinically significant magnitude for these difficult to treat patients, and similar to those seen with medication-placebo comparisons in TRD…"

Meta-Analysis	No. studies	No. patients	Effect size (95% CI)	Conclusions
Schutter (2009)	30	1,164	0.39 (0.25, 0.54)	"…high frequency TMS over the left DLPFC is superior to sham in the treatment of depression. The effect size is robust and comparable to at least a subset of commercially available antidepressant drug agents…"
Slotema (2010)	34	1,383	0.55 (0.38, 0.72)	"…rTMS deserves a place in the standard toolbox of psychiatric treatment methods, as it is effective for depression and has a mild side effect profile...Although rTMS cannot replace ECT in depressive patients, there may be subgroups in which rTMS can replace antidepressant medication…"
Allan (2011)	31	1,531	0.64 (0.50, 0.79)	"…Our meta-analysis of changes in depression scales, and clinical improvement of more than 50% on such scales, confirms a moderate statistically significant effect of active therapy…"
Berlim (2013)	29	1,371	OR for remission rate = 3.3 (2.0, 5.3)	"…overall, HF-rTMS seems to be an acceptable treatment for MDD, and is associated with clinically relevant antidepressant effects (especially considering that it has been most investigated in samples with TRD…"

CI = confidence interval; DLPFC = dorsolateral prefrontal cortex; ECT = electroconvulsive therapy; HF-rTMS = high frequency rTMS; MDD = major depressive disorder; NNT = number need to treat; OR = odds ratio; rTMS = repetitive TMS; TMS = Transcranial Magnetic Stimulation; TRD = treatment-resistant depression; WMD = weighted mean difference

Table 7: Overview of open-label clinical trials evaluating the acute safety and effectiveness of the NeuroStar TMS Therapy system in patients with TRD

Trial Type	Patient Population/Study Design	Key Findings
Open-Label, Uncontrolled Multicenter Trial 1. Avery, et al J. Clin. Psychiatry (2008); 69,441-451 2. Demitrack, MA and Thase, ME. Psychopharmacology Bulletin (2009); 42(2):5-38.	- Sponsor: Neuronetics, Inc. - Multicenter (23 sites), open-label extension - N=158 patients with MDD who had participated, but not benefited from treatment in O'Reardon 2007 study (either active or sham TMS), demonstrated treatment resistance from 1 through 4 research-grade antidepressant medication in current episode (ATHF verified) - Same acute phase treatment design as in O'Reardon 2007 study	Acute Phase Outcomes: - ATHF 1 - 4 cohort (RCT sham to open-label active TMS group, N=85): MADRS response rate @ 6 weeks = 42.4% HAMD24 response rate @ 6 weeks = 42.4% MADRS remission rate @ 6 weeks = 20.0% HAMD24 remission rate @ 6 weeks = 27.1% - ATHF 1 cohort (RCT sham to open-label active TMS group, N=43): MADRS response rate @ 6 weeks = 53.5% HAMD24 response rate @ 6 weeks = 53.5% MADRS remission rate @ 6 weeks = 23.3% HAMD24 remission rate @ 6 weeks = 32.6%
Open-Label, Uncontrolled Multicenter Trial McDonald, et al., (2011);28(11):973-980	- Sponsor: National Institute of Mental Health, NIH - Study OPT-TMS Phase 2: Multicenter (4 sites),active sham-controlled - N=67 patients with MDD, who had participated, but not benefited from treatment in George 2010 study (either active or sham TMS), demonstrated treatment resistance from 1 through 4 research-grade antidepressant medication in current episode (ATHF verified) -6 week fixed acute phase	Acute Phase Outcomes: - ATHF 1 - 4 cohort (RCT sham to open-label active TMS group, N=24): HAMD24 remission rate @ 6 weeks = 29.6% - ATHF 1 - 4 cohort (RCT active TMS to open-label active TMS group, N=43): HAMD24 remission rate @ 6 weeks = 30.2%

Trial Type	Patient Population/Study Design	Key Findings
Multicenter, Naturalistic, Observational Study 1. Carpenter, LL, et al. Depression and Anxiety (2012); 29:587-596. 2. Janicak, et al., CNS Spectrums (2013):1-11.	- Sponsor: Neuronetics, Inc. - Multicenter (42 sites), observational design - N=307 patients with primary clinical diagnosis of TRD (clinician-verified) - Acute phase treatment per labelled guidelines; duration of treatment defined by clinician-determined clinical outcome - Primary efficacy outcome: CGI-S; change from baseline at end of acute treatment - Key secondary outcomes: IDS-SR change from baseline; PHQ-9 change from baseline; Response and remission outcomes (CGI-S, IDS-SR and PHQ-9) at end of acute treatment; Quality of Life (Euro QOL EQ5-D) and Functional Status (SF-36 v1)	Primary Outcome: - Clinician-rated: CGI-S change from baseline @ end of acute treatment (-1.9 points ±1.4, P<0.0001) Secondary Outcomes: - CGI-S: Responder rate: 58.0%, Remitter rate: 37.1% - PHQ-9: Change from baseline @ end of acute treatment (-8.7 points ±7.2, P<0.0001) Responder rate: 56.4% Remitter rate: 28.7% - IDS-SR: Change from baseline @ end of acute treatment (-18.3 points ±14.9, P<0.0001) Responder rate: 41.5%, Remitter rate: 26.5% - EQ-5D Statistically significant improvement in all domains, VAS General Health Perception Score and Health Utility Index score. - SF-36 Statistically significant improvement in Physical and Mental Component Scores

ATHF = antidepressant treatment history form; CGI-S = Clinical Global Impression – Severity scale; CI = confidence interval; HAMD = Hamilton depression rating scale; IDS-SR = Inventory of Depressive Symptomatology – self-report; MADRS = Montgomery-Asberg depression rating scale; MDD = major depressive disorder; N= number; NIH = National Institutes of Health; PHQ-9 = patient health questionnaire; QOL = quality of life; RCT = randomised controlled trial; TMS = Transcranial Magnetic Stimulation;TRD = VAS = visual analogue scale

Long term effects of rTMS vs sham

Reports of the sustained durability of effect with rTMS using various devices and treatment protocols have been described in published reports that have intervals of observational follow up that extend for periods up to six years following successful acute treatment (Dannon, et al. 2002; Fitzgerald, et al. 2006; Demirtas-Tatlidede, et al. 2008; Cohen, et al, 2004). The specific long-term durability of effect outcomes of the NeuroStar rTMS Therapy device following a standardized acute treatment course of high-frequency, left prefrontal rTMS have been described in the peer-reviewed literature in two different open-label extension studies of research populations from each of the two multisite RCTs described above (see Table 5). These two reports describe outcomes over periods extending for three months (Mantovani, et al., 2012), and six months (Janicak, et al. 2010) following the end of acute treatment. A third report has examined a longer duration of observation in a real-world clinical population for a period of 12 months following the end of acute treatment.

This latter dataset includes patients who participated in the large, multisite naturalistic study described previously (Carpenter, et al., 2012; Janicak, et al., 2013) and who separately consented to observation in long-term naturalistic clinical follow-up of treatment as usual (Dunner, et al., submitted for publication). NeuroStar rTMS Therapy has not been evaluated for durability of antidepressant effect in controlled clinical trials.

The report by Mantovani, et al. (2012) followed a cohort of patients (N=50) for three months who had achieved remission (HAM-D24 < 10) following acute treatment with NeuroStar TMS Therapy in either the RCT or open-label follow-on phase in the OPT-TMS Study and underwent a taper phase of rTMS with transition to pharmacotherapy maintenance. Among this patient cohort, 29 of 50 patients (58.0%) remained in remission (HAM-D24 <11) at three months of observation. The investigators reported an overall relapse rate of 13.5% in this study population, defined as the emergence of a HAM-D24 total score >20. They concluded that most patients experienced persistence

of benefit from acute treatment with rTMS over three months of follow-up. See Table for details on trial design and results.

Table 8: Overview of open-label clinical trials evaluating the long-term durability of effect of the NeuroStar TMS Therapy System in patients with TRD

Trial Type	Patient Population/Study Design	Key Findings
Multicenter, open-label continuation study Mantovani, A, et al., (2012) Depression and Anxiety, 00:1-8.	- Sponsor: National Institute of Mental Health, NIH - Multicenter (4 sites), open-label extension study - N=61 patients with primary clinical diagnosis of TRD MDD (clinician-verified), successfully remitted following acute phase treatment in RCT study -Primary efficacy outcome: Incidence of illness relapse during three month of follow-up (emergence of HAMD24 > 20) - Secondary efficacy outcome: % of patients remaining in remission (HAMD24 < 11)	Primary outcome: Among patients in remission at the end of acute treatment who completed 3 month follow-up, 13.5% of patients experienced relapse of illness Secondary outcome: Among patients in remission at the end of acute treatment who completed 3 month follow-up, 29 of 50 (58%) remained in remission
Multicenter, open-label continuation study Janicak, et al, Brain Stimulation, 2010; 3(4): 187-199.	- Sponsor: Neuronetics, Inc. - Multicenter (23 sites), open-label extension - N=99 patients with MDD who had participated in either the RCT or open-label Neuronetics studies, and had benefited from acute phase treatment (either active or sham rTMS), demonstrated treatment resistance from 1 through 4 research-grade antidepressant medication in current episode (ATHF-verified) - Single antidepressant medication maintenance (no changes permitted); Access to rTMS add-on permitted for symptom recurrence	- Through 6 months of follow-up after successful acute phase treatment with rTMS: Ten of 99 (10%; Kaplan-Meier survival estimate = 12.9%) patients *relapsed* Thirty-eight (38.4%) patients met criteria for *symptom worsening* and 32 of these 38 patients (84.2%) re-achieved symptomatic benefit with adjunctive rTMS
Multicenter, naturalistic, observational study Neuronetics, data on file (2013)	- Sponsor: Neuronetics, Inc. - Multicenter (42 sites), observational design - N=257 patients with primary clinical diagnosis of TRD (clinician-verified), who successfully completed acute phase treatment per labelled guidelines and were followed for one year - Primary efficacy outcome: Incidence of illness relapse during one year of follow-up among end of acute remitters - Key secondary outcomes: CGI-S, PHQ-9 and IDS-SR total score change from baseline; Response and remission outcomes (CGI-S, IDS-SR and PHQ-9) at end of long term follow-up; Durability analysis (% of sustained responders; % of population requiring TMS reintroduction)	Primary outcome: - Among patients in remission at the end of acute treatment, 29.5% of patients experienced relapse of illness during 12 months of follow-up Secondary outcomes: - Change from baseline at end of 12 months of follow-up: CGI-Severity: (-2.2 points ±1.55, P<0.0001) CGI-S Responder rate: 67.7% CGI-S Remitter rate: 45.1% PHQ-9: (-9.5 points ±7.7, P<0.0001) PHQ-9 Responder rate: 60.7% PHQ-9 Remitter rate: 37.0% IDS-SR: (-19.4 points ±16.0, P<0.0001) IDS-SR Responder rate: 44.1% IDS-SR Remitter rate: 29.3% - Among responders at the end of acute treatment, 62.5% remained in sustained response across every evaluation time point during 12 months of follow-up - 36.2% of patients experienced symptom recurrence and received NeuroStar rTMS reintroduction through 12 months of follow-up - Average number of rTMS treatment days/patient = 16.2

ATHF = antidepressant treatment history form; CGI-S = Clinical Global Impression – Severity scale; HAMD = Hamilton depression rating scale; IDS-SR = Inventory of Depressive Symptomatology – self-report; MDD = major depressive disorder; N= number; NIH = National Institutes of Health; PHQ-9 = patient health questionnaire; RCT = randomised controlled trial; TMS = Transcranial Magnetic Stimulation; TRD = treatment resistant depression

The open label study by Janicak (2010) described the clinical outcome over six months of follow up in a larger cohort of 99 patients who had benefited from acute treatment with

NeuroStar rTMS Therapy in the Neuronetics registration studies, and who then had successfully transitioned to maintenance antidepressant medication monotherapy during a three week transition. Long-term durability of effect was then examined over the subsequent six months. During this period of follow up, the chosen maintenance antidepressant medication could not be switched or combined with other medications, however, rTMS was re-administered if patients met protocol-specified criteria for symptom re-emergence. Relapse was the primary outcome, defined as either the re-emergence of the full DSM-IIIR criteria for MDD at any point, or the failure of symptom resolution upon a six week course of NeuroStar rTMS reintroduction. In this analysis, 10 of 99 patients (10%; Kaplan-Meier survival estimate = 12.9%) met criteria for relapse during the six months of follow-up. Thirty-eight (38.4%) met criteria for symptom worsening and 32/38 (84.2%) re-achieved symptomatic benefit with adjunctive NeuroStar rTMS.

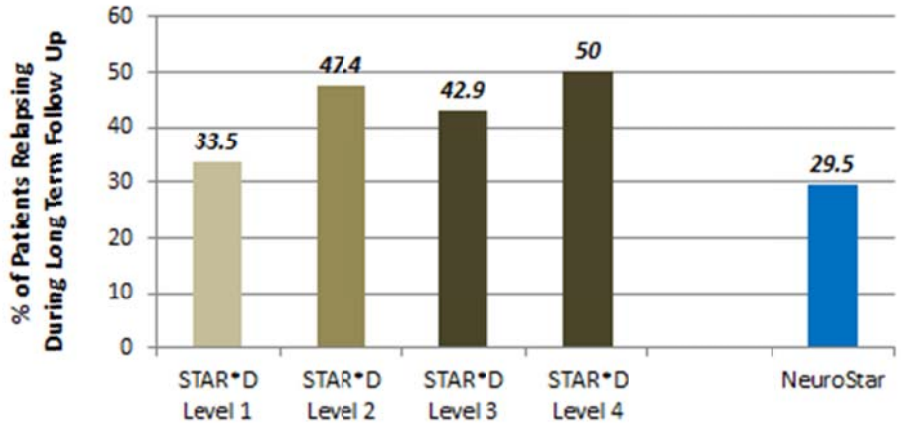
These data from a controlled research setting have recently been confirmed in a third, separate patient population treated in a routine clinical practice setting, in the prospective, naturalistic observational clinical trial with NeuroStar rTMS Therapy described above (Carpenter, et al., 2012; Janicak, et al., 2013). The long term, 12 month follow-up data from this study were first reported in abstract form at the 2013 annual meeting of the American Psychiatric Association and have been submitted for publication (Dunner, et al., 2013). In this naturalistic observational study, N=257 patients who had participated in the acute treatment outcomes reported in Carpenter, et al. (2012), were tapered from their acute treatment rTMS regimen, and consented to long-term follow up of their clinical and treatment outcomes over the next twelve months. Clinical assessments (CGI-Severity of Illness, PHQ-9 and IDS-SR) were obtained at 3, 6, 9, and 12 months. A total of N=205 patients provided data across the entire study period. Concurrent medication use and rTMS reintroduction for recurrent symptoms was recorded and summarized during the long-term follow up.

Compared with baseline scores obtained prior to acute treatment, there was a statistically significant reduction in mean [SD] CGI-S, PHQ-9 and IDS-SR total scores at the end of acute treatment (Baseline vs End of Acute Treatment: 5.0 [0.9] vs. 3.0 [1.4], 18.0 [5.3] vs. 8.8 [6.7], and 44.9 [11.1] vs. 25.7 [15.5] respectively, all $P<0.0001$), which was sustained throughout the one year follow-up (End of 12 Months Follow-Up: 2.8 [1.5], 8.6 [6.9], and 25.6 [15.8] respectively, all $P<0.0001$). The proportion of patients who achieved remission at the conclusion of acute treatment remained similar to that observed following the conclusion of the long-term follow-up phase: CGI-S (total score 1 or 2), 41.2% (end of acute) and 45.1% (end of long-term); PHQ-9 (total score < 5), 31.1% (end of acute) and 37.0% (end of long-term); IDS-SR (total score <15), 29.7% (end of acute) and 29.3% (end of long-term).

Durability of clinical benefit was examined by calculating the probability of patients maintaining a pattern of sustained response by IDS-SR criteria at each of the long term follow-up time points among those patients who had completed the acute phase as treatment responders. In this analysis, the criterion for maintaining sustained response was reduced to at least 40% improvement relative to baseline, and the patient was required to meet this criterion at every observation time point during the long term follow-up phase. A total of 120 (46.5%) patients met IDS-SR responder or remitter criteria at entry into long term follow up, and among these, 75 (62.5%) met criteria for sustained response by IDS-SR criteria at every time point during long term follow-up, indicating that a majority of patients who received acute benefit from NeuroStar rTMS Therapy retained this benefit.

As a further demonstration of the durability of the acute benefit of NeuroStar rTMS Therapy, among those patients who had achieved complete remission of their illness at the end of the acute treatment phase (QIDS-SR end of acute treatment score <6; N=78 patients), the proportion of patients who subsequently experienced illness relapse (defined as a QIDS-SR total score > 11 at any observation time point during the long-term follow-up) was only 29.5% (N=23 patients), indicating that nearly three-quarters of patients who achieved remission at the end of acute treatment did not experience relapse of their illness over 12 months of long-term follow-up. These data are highlight the favourable long-term durability of NeuroStar rTMS when compared to the published outcomes in 12 months of naturalistic follow-up of patients who achieved remission after acute phase treatment in the STAR*D study (Rush, et al., 2006). In that report, patients who had achieved remission after having failed to benefit from two to three prior antidepressant treatment attempts (i.e. those patients most comparable to the patients in the NeuroStar TMS Therapy long-term follow-up study), experienced relapse rates of 42.9% (Level 3) and 50.0% (Level 4)(Rush, et al., 2006)(Figure 3). Patients who failed two adequate antidepressant courses in their current illness episode (Level 3, ATHF=2) can be considered as closely comparable to the MBS target population.

Figure 3: Comparison of relapse rate over 12 months of naturalistic, long-term follow-up: NeuroStar Outcomes Study versus STAR*D Study levels 1 through 4



NOTE: All patients entered long-term follow-up in either the Outcomes Study or the STAR*D Study in remission defined by a QIDS-SR score of < 6. Relapse was defined as the emergence of a QIDS-SR score > 11 at any point during 12 months of long-term follow-up in either study.

Finally, following completion of tapering of acute treatment with NeuroStar rTMS Therapy, only 93 of the 257 patients in long-term follow-up (36.2% of all patients) subsequently received reintroduction of rTMS based on clinician decision for clinical worsening. In this group, the mean [SD] number of rTMS treatment days was 16.2 [21.1] over the period of long-term follow-up.

Is rTMS effective versus antidepressant medication?

The established alternative to rTMS therapy is an additional trial of antidepressant medication. Since head-to-head comparative trials have not been conducted between TMS therapy and antidepressant medication, comparative analysis requires an indirect comparison of TMS study outcomes against large, established reference benchmark outcomes from studies using antidepressant medications. This is similar to the situation

with different classes of drug therapy, because, as is the case for NeuroStar TMS, antidepressant registration trials are placebo-controlled for purposes of regulatory approval and are not conducted as comparative trials. Therefore, comparison among antidepressant drug alternatives commonly also requires an indirect comparison among different classes of drugs.

In this section, we review the comparative effectiveness of rTMS therapy and antidepressant medication using two separate types of study designs:

a) RCTs with sham/placebo as the common comparator (Demitrack and Thase 2009). This comparative analysis uses valid statistical methods to compare the results of RCTs for TMS therapy (using data from the NeuroStar clinical evaluation program) versus sham TMS, against various antidepressant medications studied in randomized controlled trials against a medication placebo control.

b) Long term open label trials using sham/placebo as the common comparator (Bonne-Barkay 2013 Conference Abstract). These pooled analyses provide a confirmatory analysis of the controlled trials by examining the comparative outcomes of NeuroStar rTMS used in open-label studies against the acute and long-term results of similar reference datasets of open-label studies of antidepressant medications. This analysis specifically examines the outcomes of NeuroStar rTMS Therapy in the large, multisite naturalistic observational study (Carpenter, et al., 2012; Janicak, et al., 2013) compared with similar outcomes in the large, multisite naturalistic Sequenced Treatment Alternatives to Relieve Depression (STAR*D) Study (Rush, et al., 2006).

It is important to appreciate patients in the NeuroStar rTMS registration trial and most rTMS studies had failed to benefit from exposure to multiple adequate drug trials, while in contrast, patients in the drug registration trials were typically receiving first line drug therapy. Therefore, patients in the NeuroStar rTMS registration trial had a treatment resistant form of depression, representing a negative bias against rTMS when compared to antidepressant medication controlled trial outcomes. In both randomized studies of the NeuroStar rTMS System, all patients had to meet the stringent ATHF definition of prior antidepressant treatment with at least 1 and as many as 4 adequate antidepressant medication treatment failures. Treatment efficacy of a second or more courses of antidepressant drug therapy have been assessed in the recently completed STAR*D Study. This landmark study has clearly shown that once resistance to an adequately dosed and administered initial intervention has been established, the subsequent likelihood of benefit is substantially diminished (Rush, et al., 2006). With each successive failure, the likelihood of benefit with future treatment attempts diminishes even further. Therefore, the NeuroStar rTMS studies evaluated a patient population who would be expected to show lower likelihood of benefit as compared to antidepressant medication trials that do not enrol these patients.

Indirect comparison to drug therapy: acute efficacy in randomised controlled trials

The published data of over 70 placebo-controlled, randomized registration studies of 11 major pharmaceutical antidepressants that are currently FDA-approved as first-line treatment for patients provide comprehensive benchmarks that can be used as a reference "gold standard" for indirectly comparing the results of NeuroStar TMS and antidepressant medications. These benchmarks are important because of their size, comprehensiveness, and the fact that they have been well-established in the peer-

reviewed literature. For example, the data from randomized controlled trials of antidepressants have been reported in several large summaries of FDA registration submission databases (Khan, et al, 2000, 2001, and 2007; Turner, et al, 2008). The comprehensive dataset utilized in the report by Turner and colleagues (2008) is of particular interest because the authors also summarized standardized effect sizes for the standard outcome of change from baseline in total depression symptom scores, enabling a valid statistical comparison of treatment effects across various studies. The NeuroStar TMS registration study also reported the same outcomes, thus facilitating a similarly statistically valid indirect comparison.

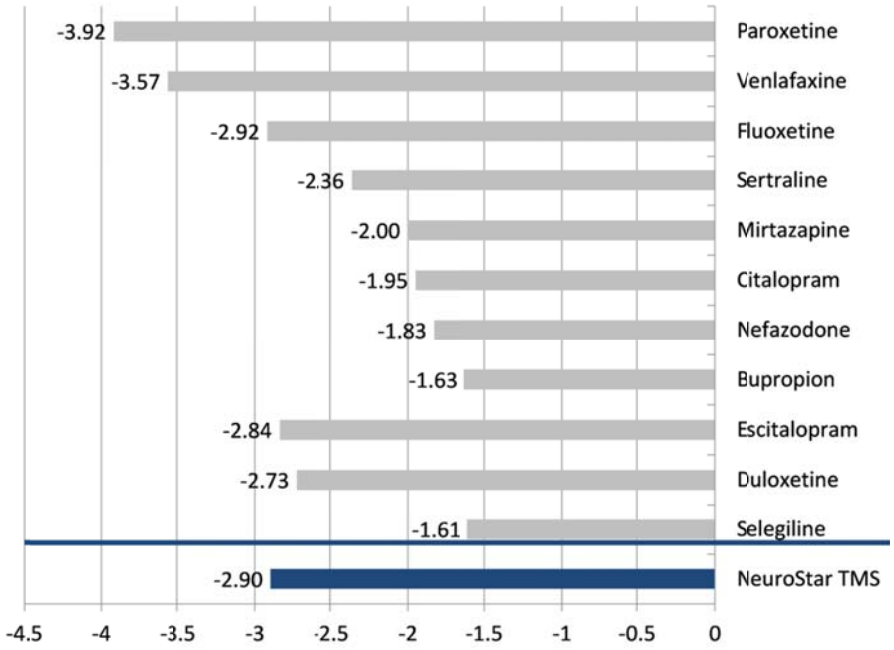
A comprehensive comparative discussion of the NeuroStar rTMS registration clinical trial results have been reported in a peer-reviewed publication (Demitrack and Thase, 2009). In that manuscript, the following observations were noted:

a) NeuroStar rTMS Therapy *treatment effects for mean change from baseline meet or exceed the treatment effects reported* for 8 of 11 FDA-approved first-line pharmaceutical antidepressants (

b) Figure 4), even though the NeuroStar TMS Therapy trial studied a patient sample comparable in treatment resistance severity to those patients treated in research studies of ECT (Prudic 2004).
c) NeuroStar rTMS Therapy treatment effects for *mean change from baseline exceed the treatment effects for atypical antipsychotic augmentation*, the only pharmaceutical treatments that are FDA approved for the treatment of patients with treatment resistant major depression (Figure 5).
d) A comparison of the standardized effect sizes shows that the NeuroStar rTMS results are large and range on the higher end of effect sizes reported for FDA-approved pharmaceutical antidepressants (**Error! Reference source not found.** and **Error! Reference source not found.**).

This analysis provides evidence that rTMS is at least as effective as common antidepressant drug therapies, exceeding effects for 8 of the 11 antidepressant drugs used for first line therapy, despite the fact that, unlike rTMS, these drugs were not studied in a treatment resistant population. Additionally, rTMS exceeded the treatment effects for second generation antipsychotic augmentation, for a patient group that is more directly comparable in treatment resistance to the TMS study population.

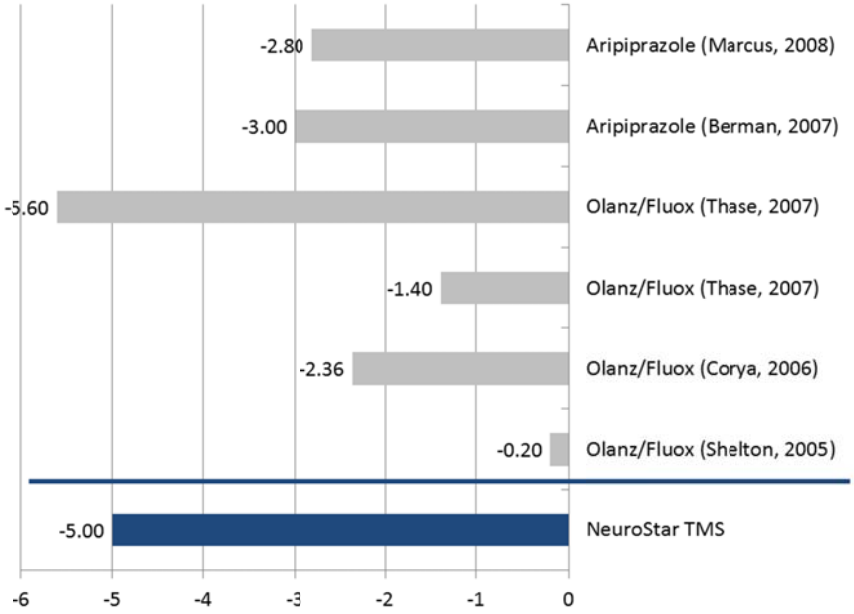
Figure 4: Treatment effects in randomised controlled trials - Change from baseline in HAMD17 total score (mean difference active vs. placebo)



NOTE: Data in figure from the following sources: Khan, et al. (2000, 2001, and 2007); Detke, et al. (2002a, 2002b); Goldstein, et al. (2002, 2004); Perahia, et al. (2006); Feiger, et al. (2006); Bodkin, et al. (2002). Each antidepressant medication shown represents the average of all available registration studies.

HAMD = Hamilton depression rating score; TMS = Transcranial Magnetic Stimulation

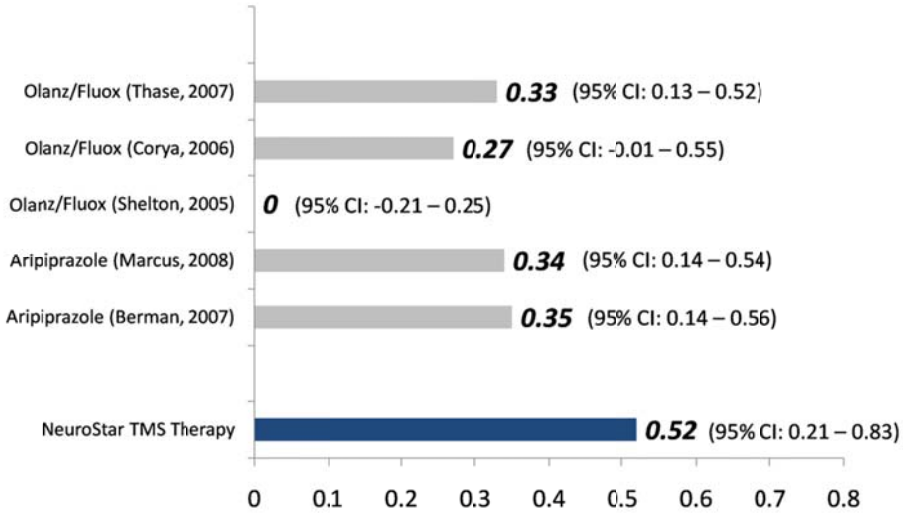
Figure 5: Treatment effects in randomised controlled trials: Change from baseline in MADRS total score (mean difference active vs. placebo [treatment-resistant study population])



NOTE: Data in figure from the following sources: Shelton, et al. (2005); Corya, et al. (2006); Thase, et al. (2007); Berman, et al. (2007); Marcus, et al. (2008). Each antidepressant shown represents a single study result.

MADRS = Montgomery-Asberg depression rating scale; TMS = Transcranial Magnetic Stimulation

Figure 6: Summary of effect sizes (Hedge's g) in randomised controlled trials of antidepressant medications and for NeuroStar TMS Therapy (treatment-resistant study populations)



NOTE: Antidepressant medication reference sources - Shelton, et al.(2005); Corya, et al. (2006); Thase, et al. (2007); Berman, et al.(2007); Marcus, et al. (2008). Method for standardized effect size computation (Hedge's g) as reported in Turner, et al. (2008).

CI = confidence interval; TMS = Transcranial Magnetic Stimulation

Indirect comparison to drug therapy: acute efficacy to open-label naturalistic clinical trials

We have completed a comparative analysis of the outcomes observed in the large, multisite naturalistic outcomes study with NeuroStar rTMS Therapy (Carpenter, et al., 2012; Janicak, et al., 2013) against the results observed in the STAR*D study, an authoritative benchmark of expected real-world treatment outcomes with antidepressant medication in routine clinical practice.. These results have been presented at the Institute for Psychiatric Services annual meeting, 2013 (Bonneh-Barkay, et al., 2013).

In this analysis, the matching was performed using a greedy algorithm of propensity score matching on measures of gender, age, income level, treatment resistance staging, symptom burden (QIDS-16 scores), and functional status (SF-12 physical and mental component scores) as matching criteria. Matching was conducted using two different strategies, either forward matching (Neuronetics Outcomes Study versus STAR*D) or reverse matching (STAR*D versus Neuronetics Outcomes Study). A logistic regression model was used for constructing propensity scores, and a 1:1 population matching was completed using both the forward and reverse matching strategies. Clinical outcomes were then compared at a standard time point of 6 weeks exposure to either NeuroStar TMS Therapy or STAR*D medication assignment between groups. Outcome categories were defined using standard severity cut points established for the QIDS-16.

Using the forward matching approach, at baseline, 69.4% and 72.2% of patients were categorized as severely ill or worse (QIDS-16 >16) for the NeuroStar rTMS and STAR*D groups, respectively. At the six week time point 27.0% (95% CI: 22.0, 32.0) of the NeuroStar group vs 5.2% (95% CI: 2.7, 7.7) of the STAR*D group were categorized

with no symptoms (QIDS-16 score <6). Using the more conservative approach of reverse matching of these populations, similar observations were obtained. Specifically, at the six week time point 53.0% (95% CI: 47.4, 58.6) of the NeuroStar group vs 38.0% (95% CI: 32.6, 43.5) of the STAR*D group were categorized with mild or no symptoms (QIDS-16 score <11).

These data confirm the evidence discussed above that, in general, treatment with rTMS therapy compares favourably to treatment with antidepressant medications as a next alternative for patients with treatment resistant depression.

Is rTMS effective versus ECT?

To date, there have been eight random-assignment, open-label studies (ranging in sample size from 30 to 46 patients each) that have directly compared the clinical outcomes of patients assigned to either rTMS or ECT for treatment of severe major depression. These data have been reviewed by Janicak and colleagues (2007), and are summarized in Table . They noted that five of the eight studies reported antidepressant equivalence between rTMS and ECT.

Table 9: Summary of clinical trials comparing TMS therapy and ECT in patients with major depressive disorder (Janicak, et al., 2007)

Trial	Study design	TMS treatment parameters	Outcome
Grunhaus (2000)	N=40 Random assignment: UL ECT (8 patients also received BL ECT) or TMS Outcome: HAMD Scale	LDPFC 10 pps, 90% MT Up to 20 sessions	TMS = ECT (non-psychotic patients) ECT + meds/ antipsychotics > TMS (psychotic patients)
Pridmore (2000)	N=32 Random assignment: Unilateral ECT or TMS Outcomes: HAMD, BDI, VAS	LDPFC 20 pps, 100% MT Avg 12 sessions	TMS = ECT
Janicak (2002)	N=31 Random assignment: BL ECT or TMS, w/crossover option available Outcome: HAMD	LDPFC 10 pps, 110% MT Avg 14 sessions	TMS = ECT
Grunhaus (2003)	N=40 Random assignment: UL ECT (7 patients also received BL ECT) or TMS Outcomes: HAMD, GAF scale	LDPFC 10 pps, 90% MT Up to 20 sessions	TMS = ECT
O'Connor (2003)	N=28 Non-random assignment: UL ECT + meds or TMS Outcomes: HAMD, Cognitive battery	LDPFC 10 pps, 90% MT Up to 10 sessions	ECT + meds > TMS alone NOTE: Greater cognitive dysfunction with ECT
Eranti (2007)	N=46 Random assignment: BL ECT or TMS Outcomes: HAMD, BDI-II	LDPFC 10 pps, 110% MT Up to 15 sessions	BL ECT > TMS, with both groups showing improvement
Schulze-Rauschenbach (2005)	N=30 Non-random assignment: UL ECT + meds or TMS + meds Outcome: HAMD	LDPFC 10 pps, 100% MT Avg 11 sessions	TMS = ECT
Rosa (2006)	N=42 Random assignment: UL ECT (2 patients received BL ECT) or TMS Outcomes: HAMD, VAS, CGI, Cognitive battery	LDPFC 10 pps, 100% MT Up to 20 sessions	TMS = ECT

Source: Table adapted from Janicak, et al (2007).

BDI = Beck depression inventory; BL = bilateral; CGI = Clinical Global Impression; ECT = electroconvulsive therapy; GAF = Global assessment of functioning; HAMD = Hamilton depression rating score; LDPFC = left dorsolateral prefrontal cortex; MT = motor threshold; N = number; pps = pulses per second, TMS = Transcranial Magnetic Stimulation; UL = unilateral; VAS = visual analogue scale

These studies were generally small in size, often performed at one investigative site, and usually diagnostically heterogeneous.

Berlim and colleagues (2013) have added to this comparative discussion in a recent systematic review and meta-analysis comparing the efficacy and acceptability of high-frequency rTMS versus ECT for major depression. They analysed data from seven randomized trials (including 6 of the 8 studies reviewed by Janicak and colleagues above) involving 294 subjects. They reported that after an average of only 15.2 TMS sessions compared with an average of 8.2 ECT sessions, 33.6% of rTMS subjects and 52% of ECT subjects were classified as remitters. They concluded that these data suggest that ECT may be more effective than rTMS, however they also acknowledged the drawbacks of the study designs that warrant further work based on currently accepted advancements in the practice of rTMS therapy.

Is rTMS effective versus psychotherapy?

No clinical studies have directly compared the efficacy of rTMS treatment to any form of psychotherapy. As such, an indirect comparison of effectiveness can only be made comparing clinical data for effectiveness of both treatments in similar populations.

The clinical role/effectiveness of psychotherapy, in particular, cognitive behavioural therapy (CBT) and interpersonal therapy (IPT) have predominately been established in non-medication resistant or non-treatment resistant depressed patients. However, some authors have suggested that these treatments can be used after antidepressant medication failure and as such it is valid to consider the possibility of these treatments as a comparator for rTMS in this patient group.

The use of these psychotherapies was considered by the AHRQ 2011 review. No studies were identified that directly compared rTMS and CBT or psychotherapy. Therefore an assessment of effectiveness or safety between these strategies is not possible.

Evidence for safety of rTMS

The evidence in the literature indicates different toxicity profiles for rTMS, antidepressants and ECT. A summary of the main types of adverse events for the three options is presented in Table .

Table 10: Summary of common adverse events for rTMS, antidepressants and ECT

Treatment	Common adverse events
rTMS	Pain at site, headaches, application site discomfort, eye pain, muscle twitching
Antidepressant therapies:	
SSRI	Nausea, agitation, sleep disturbance, sexual dysfunction, headaches
SNRI	Nausea, anxiety, fatigue, sexual dysfunction, headaches
RIMA	Headaches, nausea or heartburn, dizziness, increased sweating
TCA	Sedation, sleepiness, dry mouth, constipation, low blood pressure, falls
NaSSA	Sedation, dizziness, increased appetite, and weight gain
NARI	Dry mouth, constipation, agitation, dizziness, headache, sexual difficulties, difficulty urinating increased heart rate, increased sweating
MAOI	Drowsiness, lethargy, insomnia, headache, dizziness, nausea or heartburn, dry mouth, blurred vision, constipation, increased sweating, muscle tremor, loss of appetite
ECT	Cognitive problems, retrograde and anterograde amnesia, post-ictal delirium, myalgia, headache, falls, cardiovascular, pulmonary and dental complications, and death.

Source: MSAC 1101, 2007

ECT = electro convulsive therapy; MAOI=Monoamine Oxidase Inhibitors; TCA= Tricyclic Anti-depressants; SSRI= Selective Serotonin Reuptake Inhibitors; NARI= Noradrenaline Reuptake Inhibitors; SNRI= Serotonin and Noradrenaline Reuptake Inhibitors; RIMA=Reversible Inhibitors of Monoamine Oxidase– A; rTMS = repetitive Transcranial Magnetic Stimulation; NaSSA=Noradrenaline Serotonin Specific Anti-depressants

A summary of the adverse events noted in the NeuroStar rTMS Therapy registration study is found in Table . Additionally, a comprehensive review of the safety profile of NeuroStar rTMS Therapy is provided by Janicak and colleagues (2008) and discussed here.

Table 11: NeuroStar rTMS Therapy: common adverse events (acute treatment phase)

Adverse event	NeuroStar rTMS (n=165) N (%)	Sham TMS (n=158) N (%)	NNH (95% CI)
Eye disorders			
- Eye pain	10 (6.1%)	3 (1.9%)	24 (-1000, 12)
Gastrointestinal disorders			
- Toothache	12 (7.3%)	1 (0.6%)	15 (40, 9)
General disorders and site-administration conditions			
- Application site discomfort	18 (10.9%)	2 (1.3%)	10 (22, 7)
- Application site pain	59 (35.8%)	6 (3.8%)	3 (4, 3)
- Facial pain	11 (6.7%)	5 (3.2%)	29 (-83, 12)
Musculoskeletal and connective tissue disorders			
- Muscle twitching	34 (20.6%)	5 (3.2%)	6 (9, 4)
Skin and subcutaneous tissue disorders			
- Pain of skin	14 (8.5%)	1 (0.6%)	13 (29, 8)

NOTE: Includes only adverse events occurring in the active treatment group at a rate of ≥ 5% and at least twice the rate of sham

NNH = number needed to harm; rTMS = Transcranial Magnetic Stimulation

The impact of NeuroStar rTMS Therapy on cognitive function was examined in the registration trials of this device. General cognitive function was assessed using the Mini Mental Status Examination, attention and short-term memory was assessed with the Buschke Selective Reminding Test, and long-term memory was evaluated with the Short Form of the Autobiographical Memory Interview. NeuroStar rTMS Therapy was shown to have no effect on cognitive function in either acute treatment or in 6 months of long-term follow-up (Janicak, et al., 2008). These data are consistent with the larger research literature on rTMS. For instance, in a comprehensive review, Guse and colleagues (2010) specifically examined the peer reviewed literature base regarding cognitive function following the administration of high frequency TMS. The authors found no evidence of negative effects on cognition.

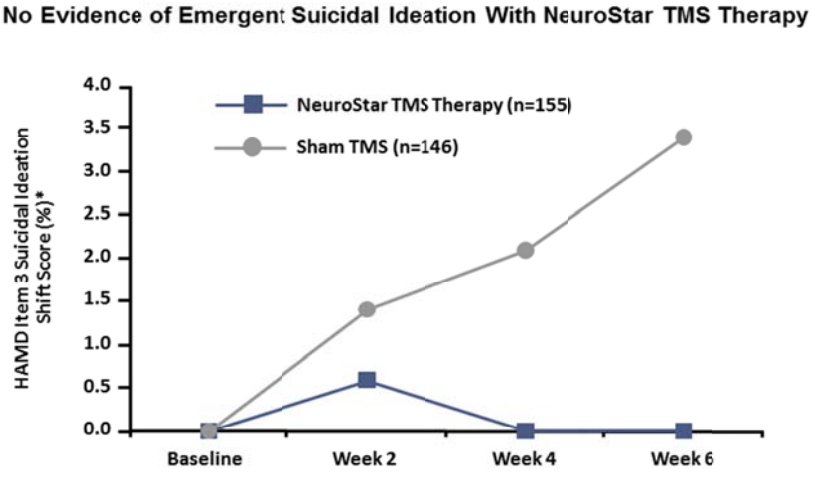
A well-known medical risk associated with the use of rTMS is the risk of inadvertent induction of a generalized seizure. The aggregate use of the NeuroStar rTMS Therapy System in two large randomized, controlled clinical trials (O'Reardon, et al., 2007; Demitrack and Thase, 2009; George, et al., 2010) and in real world clinical use since product launch in 2008. No seizures were reported in the research clinical trials of the NeuroStar rTMS Therapy System (Janicak, et al., 2008; George, et al., 2010). Since market introduction of the NeuroStar rTMS device, the incidence of seizures with this device has been rare. In post-market use, the incident risk of seizure with the NeuroStar rTMS Therapy System under recommended operating conditions is estimated to be less than 0.1% per patient. This rate of seizure occurrence is lower than what is typically seen with the use of commercially available antidepressant medications (Ref: Medication Product Labels for fluoxetine, paroxetine, sertraline, citalopram, escitalopram, venlafaxine, desvenlafaxine, duloxetine, bupropion, mirtazapine, tranylcypromine combination).

It should be noted that because the technical and design characteristics of rTMS devices from different manufacturers vary in magnetic coil design and product specifications, the general safety profile of a specific rTMS device should be appraised based on the experience with that specific rTMS device design and indication for use. The cumulative safety experience in registration studies and in post-market surveillance with the

NeuroStar rTMS Therapy System is the largest such safety database of any commercially available rTMS device indicated for therapeutic use.

In the development of a new antidepressant, a compulsory area of safety concern is to determine whether or not patients experience emergent worsening of their depressive symptoms during acute treatment. All currently marketed pharmaceutical antidepressants carry a "black box" warning for this phenomenon for adolescent and young adult patient populations, though the incidence of this event is rare. Assessment for emergent suicidal ideation was performed in the NeuroStar study safety analysis by determining what percentage of patients who reported no or minimal suicidal ideation (as defined by a rating of 0 or 1 on the Suicidal Ideation Item 3 of the Hamilton Depression Rating Scale) at study entry subsequently experienced an abrupt worsening to the most extreme suicide rating (HAMD Item of 3 or 4) at any later time point. These results are shown graphically in Figure and demonstrate that there is no evidence of emergent suicidal ideation during acute treatment with the NeuroStar rTMS Therapy System.

Figure 7: Absence of emergent suicidal ideation during acute treatment with the NeuroStar TMS Therapy



* Shift Score indicates the percent of subjects who experienced a change in HAMD Item 3 score from 0 or 1 at baseline to 3 or 4 at later point in time.

HAMD = Hamilton depression rating scale; TMS = Transcranial Magnetic Stimulation

In clinical trials with the NeuroStar rTMS Therapy System, patient acceptance of and adherence to the prescribed treatment regimen is good. For example, the discontinuation rate due to intolerable adverse events due to NeuroStar rTMS Therapy in the NeuroStar TMS randomized controlled trials was less than 5% (Janicak, et al., 2008). A similar rate of discontinuation was reported in the NIMH-sponsored OPT-TMS study, which used the same device and treatment protocol as in the NeuroStar rTMS registration studies (George, et al., 2010).

Safety of NeuroStar rTMS Therapy: post-market data

Commonly experienced non-serious adverse events observed with acute, extended or repeated courses of NeuroStar rTMS are post-treatment headache and pain or discomfort at the treatment area which are generally mild to moderate in severity.

The magnetic pulse produces an audible high-frequency clicking sound. Therefore, ear protection (earplugs) of at least 30 dB sound reduction, is used for both patients and administrators during NeuroStar rTMS treatments.

The most significant medical risk associated with the use of NeuroStar rTMS Therapy is the inadvertent induction of a seizure. Since market introduction of the NeuroStar TMS Therapy System in October 2008, seven seizures have been reported with NeuroStar TMS Therapy over a usage of more than 300,000 NeuroStar TMS treatment sessions, and over 14,000 patients. In five of the seven seizures, patients had concurrent use of medications that may have altered seizure threshold. In one of these events, and in one additional seizure, potential incorrect coil placement which may have contributed to the seizure. The remaining one seizure appeared to be characteristic of syncope.

In clinical use of NeuroStar rTMS, the use of procedure consent, pre-treatment clinical screening for potential seizure risk, clinical monitoring during rTMS treatment and appropriate seizure management, and use within the rTMS safety treatment parameters appear to minimize further the risk of seizure with rTMS therapy.

rTMS vs. Sham

NeuroStar Study 103 evaluated the long term safety of NeuroStar rTMS Therapy in a 6-month durability of effect study (Janicak, et al., 2008) that identified no long term adverse effects. The safety information that has been obtained from the extensive published literature on the use of pulsed magnetic fields in the context of MRI technology provides relevant data for the long-term safety considerations for rTMS. This is because rTMS utilizes a magnetic field that is clinically comparable to the pulsed gradient field used in MRI. It is now well-established that there are no clinically significant long term safety issues with MRI, which is directly applicable to the safety of rTMS devices.

rTMS vs. Antidepressant medications

Compared to antidepressant medication therapy, NeuroStar TMS Therapy is free of the systemic side effects often associated with antidepressant medications including the medically serious side effects that can result from second generation antipsychotic use as an augmenting agent to an antidepressant.

Adverse effects of antidepresssant therapy include weight gain, dry mouth, constipation, nausea, reduced libido, agitation, insomnia, diarrhoea, dizziness, fatigue, abnormal ejaculation, sweating, impotence, anxiety, weakness, and tremor. rTMS therapy is also not associated with many of the more medically serious side effects that can result from atypical antipsychotic use as augmentation to an antidepressant (tardive dyskinesia, hyperglycaemia, weight gain, metabolic syndrome, blood dyscrasias, neuroleptic malignant syndrome, cognitive and motor impairment, coma and death). The most clinically significant side effect associated with rTMS is seizure. However, the incident risk of seizure under recommended operating conditions is estimated to be less than 0.1% per patient for NeuroStar TMS, based on over four years of post-market safety surveillance. Adverse events associated with the use of TMS in the NeuroStar registration trials are summarized in Table .

rTMS vs. ECT

The clinical use of electroconvulsive therapy (ECT) carries with it a number of medical risks not associated with rTMS therapy. In addition to the risks of anaesthesia necessary during treatment, ECT has been documented to cause retrograde and anterograde amnesia, post-ictal delirium, headaches, myalgia, cardiovascular, pulmonary and dental complications, and death. (American Psychiatric Association Task Force Report on Electroconvulsive Therapy, Second Edition, Sackeim 2007; FDA Executive Summary, ECT 515[i]).

Summary of evidence for rTMS

A summary of the clinical evidence for assessing the effectiveness and safety of rTMS compared to the two main comparators in this application are provided in Table 1.

Table 1: Summary of clinical evidence for rTMS versus comparator(s)

rTMS versus.	Efficacy	Safety	Economic models
Antidepressant medications	Equivalent or superior	Superior	Cost utility analysis
ECT	Equivalent	Superior	Cost utility analysis
Psychotherapy	Insufficient evidence	Insufficient evidence	Not undertaken[1]

ECT = Electroconvulsive therapy; rTMS = repetitive Transcranial Magnetic Stimulation;

[1] Psychotherapy is assumed to occur equally across the arms in the economic study and therefore costs and effects are omitted.

rTMS vs. Antidepressant therapy

Efficacy: There is an absence of clinical trials directly comparing the efficacy of antidepressant medication and TMS treatment. The evidence suggests that rTMS has a similar effect size to common antidepressant drugs in first-line therapy. In second-line setting, treatment effects of rTMS exceeded antidepressant therapy, which is more relevant to the proposed listing (i.e. patients are resistant to at least two adequate antidepressant drug therapies).

Safety: rTMS is not associated with many of the side effects often associated with oral antidepressants and medically serious side effects that can result from atypical antipsychotic used to augment antidepressant use. The most clinically significant side effect associated with rTMS is seizure, which was estimated to occur in less than 0.1% of patients according to a NeuroStar TMS four-year post-market safety surveillance report.

rTMS vs. ECT

Efficacy: The evidence suggests that ECT may be more effective than rTMS. However, several randomised controlled trials comparing rTMS and ECT indicate that in non-psychotic patients, rTMS appears to have a similar rate of response to ECT (Fitzgerald *et al.* 2004). Non-psychotic patients are the focus of this application. rTMS is seen as an effective option for depressed patients who remain significantly disabled despite the use of antidepressant drugs but cannot tolerate or refuse ECT.

Safety: ECT therapy contains medical risks that are not associated with rTMS such as the anaesthesia-related events during treatment, amnesia, myalgia, cardiovascular, pulmonary complications, and death. Therefore, rTMS is considered to have a superior safety profile than ECT.

rTMS vs. psychotherapy

No studies have directly compared the effectiveness of psychotherapy and rTMS in treatment-resistant depression. There is very limited evidence to support the use of structured forms of psychotherapy in treatment-resistant depression, with no quality studies comparing psychotherapy approaches to control treatment in individuals with a failure to respond to two previous medication treatments as is relevant for this application. There are no meaningful data on which to compare safety between rTMS and CBT.

What are the economic considerations?

Overview of the economic considerations

The economic considerations appropriate to this application include:

1) An assessment of the cost-effectiveness of rTMS versus two comparators: antidepressant medication, and ECT in patients who have failed at least two antidepressant drug therapies; and
2) An assessment of the financial implications of the proposed reimbursement of rTMS for the proposed indication.

Published economic literature

A literature review for relevant economic studies was undertaken to inform the cost-effectiveness analysis.

rTMS vs. Antidepressants

One published economic evaluation was identified as relevant to this application (Simpson et al., 2009), which compared rTMS to sham, and to pharmacotherapies in the treatment of major depression. The study was US-based and costs were reported in US dollars and reflect US prices and resources. A Markov model was used to estimate the illness course over a full year of treatment follow-up. Healthcare resource use data were based on a multicentre RCT (O'Reardon *et al.* 2007) and the published STAR*D study. The cost-effectiveness of rTMS was described using an incremental cost-effectiveness ratio (ICER) per quality-adjusted life year (QALY) gained and was based on a direct cost per patient basis.

In a trial context, compared with sham treatment and at a cost of US$300 per treatment session, rTMS provided an ICER of US$34,999 per QALY gained. When productivity gains due to clinical recovery were included, the ICER was reduced to US$6,667 per QALY gained. In open-label conditions, rTMS provided a net cost saving of US$1,123 per QALY gained compared with the current standard of care (i.e. antidepressant medication therapies). The cost savings increased further when the costs for productivity losses were included in the model (net savings of US$7,621).

The applicability of the findings of Simpson *et al.* (2009) to the Australian setting may not be valid given rTMS is proposed to be used as third-line therapy onward. Additionally, the reimbursement structures of the US and Australian health care systems are not directly comparable, which have implications on health resource use and costing.

rTMS vs. ECT

Two publications and an HTA report were identified as relevant to this application. One publication (Knapp et al., 2008) was based on the UK HTA report (McLoughlin et al., 2007).

McLoughlin *et al.* 2007 (and subsequently Knapp *et al.* 2008) presented the clinical effectiveness and cost of rTMS versus ECT, based on a two-group RCT for patients with MDD who had been referred to ECT. The study was UK-based and costs were reported in pounds. A full course of rTMS comprised 15 daily sessions (n=24) while ECT was administered twice weekly (n=22). End-of-treatment assessment was carried out 2-3 days after the final treatment sessions and patients were followed up for 6 months. The primary outcome was the HAM-D17 score at the end of treatment period, and rate of remission (defined as HAM-D17 ≤8). Secondary outcomes included relapse rate after 6 months (defined as HAM-D17 ≥12), and other depression instrument scores.

The trial results showed that ECT was a more effective treatment than rTMS for severe depression. End-of-treatment remission rates were 13/22 (59%) for ECT versus 4/24 (17%) for rTMS ($p<0.005$). However, it suggested that rTMS might be as effective as ECT if patients received more weeks of high-intensity treatment. No differences were found in cognitive examination measures between the ECT and rTMS groups.

The economic evaluation in McLoughlin *et al.* 2007 suggested that the cost of a single rTMS session was lower than the cost of an ECT session. However, patients in the rTMS arm received more treatment sessions and direct treatment costs were not much higher. Overall, the sum of formal and informal care costs during the 6-month follow up period was equivalent to £222 per week per rTMS patient, and £78 per week per ECT patient. Knapp *et al.* 2008 found that the incremental QALY gained with rTMS versus ECT treatment was 0.0003. Because QALY gains were negligible, the probability of cost-effectiveness, at a willingness-to-pay threshold of £30,000 per additional QALY, was less than 20%. The study concluded that rTMS has a very low probability of being seen as a cost-effective alternative to ECT for treatment-resistant depression.

Both McLoughlin *et al.* 2007 and Knapp *et al.* 2008 did not describe the economic model in sufficient detail; there was no information on cycle length, health states, associated utility weights and transition probabilities. Therefore, it is difficult to evaluate the merits and validity of the model or if it could be translated into the Australian context.

The second publication, (Kozel et al., 2004), developed a one-year decision-analytic model to compare three treatment arms: ECT monotherapy, rTMs monotherapy and rTMS followed by ECT for non-responders. The study was US-based and costs were reported in US dollars and reflect US prices and resources. The primary outcomes were response and relapse rates. All the health states were based on the response and relapse rates although there is no clear definition of either rate. The ICER for rTMS versus ECT was estimated at US$406 per QALY gained. Compared with rTMS-then-ECT, the ICER for rTMS was $34 per QALY gained, which lead to the author's conclusion that there was a large economic benefit of using rTMS to treat major depression. A limitation of this study is its simple decision tree design that considers only response and relapse. Additionally, the quality of outcome data was poor, as acknowledged by the authors, due to the lack of large RCTs comparing rTMS with ECT directly or indirectly via a common comparator.

These economic studies are not directly applicable to the Australian setting because a) there is insufficient information about the models used in each study to ensure the treatment algorithm is compatible with the Australian practice and b) the studies are out of date (since 2004 and 2007) and new (and larger) trials and studies might better reflect the current treatment practice for major depression.

Economic evaluation

An economic evaluation was undertaken to model the costs and effects of rTMS, antidepressants and ECT in the treatment of patients with major depressive disorder who have failed at least two adequate antidepressant medications. Psychotherapy was assumed to occur concurrently with these three options and therefore, as psychotherapy is common to each arm, is omitted from this cost-utility analysis.

Model structure

A Markov micro-simulation model was constructed and analysed in TreeAge Pro 2014 software. The model draws on evidence from the literature, and compares three treatment strategies for patients with MDD who enter the model after they have already failed at least two adequate antidepressant drug therapies. In the absence of long-term clinical data, the model duration was three years with two-monthly cycles. Three years was also considered appropriate to model several courses of treatment or switching between treatments. 'Tracker variables' were used so that the number of treatments was monitored for each person to ensure patients moved out to the next treatment when appropriate. The main outcomes of the model are costs and QALYs.

The model contains eight health states:

- Main treatment: HAM-D 17 score ≥ 20
- Full remission: HAM-D 17 score <8
- Partial remission: 8 ≤ HAM-D 17 score <20
- No response/Relapse: HAM-D 17 score ≥ 20
- Post ECT treatment after failing the main treatment
- Post augmented Lithium/antidepressant after failing the main treatment
- Hospitalisation, and
- Death

All patients start in the model after failing two antidepressant medications from two classes, in line with the proposed MBS population. For each treatment arm, a patient will start with the main treatment and may experience adverse events, with their associated costs and disutility. The patient then either (i) gains full remission (HAM-D17 score < 8) until losing full remission (HAM-D17 score ≥ 8), or (ii) gains partial remission or (iii) does not respond at all, or (iv) experiences an acute episode that requires hospitalisation.

When a patient enters the 'full remission' state, the patient can receive maintenance treatment (if the acute treatment was rTMS) where they may experience adverse events. After receiving maintenance treatment, patients can remain in full remission or move to partial remission. For patients who did not receive maintenance treatment (acute treatment was ECT or anti-depressants), they can remain in full remission or move to partial remission.

When a patient enters the 'partial remission' state, the patient can either remain in partial remission or lose response and move to the 'no response/relapse' state. Once a patient enters the 'no response/relapse state', the patient can start re-treatment (i.e. move to acute treatment again) or receive no re-treatment. If the patient receives no re-treatment, then the patient may experience an acute episode (i.e. hospitalisation) or change

treatment and move to either post ECT treatment or post lithium augmentation treatment.

All patients are allowed to stay on the main treatment for a maximum of three courses before moving to an alternative treatment. For patients in the rTMS, the alternative treatments can be either ECT or lithium augmentation, with a maximum of two courses each before switching to the other. For patients receiving antidepressant therapy, they will move to ECT for a maximum of two courses before going back to antidepressants likely with lithium or antipsychotic augmentation. For patients in ECT, the alternative treatment is lithium augmentation for a maximum of two courses before going back to ECT.

If patients enter the 'post-ECT treatment' state or the 'post-lithium augmentation treatment' state, then patients start to receive the appropriate treatment where they may experience adverse event. Patients may then gain full remission (i.e. move to 'full remission' state), partially respond (i.e. remain on their post-treatment, ECT or lithium augmentation), not respond at all (i.e. move to the other treatment alternative), or experience an acute episode and move to 'hospitalisation' state.

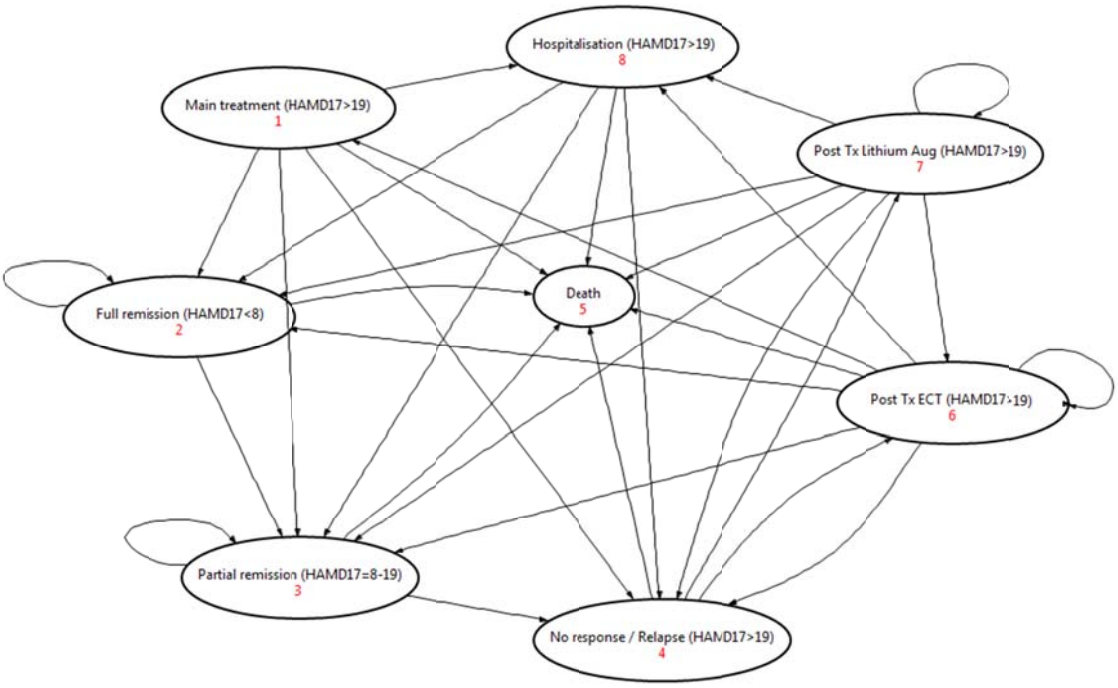
Once a patient enters the 'hospitalisation' state, the patient may remain in that state or gain full remission and move to the 'full remission' state.

At any given time, a patient can die due to common or MDD-related causes. Mortality risk is higher for patients in acute depression (no response/relapse health state) or in moderate depression (partial remission). Patients who do not achieve a treatment response are also at risk of an acute episode that requires hospitalisation. It is also assumed that patients on all treatment arms will continue with their regular depression treatment (either medical and/or psychological treatment).

The patient movement between health states is illustrated in

Figure .

Figure 8: State transition diagram of the economic model



Model inputs and justification for data sources

Transition probabilities

rTMS

Several RCTs and meta-analyses report response and remission rates for patients who have received rTMS:

1. (Berlim et al., 2014) reported the response, remission and drop-out rates following high-frequency rTMS versus sham in a comprehensive meta-analysis of RCTs. They reported a response rate of 29.3% and a remission rate of 18.6% for patients in the rTMS arms.
2. A similar meta-analysis published by (Berlim et al., 2013a) investigated the efficacy and acceptability of low-frequency rTMS versus sham. Their reported response and remission rates for rTMS patients are 38.2% and 34.6%, respectively.
3. (Berlim et al., 2013b) published a meta-analysis comparing the efficacy of rTMS versus ECT. The remission rates for the rTMS arm and the ECT arm are 33.6% and 52%, respectively. No response rates were reported here.
4. Another systematic review and meta-analysis study by (Ren et al., 2014) (*forthcoming*) used the same RCTs comparing rTMS and ECT as Berlim *et al* 2013. The reported results however are very different from the latter. A closer check of report accuracy reveals that this publication cited incorrect number of remitters and responders from RCT. For this reason, the study is disregarded.

All these meta-analyses share a common limitation: inclusion of heterogeneous studies with poor-quality trials and inconsistent criteria to measure remission and response rates.

Additionally, some meta-analyses erroneously used response rates as remission rates, and vice versa, when that particular rate was not reported in the RCT. Therefore, new meta-analyses were performed during the evaluation and the results were subsequently used in the economic model.

Two meta-analyses were performed: rTMS versus sham, and rTMS versus ECT. Whenever there are discrepancies in the response and remission rates derived from the literature, one set of results were used in the base case, and the other was used in the sensitivity analysis. The meta-analysis results are presented in Appendix D. The remission rate for rTMS was 21.5% versus 13.6% for antidepressants and 46.3% for ECT.

The antidepressant resistant profiles of patients from the included RCTs vary significantly. Some RCTs included patients who had, on average, failed six adequate antidepressant courses while others only included patients who had failed 1.6 courses. The meta-analysis results, therefore, reflect this patient mix and their "average" efficacy outcomes, which is comparable to the target MBS population (who have failed at least two adequate antidepressant courses).

The probabilities of losing remission are not reported in the literature. However some studies reported limited information on worsening and relapse rates after three and six months of rTMS treatment. (Janicak et al., 2010) followed rTMS patients for 6 months and estimated a 41% worsening rates with mean time to first rTMS reintroduction of 16 weeks. These patients received rTMS reintroduction/maintenance or medication maintenance over the study duration. (Mantovani et al., 2012) reported that 42% of patients lost remission by 3 months and a relapse rate of 13.5%. These patients did not receive any rTMS reintroduction/maintenance. These rates are equivalent to a 12%-17% monthly probability of losing remission (see Table 3).

ECT

There are two meta-analyses reporting remission rates for patients treated with rTMS versus those treated with ECT (Berlim et al., 2013b; Ren et al., 2014). Since the quality of both studies is questionable, inputs for the economic model were derived from the meta-analyses conducted during the evaluation (see discussion above).

Similar to rTMS, the probability of losing remission after ECT treatment is derived from relapse rates. These rates were sourced from (Sackeim et al., 2001).

Antidepressant medications

The efficacy outcome for antidepressant medication was derived from the STAR*D trial (Rush, 2007; Sinyor et al., 2010). This study reported major outcomes (remission, response and side effects) for four treatment steps. Patients who failed two adequate antidepressant courses in their current illness episode (Level 3, ATHF=2) can be considered as comparable to the MBS target population. Therefore, the efficacy outcomes used in the economic model for the antidepressant arm were derived from Level 3 patients.

The relapse rate for Level 3 reported in Rush *et al* 2006 (65% with average 3.1 months until relapse) was also used to calculated the probability of losing remission after antidepressant treatment. This relapse rate is equivalent to a 28.1% monthly rate of losing remission.

All three treatment arms

Treatment efficacy tends to decrease if patients failed previous treatment (O'Reardon *et al.* 2007). For instance, the strongest predictor of response to rTMS was a lower score on the ATHF indicating that the patient had failed fewer previous adequate antidepressant trials (Simpson *et al* 2009). The reduction of antidepressant efficacy was also observed in the STAR*D study (Sinyor *et al* 2010). The decrement is however not reported quantitatively. The rates of efficacy reduction (for each subsequent treatment) were therefore assumed to be 20% and 15% for remission and response rates, respectively.

NeuroNetics reported the re-treatment rate for rTMS (36.2%; also see the financial estimates) while no quantitative information is available for ECT and antidepressant treatment. Therefore, the retreatment rate was assumed to be the same for the three treatment arms).

In the absence of information available from published literature, probability assumptions were necessary and applied for all three treatment arms for: (i) the relapse rate if a patient is in partial remission (without treatment); (ii) the percentage decrement of the relapse rate from partial remission for each subsequent treatment; and (iii) the probability of getting post-treatment ECT. For the adverse event rates during treatment, a value was available for rTMS only (O'Reardon *et al.* 2007) and this value was assumed to be the same for the ECT and antidepressant arms.

Utility weights

Utility and disutility values are required for different health states in the economic model. Published sources were identified from a systematic review of clinical trials and economic evaluations of MDD treatment. Utility values for relevant health state are taken from (Hawthorne et al., 2003), which uses the Australian AQoL utility instrument. Disutilities associated with adverse events were calculated using information from (Sullivan et al., 2004). Further details are provided in Appendix D.

Mortality rates

The ABS Australian life tables were applied for patients in the remission health state. For other health states it is assumed that patients have a higher chance of dying compared to the general Australian population. An inflation factor of 1.81 was applied for the partial remission health state (equivalent to moderate depression), and a factor of 6 was applied for the no response/relapse health state (equivalent to severe/very severe depression). These inflation factors were sourced from the literature (Cuijers *et al.* 2002, Olin *et al.* 2012).

Health resource consumption and costs

The list of inputs relating to healthcare resource items and a detailed discussion of the sources and calculation of these inputs are presented in Appendix D. Costs considered in the base case of the evaluation are presented in Table 2. To obtain the monthly treatment cost for antidepressant, rTMS, ECT arms, costs were converted to monthly values. In general, the duration per rTMS treatment course is between 4-6 weeks while that of ECT is slightly shorter. The recommended treatment duration for antidepressant is 6 months (HESP advice). For simplicity, cost per treatment course is assumed to occur within one cycle. The monthly treatment cost for rTMS maintenance included two rTMS sessions

per month. Psychiatric consultation for treatment and management plan incurred a cost applied once for each treatment course (including rTMS maintenance). Subsequent psychiatric consultation and short visits were part of regular MDD monitoring.

Table 2: Summary of resources and costs used in the economic model

	Unit	Unit price	Total cost	Sources and Notes
rTMS: major treatment				
Acute treatment				
Average number of sessions per acute treatment course	28.3	$150.00	$4,245.00	Carpenter 2012 and Protocol p14
Psychiatrist consultation for rTMS setup (initial acute treatment and reintroduction)	1	$350.00	$350.00	Protocol p14
Total cost			$4,595.00	
Maintenance				
Average number of sessions per maintenance course	3	$150.00	$450.00	Protocol p8 (26 per year)
Psychiatrist consultation for rTMS maintenance setup	1	$350.00	$350.00	Protocol p23
Total cost			$800.00	
ECT: major treatment and treatment after failing rTMS and Antidepressant				
Average number of ECT sessions per course	10	$814.00	$8,140.00	u40Z (including hoteling and anaesthesia cost); AR-DRG version 6
Psychiatrist consultation	1	$350.00	$350.00	Protocol p23
Total			$8,490.00	
Antidepressant (major treatment)				
Average cost of antidepressant per week	12	$17.27	$207.21	Assuming efficacy realised by week 4; 3-months cost summing into one cycle; 3-month treatment takes into account compliance and drop-out.
Psychiatrist consultation (treatment plan)	1	$224.35	$224.35	MBS item 132 (for treatment and management plan)
Psychiatrist consultation (second visit - within 2 months of treatment)	1	$73.50	$73.50	Assuming 15-30mins consultation; MBS item 302 (85% fee) (MBS online)
Total			$505.06	
Lithium augmentation: after failing rTMS and ECT treatments				
Quantity required per course of treatment (at least 2 months)	1	$17.10	$17.10	PBS online
Number of lithium monitoring tests on average per person	4	$15.45	$61.80	MBS item 66800 (85% of fee) (MBS online)
Psychiatrist consultation	1	$73.50	$73.50	Assuming 15-30mins consultation; MBS item 302 (85% fee) (MBS online)
Total cost			$152.40	
Hospitalisation				
Major affective disorder A>69-Css	5.2%	$20,484.00		U63A - AR-DRG Version 6
Major affective disorder A<70-Css	37.0%	$13,106.00		U63B - AR-DRG Version 6
Average cost per hospitalisation (including only U63A and U63B)			$14,017.54	
Costs during partial remission				
Psychiatrist consultation	1	$73.50	$73.50	Assume once a month, 15-30mins consultation; MBS item 302 (85% fee) (MBS online)

Source: rTMS Section D working table.xlsx

The key parameters of the model are summarised in Table 3 together with the sources. The structure of the model is provided in Appendix D.

Table 3: Parameters used in the economic model

Description	Base	Low	High	Distribution	Source
Model specifications					
Model duration (months)	36	24	60	-	Assumption
Cycle length (months)	2	-	-	-	Assumption
Health states	8	-	-	-	Assumption
Discounting (both cost and effects)	5%	-	-	-	PBAC Guidelines
Probabilities					
rTMS					
REM: 1st treatment	21.5%	19.7%	31.2%	-	Meta-analysis during evaluation
RESP: 1st treatment	37.5%	33.2%	48.7%	-	Meta-analysis during evaluation
Start maintenance	10.0%	5.0%	15.0%	-	Protocol 1196
Lose remission (no maintenance)	16.6%	10.0%	20.0%	-	Calculated
Lose remission with maintenance	12.0%	8.0%	16.0%	-	Calculated
Antidepressant medications					
REM: 1st treatment [1]	13.6%	13.0%	36.8%	-	Rush 2006
RESP: 1st treatment	16.8%	16.0%	48.6%	-	Rush 2006
Lose remission	28.1%	20.0%	40.0%	-	Rush 2006
ECT					
REM: 1st treatment	46.3%	20.0%	70.0%	-	Meta-analysis during evaluation
RESP: 1st treatment	60.9%	40.0%	80.0%	-	Meta-analysis during evaluation
Lose remission	22.3%	15.0%	35.0%	-	Sackiem 2001
For all treatment arms					
Hospitalisation	10.4%	8.0%	12.0%	-	Estimation
Gaining REM after hospitalisation	35.0%	20.0%	50.0%	-	Assumption
REM: % decrement for each subsequent treatment	20.0%	15.0%	25.0%	-	Assumption
RESP: % decrement for each subsequent treatment	15.0%	10.0%	20.0%	-	Assumption
Retreatment after relapse	36.2%	25.0%	45.0%	-	NeuroNetics for rTMS; assumed equivalent for ECT and Antidepressant
Relapse from partial remission	50.0%	40.0%	58.0%	-	Assumption
Relapse: % increase for each subsequent treatment	10.0%	5.0%	15.0%	-	Assumption
Getting ECT after failing the main treatment	25.0%	20.0%	30.0%	-	Assumption
Having adverse events during treatment	5.8%	4.0%	8.0%	-	O'Reardon 2007 for rTMS; equivalent assumed for ECT and Antidepressant
Mortality risk					
Mortality risk by all causes	Life table	-	-	-	ABS
Mortality risk – partial remission	Mortality risk by all causes * 1.81	-	-	-	Cuijpers 2002

Description	Base	Low	High	Distribution	Source
Mortality risk – no response/ relapse	Mortality risk by all causes * 6	-	-	-	Olin 2012
Utilities					
Full remission	0.860	0.750	0.900	Beta	Appendix D
Partial remission	0.710	0.650	0.820	Beta	Appendix D
No response / Relapse	0.540	0.250	0.580	Beta	Appendix D
Hospitalisation	0.300	0.090	0.400	Beta	Appendix D
Decrement due to rTMS treatment	-0.101	-0.050	-0.150	Beta	Appendix D
Decrement due to ECT treatment	-0.104	-0.050	-0.150	Beta	Appendix D
Decrement due to Antidepressant	-0.066	-0.040	-0.100	Beta	Appendix D
Costs					
Treatment and monitoring cost					
rTMS dose [2] (per course of acute treatment)	28.3	20.0	30.0	-	Table 2
rTMS dose [2] (per month for maintenance)	4.3	1.0	4.0	-	Table 2
ECT dose [2] (per course of acute treatment)	10.0	8.0	12.0	-	Table 2
Antidepressant (per course of acute treatment)	12.0	8.0	20.0	-	Table 2
rTMS – acute treatment	$4,595	-	-	-	Table 2
rTMS – maintenance	$1,000	-	-	-	Table 2
ECT	$8,490	-	-	-	Table 2
Antidepressant – acute treatment	$505	-	-	-	Table 2
Lithium augmentation (after main treatment)	$152	-	-	-	Table 2
Hospitalisation	$14,018	$13,106	$20,484	Gamma	Table 2
Monitoring cost during partial remission	$73.5	-	-	-	Table 2
Adverse events					
rTMS	$82	-	-	Gamma	Appendix
ECT	$72	-	-	Gamma	Appendix
Antidepressant	$81	-	-	Gamma	Appendix

Source: rTMS Section D working table.xlsx

ECT = Electroconvulsive therapy; rTMS = repetitive Transcranial Magnetic Stimulation;

[1] First treatment after failing two adequate course of antidepressants (third line treatment); equivalent to Level 3 in STAR*D study (Rush 2006)

[2] Dose here refers to per session of treatment.

Base case and sensitivity analyses

A micro-simulation was performed with 50,000 trials to achieve stable results. The costs and QALYs were averaged to produce mean outcomes for each treatment arm. Sensitivity analyses were undertaken as these are standard practice and warranted by the numerous assumptions made in the data parameters. One-way sensitivity analyses were undertaken for selected variables using either the 95% confidence intervals for the high and low values, where available, or estimates assigned to reflect wide variation in the base value, or distributions assumed to approximate the variation of the variable (beta distribution for utilities and gamma distribution for cost).

The results of the economic model are presented in Table 4 to Table 6.

Table 4: Key economic evaluation findings (3 year duration)

Strategy	Mean Costs	Mean QALYs	ΔCost	ΔQALY	ICER
rTMS	$29,670	1.250	referent	referent	referent
Antidepressants	$31,330	1.180	-$1,660	0.070	rTMS dominant
ECT	$31,260	1.280	-$1,591	-0.030	$75,844

Source: rTMS final results - base case and sensitivity analysis.xlsx

ECT = Electroconvulsive therapy; rTMS = repetitive Transcranial Magnetic Stimulation; QALY = quality-adjusted life years; ICER = incremental cost effectiveness ratio

Table 5: Results of the economic model – rTMS vs Antidepressants

	rTMS		AntiDep		rTMS vs. Antidepressant		
	Cost	QALY	Cost	QALY	ΔCost	ΔQALY	ICER
Base case							
50,000 trials	$29,670	1.2500	$31,330	1.1800	-$1,660	0.0700	Dominant
One-way sensitivity analyses (selected) [a]							
100 samples of 50,000 trials	$29,675	1.2500	$31,371	1.1800	-$1,696	0.0700	Dominant
Transition probabilities							
Antidepressant REM: 1st treatment (24.9%; base=13.6%)	$28,035	1.2653	$27,496	1.2152	$539	0.0501	$10,761
Antidepressant REM: 1st treatment (36.8%; base=13.6%)	$26,611	1.2777	$23,897	1.2506	$2,713	0.0271	$100,088
Lose REM after Antidepressant treatment (20%; base=28.1%)	$29,703	1.2553	$29,678	1.2109	$25	0.0443	$573
Utility							
Remission (0.75; base=0.86)	$29,639	1.1911	$31,253	1.1355	-$1,615	0.0556	Dominant
Remission (0.90; base=0.86)	$29,590	1.2870	$31,346	1.2020	-$1,755	0.0850	Dominant
Partial remission (0.65; base=0.71)	$29,742	1.2405	$31,424	1.1643	-$1,682	0.0762	Dominant
Partial remission (0.82; base=0.71)	$29,470	1.2785	$31,154	1.2040	-$1,684	0.0745	Dominant
Relapse (0.25; base=0.54)	$29,446	1.0195	$31,207	0.9020	-$1,761	0.1175	Dominant
Relapse (0.58; base=0.54)	$29,759	1.2640	$31,504	1.1898	-$1,745	0.0742	Dominant
Hospitalisation (0.09; base=0.3)	$29,705	1.2178	$31,386	1.1349	-$1,681	0.0829	Dominant
Hospitalisation (0.40; base=0.3)	$29,746	1.2712	$31,374	1.1990	-$1,627	0.0722	Dominant
Multivariate sensitivity analysis							
Decrement due to AE for all three treatment arms (beta distribution)	$29,663	1.2500	$31,371	1.1800	-$1,708	0.0700	Dominant
Cost of AE for all treatment arms (gamma distribution)	$29,670	1.2500	$31,389	1.1800	-$1,719	0.0700	Dominant

Source: rTMS final results - base case and sensitivity analysis.xlsx

ECT = Electroconvulsive therapy; rTMS = repetitive Transcranial Magnetic Stimulation; REM = remission; AE = adverse events;

[a] The full sensitivity analysis results can be found in Appendix D and the excel file (rTMS final results - base case and sensitivity analysis.xlsx).

Table 6: Results of the economic model – rTMS vs ECT

	rTMS		ECT		rTMS vs. ECT		
	Cost	QALY	Cost	QALY	ΔCost	ΔQALY	ICER
Base case							
50,000 trials	$29,670	1.2500	$31,261	1.2800	-$1,591	-0.0300	$75,844
One-way sensitivity analyses (selected) a							
100 samples of 50,000 trials	$29,675	1.2500	$31,301	1.2800	-$1,626	-0.0300	$74,291
Transition probabilities							
rTMS REM: 1st treatment (19.7%; base=21.5%)	$30,087	1.2500	$31,364	1.2762	-$1,277	-0.0262	$48,809
rTMS REM: 1st treatment (31.2%; base=21.5%)	$27,670	1.2776	$31,295	1.2755	-$3,625	0.0022	Dominant
Lose REM after rTMS, no maintenance (10%; base = 16.6%)	$27,409	1.2957	$31,300	1.2746	-$3,891	0.0211	Dominant
Lose REM after rTMS, no maintenance (20%; base = 16.6%)	$30,532	1.2360	$31,263	1.2762	-$731	-0.0402	$18,192
Lose REM after rTMS, on maintenance (8%; base=12%)	$29,403	1.2571	$31,345	1.2744	-$1,942	-0.0174	$111,944
ETC REM: 1st treatment (35%; base=46.3%)	$31,268	1.2408	$34,851	1.2401	-$3,582	0.0007	Dominant
ETC REM: 1st treatment (55%; base=46.3%)	$28,628	1.2652	$28,789	1.3036	-$161	-0.0384	$4,192
ECT RESP: 1st treatment, net REM (5%; base = 14.6%)	$29,395	1.2549	$31,448	1.2741	-$2,054	-0.0192	$106,918
Lose REM after ECT (15%; base=22.3%)	$29,597	1.2550	$28,321	1.3213	$1,276	-0.0662	Dominated
Lose REM after ECT (35%; base=22.3%)	$29,727	1.2521	$34,714	1.2225	-$4,988	0.0296	Dominant
Gain REM after hospitalisation (20%; base=35%)	$35,987	1.2163	$36,489	1.2452	-$502	-0.0289	$17,364
Gain REM after hospitalisation (50%; base=35%)	$26,511	1.2741	$28,667	1.2921	-$2,156	-0.0180	$119,649
Cost							
rTMS dose (per treatment course) (25; base=28.3)	$30,413	1.2540	$31,311	1.2767	-$898	-0.0227	$39,562
rTMS dose (per treatment course) (30; base=28.3)	$31,139	1.2534	$31,350	1.2747	-$211	-0.0213	$9,876
ECT dose (per treatment course) (8; base=10)	$27,580	1.2547	$27,725	1.2760	-$145	-0.0213	$6,809
ECT dose (per treatment course) (12; base=10)	$31,847	1.2542	$34,925	1.2754	-$3,078	-0.0212	$145,239
Utility							
Remission (0.75; base=0.86)	$29,639	1.1911	$31,244	1.2117	-$1,605	-0.0206	$77,867
Remission (0.90; base=0.86)	$29,590	1.2870	$31,273	1.3082	-$1,682	-0.0212	$79,498
Partial remission (0.65; base=0.71)	$29,742	1.2405	$31,291	1.2603	-$1,549	-0.0198	$78,267
Partial remission (0.82; base=0.71)	$29,470	1.2785	$31,048	1.3059	-$1,579	-0.0274	$57,708
Relapse (0.25; base=0.54)	$29,446	1.0195	$31,214	1.0501	-$1,768	-0.0306	$57,718

	rTMS		ECT		rTMS vs. ECT		
	Cost	QALY	Cost	QALY	ΔCost	ΔQALY	ICER
Base case							
50,000 trials	$29,670	1.2500	$31,261	1.2800	-$1,591	-0.0300	$75,844
Relapse (0.58; base=0.54)	$29,759	1.2640	$31,396	1.2851	-$1,637	-0.0211	$77,463
Hospitalisation (0.09; base=0.3)	$29,705	1.2178	$31,388	1.2435	-$1,684	-0.0257	$65,562
Hospitalisation (0.40; base=0.3)	$29,746	1.2712	$31,315	1.2913	-$1,569	-0.0201	$77,996
Multivariate sensitivity analysis							
Decrement due to AE for all three treatment arms (beta distribution)	$29,663	1.2500	$31,291	1.2800	-$1,628	-0.0300	$74,322
Cost of AE for all treatment arms (gamma distribution)	$29,670	1.2500	$31,308	1.2800	-$1,638	-0.0300	$75,621

Source: rTMS final results - base case and sensitivity analysis.xlsx

ECT = Electroconvulsive therapy; rTMS = repetitive Transcranial Magnetic Stimulation; REM = remission; AE = adverse events;

[a] The full sensitivity analysis result can be found in Appendix D and the excel file (rTMS final results - base case and sensitivity analysis.xlsx).

In the base case analysis over three years, rTMS was the least costly treatment option followed by the antidepressant comparator. However, the cost differences were relatively small. The model predicted that ECT would produce the highest QALYs followed by rTMS and antidepressant. Therefore, rTMS could be considered superior to antidepressant as it was less costly and more effective, based on the model assumptions. rTMS produced lower costs but lower QALYs compared with ECT and the estimated ICER is $75,844 per QALY.

The sensitivity analyses found that the base case results were relatively robust with respect to input values and model assumptions. The most sensitive variables were the:

- Probability of gaining and losing remission after treatment (for all three treatment options)
- Probability of gaining remission after hospitalisation
- Probability of receiving ECT after the main treatment; and the
- Number of rTMS and ECT sessions per treatment course.

Comparing the ICERs for each strategy for 50,000 trials, the percentage of trials where rTMS is cost-effective relative to antidepressants is 70.5% at a willingness-to-pay threshold of $50,000 per QALY gain, and subject to the model assumptions. Conversely, the percentage of trials where rTMS was cost-effective relative to ECT was 38.8%.

Hence, the findings suggest that rTMS is not a cost-effective alternative to ECT for treatment resistant depressant patients in most cases. However, given that ECT is more commonly used in an emergency type setting for psychotic patients a comparison between rTMS and antidepressants may be more appropriate here for non-psychotic patients.

Estimated extent of use and financial implications

Overview

The expected extent of rTMS use and the associated financial implications to the MBS are presented in this section. It is proposed that rTMS will either be used as a replacement for, or in addition to, antidepressant medication or as a replacement for ECT. Psychological therapies such as CBT may also be used in conjunction with rTMS. If patients respond well to rTMS then their use of antidepressant medication, psychological therapy and ECT may cease, although it is expected that antidepressant therapy will still be required to prevent relapse.

An epidemiological approach is taken in this analysis. Estimates of patient numbers considered eligible for rTMS during the five years following listing on the MBS are taken from a review of epidemiological data and the associated costs are then analysed. The extent of potential cost savings is estimated, as are the net financial implications to the MBS, PBS and overall Government healthcare budget.

Data sources and assumptions

Epidemiology of treatment resistant depression in Australia

The projected Australian population aged 18-85 years was based on projections provided by the Australian Bureau of Statistics (ABS). For the period 2014 to 2019 the adult population is projected to increase from 17.8 million to 19.4 million. The ABS reported in the National Survey of Mental Health and Wellbeing - 2007 that the 12-month prevalence of depressive episodes in the Australian population is 4.1%. This survey collected information from approximately 8,800 Australians aged 16-85 years and the definition of "depressive episode" included severe, moderate and mild depression.

The proposed listing of rTMS limits use to a well-defined, specific patient sub-group. This patient group consists of those with major depression (DSM-5 rating) with antidepressant medication resistance.

The often cited STAR*D study was designed to assess effectiveness of treatments in generalizable samples and ensure the delivery of adequate treatments. The study (a naturalistic, real-world population study) enrolled approximately 4,200 outpatients with major depressive disorder and employed one or more acute treatment steps aimed to achieve symptom remission. The STAR*D report found that 36.8% of patients achieved remission after one treatment, 56.1% after two treatments and 67% after four treatment steps (i.e. 63.2% do not achieve remission after one treatment, 43.9% do not achieve remission after two treatments and 37% do not achieve remission after four). The primary outcome of remission was defined as a QIDS-SR16 score ≤5 (corresponding to an HRSD17 score of ≤ 7) after 14 weeks. Response was defined as 50% reduction in symptoms on the QIDS-SR over the same time scale.

Of the patients who do not achieve remission after two antidepressant treatments, it is estimated that approximately 0.56% would be referred for rTMS annually. This is based upon the rate of referrals for rTMS among those with private health insurance in South Australia, where rTMS is available through the Adelaide Clinic (78/754,600 =0.01%). This figure was multiplied by the relevant Australian population (18.1 million) and

divided by the number of patients estimated with TRD (43.9% or 326,568). If funded, the majority of the clinical use of rTMS is likely to remain in private hospitals and the Adelaide Clinic is a typical example of this. MSAC approval will, however, facilitate equitable access to non-privately insured patients, and as the availability and accessibility of rTMS increases, it is expected that the rate of use will rise.

Neuronetics data, which monitored 257 patients who successfully completed acute phase rTMS treatment for one year, reports that 36.2% of rTMS patients experienced symptom recurrence and required rTMS reintroduction. HESP expert opinion estimates that 10% of patients will require maintenance rTMS therapy.

The following analysis of eligible patients will assume that:

- The 12-month prevalence of a depressive episode is 4.1% (ABS);
- 43.9% of these patients will have depression which is resistant to two antidepressant medications (STAR*D);
- Of these patients, 0.56% will opt for rTMS treatment (Protocol 1196);
- 36.2% of patients will require rTMS reintroduction over the course of 12 months follow-up (Neuronetics data);
- 10% of patients will receive maintenance rTMS therapy (Protocol 1196).

Most acute patients undergo a course of treatment consisting of 20 to 30 rTMS treatments (five days per week for four to six weeks). A large observational study of rTMS by Carpenter 2012 was used to calculate the average treatment course. This study followed 307 patients with acute depression who received rTMS treatment and the average number of rTMS sessions across the acute phase was 28.3. The Neuronetics one year follow-up data found that for those patients who required retreatment with rTMS, the average number of extra treatment days was 16.2. Maintenance rTMS therapy consists of one treatment per fortnight.

The analysis of costs will assume that:

- The average number of treatments per course of rTMS is 28.3 (Carpenter 2012);
- For patients requiring reintroduction of rTMS therapy, the average number of additional treatments is 16.2 (Neuronetics data);
- Maintenance rTMS therapy consists of one treatment per fortnight (Protocol 1196).

The Excel spreadsheet used to perform the calculations is provided along with the Assessment Report (rTMS Section E.xls).

MBS statistics

To help understand possible uptake rates of rTMS, MBS statistics for ECT use are presented below in Table 7. According to the RANZCP patients typically receive eight to twelve treatments of ECT, at a frequency of about three per week per course.

Table 7: Estimated number of ECT courses

	2009	2010	2011	2012	2013
ECT claims on MBS	22,344	24,714	25,384	27,680	28,686
Average number of treatments per ECT course	10	10	10	10	10
Number of ECT courses delivered per year	2,234	2,471	2,538	2,768	2,869

Source: Excel spreadsheet (rTMS Section E.xls)
ECT = electroconvulsive therapy; MBS = Medicare Benefits Schedule

Assuming that each patient receives an average of 10 treatments per course, the number of patients receiving ECT in Australia on the MBS in the last year was approximately 2,870. The number of ECT courses claimed on the MBS has been increasing at a rate of approximately 130 courses per year for the last five years.

At present, the number of rTMS treatment centres in Australia is estimated to be five. Thus it is expected that initially, the number of patients who would access rTMS would be fewer than those accessing ECT. However, use of rTMS is expected to increase as therapy becomes more accessible.

Estimation of use and costs of rTMS

Number of patients potentially eligible for rTMS each year

The number of patients who would potentially be eligible for rTMS treatment under the proposed indication (i.e. those with treatment-resistant depression) is estimated in Table 8 below.

Table 8: Estimate of patients eligible for rTMS

		Method	Year 1 2015	Year 2 2016	Year 3 2017	Year 4 2018	Year 5 2019
A	Australian population aged 18-85 years	ABS	18,145,369	18,460,568	18,777,737	19,096,125	19,412,072
B	Those with a depressive episode	Ax4.1%	743,960	756,883	769,887	782,941	795,895
C	Estimate of population with TRD	Bx43.9%	326,598	332,272	337,980	343,711	349,398

Source: Excel spreadsheet (rTMS Section E.xls)
ABS = Australian Bureau of Statistics; rTMS = repetitive Transcranial Magnetic Stimulation; TRD = treatment resistant depression

Over the next five years it is predicted that approximately 340,000 patients per year will suffer from treatment-resistant depression, making them eligible for rTMS therapy.

Expected uptake among eligible patients

Whilst most eligible patients will opt for third- and subsequent-line medications and/or psychological therapies, it is expected that, at least initially, approximately 0.56% will opt for rTMS (see Table).

Table 20: Estimated use of rTMS among eligible patients

		Method	Year 1 2015	Year 2 2016	Year 3 2017	Year 4 2018	Year 5 2019
C	Estimate of patients eligible for rTMS	From above	326,598	332,272	337,980	343,711	349,398
D	Expected number of rTMS patients	Cx0.56%	1,829	1,861	1,893	1,925	1,957

Source: Excel spreadsheet (rTMS Section E.xls)
rTMS = repetitive Transcranial Magnetic Stimulation

From the eligible population, it is estimated that approximately 1,830 patients will receive rTMS in Year 1 of its availability. If this rate of uptake is maintained, an estimated 1,957 patients will use rTMS therapy in Year 5. These numbers seem appropriate when compared to the numbers of patients currently receiving ECT, as calculated above.

Adjustment for gradual uptake

The above estimates for rTMS uptake reflect current machine availability and accessibility. In practice, it is predicted that as accessibility improves following MBS listing, uptake will increase. The uptake of ECT, following its addition to the MBS in 1999, was reviewed. In the five years following its addition, usage increased by approximately 30% (see Excel spreadsheet). As rTMS is a safer option, with a decreased side effect profile compared to ECT, it is expected that rTMS use would increase more rapidly. This adjustment is made in Table and alternative uptake rates are considered in the sensitivity analysis.

Table 21: Estimated use of rTMS, adjusted for gradual increase in uptake rates

		Method	Year 1 2015	Year 2 2016	Year 3 2017	Year 4 2018	Year 5 2019
D	Expected number of rTMS patients	From above	1,829	1,861	1,893	1,925	1,957
E	Adjustment for gradual uptake	Assume	10%	20%	30%	40%	50%
F	Adjusted rTMS patient number	DxE	2,012	2,233	2,460	2,695	2,935

Source: Excel spreadsheet (rTMS Section E.xls)
rTMS = repetitive Transcranial Magnetic Stimulation

If uptake is increased at a rate of 10% per year, it is expected that over the course of the next five years 12,335 patients will receive rTMS therapy.

Adjustment for outcome

There are three possible outcomes following rTMS therapy:

1. Does not respond (in which case another form of treatment or adjunctive treatments would be trialled);
2. Responds then relapses, requiring reintroduction of rTMS;
3. Responds and recovers, with no retreatment required (although maintenance treatment may be used).

The Neuronetics data found that 36.2% of patients experienced symptom recurrence and received rTMS reintroduction based on this clinical worsening through 12 months of follow-up. Expert opinion in the Protocol 1196 states that approximately 10% of patients will require maintenance rTMS. This consists of one treatment a fortnight (26 treatments per year). See Table 9 below.

Table 9: Total estimated use of rTMS, adjusted for outcome

		Method	Year 1 2015	Year 2 2016	Year 3 2017	Year 4 2018	Year 5 2019
F	Adjusted rTMS patient number	From above	2,012	2,233	2,460	2,695	2,935
G	Number who will require reintroduction of rTMS	Fx36.2%	728	808	891	975	1,062
H	Number who will require maintenance rTMS	Fx10%	201	223	246	269	293

Source: Excel spreadsheet (rTMS Section E.xls)
rTMS = repetitive Transcranial Magnetic Stimulation

It is expected that 728 patients will require an additional course of rTMS in Year 1, with this number increasing to 1,062 in Year 5. Over this time period 1,232 patients will require rTMS maintenance therapy.

Expected costs to the MBS

For acute-phase major depression, a standard course of rTMS is 20 to 30 treatments (three to five days per week for four to six weeks), with the average patient receiving 28.3 treatments. On average, those who experience symptom recurrence and require reintroduction of rTMS, receive an additional 16.2 treatments over the course of 12 months. Those on maintenance therapy will receive one treatment a fortnight. Based on this information the total number of rTMS treatments provided on the MBS each year can now be estimated (see Table 10).

Table 10: Estimated rTMS services provided on the MBS

		Method	Year 1 2015	Year 2 2016	Year 3 2017	Year 4 2018	Year 5 2019
F	Adjusted rTMS patient number	From above	2,012	2,233	2,460	2,695	2,935
I	Number of treatments per year	Fx28.3	56,935	63,190	69,632	76,260	83,059
G	Patients requiring reintroduction	From above	728	808	891	975	1,062
J	Number of treatments per year	Gx16.2	20,611	22,875	25,207	27,606	30,067
H	Patients requiring maintenance	From above	201	223	246	269	293
K	Number of treatments per year	Hx26	5,231	5,805	6,397	7,006	7,631
L	Total number of treatments per year	I+J+K	82,777	91,870	101,236	110,872	120,757

Source: Excel spreadsheet (rTMS Section E.xls)
MBS = Medicare Benefits Schedule; rTMS = repetitive Transcranial Magnetic Stimulation

When initial course, reintroduction and maintenance patients are combined it is expected that approximately 82,880 rTMS treatments will be delivered in Year 1. This figure is expected to increase to 120,760 by Year 5.

The Protocol 1196 states that a psychiatrist consult is required prior to initiation of rTMS to determine if the patient is eligible for treatment and to then prescribe rTMS therapy. If reintroduction of rTMS occurs, it is assumed an additional psychiatrist consultation and prescription would be required. For those on maintenance, expert opinion is that patients will have a psychiatrist consultation prior to commencing maintenance therapy and then every three months (Table 11 below).

Table 11: Estimated psychiatrist services provided on the MBS

		Method	Year 1 2015	Year 2 2016	Year 3 2017	Year 4 2018	Year 5 2019
F	Adjusted rTMS patient number	From above	2,012	2,233	2,460	2,695	2,935
M	Number of psychiatrist visits per year	Fx1	2,012	2,233	2,460	2,695	2,935
G	Patients requiring reintroduction	From above	728	808	891	975	1,062
N	Number of psychiatrist visits per year	Gx1	728	808	891	975	1,062
H	Patients requiring maintenance	From above	201	223	246	269	293
O	Number of psychiatrist visits per year	Hx3	604	670	738	808	880
P	Total number of psychiatrist visits per year	M+N+O	3,344	3,711	4,089	4,479	4,878

Source: Excel spreadsheet (rTMS Section E.xls)

MBS = Medicare Benefits Schedule; rTMS = repetitive Transcranial Magnetic Stimulation

In total, it is expected that rTMS treatment will result in 3,344 psychiatrist visits in Year 1 and a total of 20,500 consultations over the next 5 years.

The proposed effective price to the MBS for the initial psychiatrist consultation is $350. At this consultation the psychiatrist would perform a "mapping" procedure to locate the motor cortex on the patients scalp (to enable measurement to the dorsolateral prefrontal cortex) and prescribe the dose of rTMS, which is a proportion of the patient's motor threshold. The proposed fee to the MBS per rTMS treatment provided by a nurse or allied health professional is $150. This fee covers the professional component ($81) and practice costs ($69). The professional component includes 10 minutes of setting up, 45 minutes of getting the patient seared and comfortable, providing ear plugs, marking out the location on the scalp for the coil, setting parameters on the rTMS machine, and applying treatment, plus 5 minutes to remove coils, check for discomfort and planning the next session. The practice costs includes miscellaneous, administrative and disposables expenses ($38), capital equipment costs ($14) and indirect costs for general overheads ($17).

Combining the costs of psychiatrist visits and treatments with the numbers estimated above allows us to estimate the overall cost of listing rTMS to the MBS (see Table 12).

Table 12: Expected rTMS use and associated costs to the MBS

		Method	Year 1 2015	Year 2 2016	Year 3 2017	Year 4 2018	Year 5 2019
L	Total number of treatments per year	From above	82,777	91,870	101,236	110,872	120,757
Q	Cost of treatments per year	Lx$150	$12,416,494	$13,780,558	$15,185,431	$16,630,825	$18,113,554
P	Total number of visits per year	From above	3,344	3,711	4,089	4,479	4,878
R	Cost of psychiatrist visits per year	Px$350	$1,170,291	$1,298,858	$1,431,272	$1,567,504	$1,707,256
S	Total cost of rTMS to the MBS	Q+R	$13,586,786	$15,079,417	$16,616,702	$18,198,329	$19,820,809

Source: Excel spreadsheet (rTMS Section E.xls)

MBS = Medicare Benefits Schedule; rTMS = repetitive Transcranial Magnetic Stimulation

rTMS therapy is expected to cost the MBS approximately $13,586,786 in Year 1, increasing to $19,820,809 in Year 5. Over the next 5 years rTMS treatment and psychiatrist consults are estimated to cost the MBS approximately $83 million.

Estimation of changes in use and cost of other therapies

The treatment algorithm provided in the Protocol suggests that rTMS (± antidepressants ± psychotherapy) is a third-line therapy along with ECT (± antidepressants ± psychotherapy) and antidepressants (± psychotherapy). As mentioned above, the applicant proposes that if a patient responds well to rTMS then their use of antidepressant medication and ECT may decrease.

Although there is no data on the proportion of patients who would cease antidepressant use following rTMS, it is expected that the majority will continue with an antidepressant to prevent relapse. Of the patients who are referred to ECT, it will be assumed that a small proportion would also be eligible and opt for rTMS, that is, they are not requiring rapid treatment due to psychosis or suicide risk, but are considered to have TRD.

As patients have been diagnosed with TRD, it is assumed that they are being cared for by a psychiatrist, therefore psychiatrist costs will be considered as common costs.

In this analysis it is assumed that:

- 20% of patients will reduce their antidepressant use following rTMS treatment (assumption);
- 10% of patients who would have had ECT will receive rTMS (assumption).
- ECT patients would have received one course (10 treatments) of ECT; and
- All patients are being cared for by a psychiatrist, therefore no extra psychiatrist fees are required for those who reduce antidepressant use or for those would have received ECT, as the MBS fee for prescribing rTMS is proposed to be the same as that for prescribing ECT (Protocol 1196).

The assumptions made above will be tested in the sensitivity analysis.

Costs of substitutable treatments

Antidepressants

The average cost for antidepressants, which was used in the economic model in this report, was calculated using figures from the DUSC review of antidepressant use, 2011 and the PBS website. The average weekly antidepressant cost was estimated to be $17.27 (or $69.08 per month).

ECT

A psychiatrist consultation is required to prescribe ECT before treatment can begin. As per the Protocol 1196 p23, this is assumed to cost the same as the rTMS initial psychiatrist consultation ($350).

In addition, the following MBS item descriptors are required per ECT treatment.

Category 3 – Therapeutic procedures
MBS 14224 ELECTROCONVULSIVE THERAPY, with or without the use of stimulus dosing techniques, including any electroencephalographic monitoring and associated consultation. (Anaes.) Fee: $70.35 Benefit: 75% = $52.80 85% = $59.80

Source: MBS online

Category 3 – Therapeutic procedures
MBS 20104 INITIATION OF MANAGEMENT OF ANAESTHESIA for electroconvulsive therapy. (4 basic units) Fee = $79.20 Benefit: 75% = $59.40 85% = $67.35

Source: MBS online

Estimated extent of substitution

Antidepressants

For the purpose of this analysis it is assumed that 20% of rTMS patients will reduce their antidepressant use. The number of patients is calculated in Table 26.

Table 26: Summary of antidepressant substitutions

		Method	Year 1 2015	Year 2 2016	Year 3 2017	Year 4 2018	Year 5 2019
F	Yearly rTMS patient number	From above	2,012	2,233	2,460	2,695	2,935
T	Number of rTMS patients reducing their antidepressant use	Fx20%	402	447	492	539	587

Source: Excel spreadsheet (rTMS Section E.xls)

rTMS = repetitive Transcranial Magnetic Stimulation

It is estimated that in Year 1 402 patients will reduce their antidepressant use. This is expected to increase to 587 in Year 5.

ECT

If 10% of patients who would have received ECT instead receive rTMS, then the following services on the MBS will not be required (see Table 27). The following calculations are based on the assumption that each patient would have received one course (10 treatments) of ECT.

Table 27: Summary of ECT substitutions

		Method	Year 1 2015	Year 2 2016	Year 3 2017	Year 4 2018	Year 5 2019
U	Number of ECT courses delivered/year	From above	2,234	2,471	2,538	2,768	2,869
V	Number of ECT courses no longer provided on the MBS	Ux10%	223	247	254	277	287
W	Number of ECT treatments no longer provided on the MBS	Wx10	2,234	2,471	2,538	2,768	2,869
X	Number of anaesthetics no longer provided on the MBS	Wx10	2,234	2,471	2,538	2,768	2,869

Source: Excel spreadsheet (rTMS Section E.xls)

ECT = electroconvulsive therapy; MBS = Medical Benefits Schedule

Estimated financial implications for the PBS and MBS

The proposed listing of rTMS will generate cost savings to the PBS which are attributable to reduced antidepressant use, and to the MBS through reduced ECT treatments and the associated reduction in anaesthesias.

Antidepressants

To calculate cost savings to the PBS, it is necessary to first estimate the percentage of patients in each PBS patient category. The averages provided in 'Expenditure and prescriptions, twelve months to 30 June 2013' were used – 67.7% of patients were assumed to be concessional patients, non-Safety Net; 20.1% were concessional, Safety Net; and 2.2% were general, Safety Net. The remaining 10.0% of patients were assumed to be general, non-Safety Net. The patient co-payment rates used for in the calculations were the 2014 co-payments of $6.00 for concessional patients and $36.90 for general patients.

As the average monthly cost of antidepressant therapy is $69.08, the Government pays on average $63.08 per concessional, non-Safety Net and general, Safety Net prescription, $32.18 per general prescription, and the full $69.08 per concessional, Safety Net prescription. The cost savings to the PBS are presented in Table 28.

Table 28: Cost savings to the PBS due to reduced antidepressant use

		Method	Year 1 2015	Year 2 2016	Year 3 2017	Year 4 2018	Year 5 2019
T	Number of rTMS patients reducing their antidepressant use	From above	402	447	492	539	587
Y	Number of antidepressant prescriptions not dispensed/year	Tx12	4,828	5,359	5,905	6,467	7,044
Z	Number of concessional rate prescriptions	Yx67.7%	3,269	3,628	3,998	4,378	4,769
AA	Cost saving to the PBS	Zx$63.08	$206,199	$228,852	$252,182	$276,186	$300,809
BB	Number of concessional Safety Net rate prescriptions	Yx20.1%	971	1,077	1,187	1,300	1,416
CC	Cost saving to the PBS	BBx$69.08	$67,043	$74,408	$81,994	$89,799	$97,805
DD	Number of general rate prescriptions	Yx10.0%	483	536	591	647	704
EE	Cost saving to the PBS	DDx$32.18	$15,538	$17,245	$19003	$20,812	$22,667
FF	Number of general Safety Net rate prescriptions	Yx2.2%	106	118	130	142	155
GG	Cost saving to the PBS	FFx$63.08	$6,701	$7,437	$8,195	$8,975	$9,775
HH	Total cost saving to the PBS	AA+CC+EE +GG	$295,481	$327,942	$361,374	$395,771	$431,056

Source: Excel spreadsheet (rTMS Section E.xls)

PBS = Pharmaceutical Benefits Scheme; rTMS = repetitive Transcranial Magnetic Stimulation

The introduction of rTMS is expected to save the PBS approximately $1.8 million over the next five years.

ECT

The financial implications of a reduction in the number of ECT treatments to the MBS are presented below in Table .

Table 29: Cost savings to the MBS due to reduced ECT

		Method	Year 1 2015	Year 2 2016	Year 3 2017	Year 4 2018	Year 5 2019
W	Number of ECT treatments not provided on the MBS/year	From above	2,234	2,471	2,538	2,768	2,869
II	Cost saving to the MBS	Wx$59.80	$133,617	$147,790	$151,796	$165,526	$171,542
X	Number of anaesthetics not provided on the MBS/year	From above	2,234	2,471	2,538	2,768	2,869
JJ	Cost saving to the MBS	Xx$67.35	$150,487	$166,449	$170,961	$186,425	$193,200
KK	Total cost saving to MBS due to reduced ECT use	II+JJ	$284,104	$314,239	$322,758	$351,951	$364,742

Source: Excel spreadsheet (rTMS Section E.xls)

ECT = electroconvulsive therapy; MBS = Medicare Benefits Schedule

The introduction of rTMS could potentially save the MBS $1.6 million over five years through reduced ECT use.

Cost to the Australian healthcare system overall

The net impact to the Government of listing rTMS on the MBS is shown in Table .

Table 30: Overall cost to the health budget of listing rTMS on the MBS

		Method	Year 1 2015	Year 2 2016	Year 3 2017	Year 4 2018	Year 5 2019
S	Total cost of rTMS to the MBS	From above	$13,586,786	$15,079,417	$16,616,702	$18,198,329	$19,820,809
HH	Total cost saving to the PBS (reduced antidepressant use)	From above	$295,481	$327,942	$361,374	$395,771	$431,056
KK	Total cost saving to MBS (reduced ECT use)	From above	$284,104	$314,239	$322,758	$351,951	$364,742
LL	Net impact to Government	S-HH-KK	$13,007,201	$14,437,236	$15,932,570	$17,450,607	$19,025,011

Source: Excel spreadsheet (rTMS Section E.xls)

ECT = electroconvulsive therapy; MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Scheme; rTMS = repetitive Transcranial Magnetic Stimulation

When the savings to the PBS, through reduced antidepressant prescribing, and to the MBS, through reduced ECT use, are taken into account, it is estimated that the addition of rTMS to the MBS will cost the Australian healthcare system approximately $79.85 million dollars over the next five years. This is $3.45 million less than the $83.30 million estimated above when these cost trade-offs were not included.

Identification, estimation and reduction of uncertainty

As noted in the above sections, there have been a number of assumptions made in estimating the financial impact to government of listing rTMS for the treatment of treatment-resistant depression. Therefore, it is appropriate to investigate the robustness of the assumptions through sensitivity analyses.

The prevalence of treatment-resistant depression

There is uncertainty surrounding the prevalence of treatment-resistant depression in Australia. The STAR*D data used, though cited regularly in the literature, was an American study which required participants to follow a strict treatment algorithm. All patients were commenced on citalopram. If treatment with this agent was unsuccessful, medications in Step 2 of the algorithm were allowed (bupropion, sertraline and venlafaxine). In Australia bupropion is only approved for smoking cessation. In addition, there are a large number of other medications available on the PBS which may be trialled and which may result in symptom remission.

For the base case analysis, 43.9% of those diagnosed with depression were assumed to develop treatment-resistant depression, and these patients formed the pool of patients eligible for rTMS therapy. A sensitivity analysis in which 43.9% ± 10% of patients developed treatment-resistant depression is presented in Table 13.

Table 13: Sensitivity analysis – Prevalence of treatment-resistant depression

	Year 1 2015	Year 2 2016	Year 3 2017	Year 4 2018	Year 5 2019
33.9% develop TRD	$9,979,569	$11,076,991	$12,229,762	$13,395,355	$14,608,211
43.9% develop TRD (base case)	$13,007,201	$14,437,236	$15,932,570	$17,450,607	$19,025,011
53.9% develop TRD	$16,034,833	$17,797,481	$19,635,379	$21,505,860	$23,441,811

Source: Excel spreadsheet (rTMS Section E.xls)

TRD = treatment-resistant depression

Increasing the incidence of treatment resistant depression to 54% increases the financial impact of rTMS to the Governments overall health budget to $98.4 million over the next five years. A 10% reduction in the incidence of treatment resistant depression results in rTMS adding approximately $61.3 million to the overall health budget over a five year time horizon.

The proportion of patients receiving rTMS

The proportion of patients who will opt for rTMS initially following listing on the MBS was estimated to be 0.56% of the eligible population. This was based on the current rate of referrals for rTMS among those with private health insurance in South Australia, and extrapolated to the Australian adult population. Although this resulted in an uptake of rTMS which, when compared to current ECT use, seems reasonable, a sensitivity analysis increasing this proportion to 1%, 1.5% and 2% of the eligible population was performed and is summarised in Table 3.

Table 32: Sensitivity analysis – Proportion of patients who opt for rTMS

	Year 1 2015	Year 2 2016	Year 3 2017	Year 4 2018	Year 5 2019
0.56% opt for rTMS (base case)	$13,007,201	$14,437,236	$15,932,570	$17,450,607	$19,025,011
1.0% opt for rTMS	$23,450,369	$26,027,681	$28,704,614	$31,438,331	$34,259,817
1.5% opt for rTMS	$35,317,606	$39,198,640	$43,218,299	$48,333,473	$51,572,097
2.0% opt for rTMS	$47,184,842	$52,369,600	$57,731,985	$63,228,614	$68,884,377

Source: Excel spreadsheet (rTMS Section E.xls)

rTMS = repetitive Transcranial Magnetic Stimulation

Increasing the uptake of rTMS among patients who are treatment resistant to 1%, 1.5% and 2% substantially increases Government expenditure.

The gradual uptake rate of rTMS

It was assumed in the base case analysis that as the availability and accessibility of rTMS improves following listing on the MBS, its uptake will increase by 10% per year. Although this is an assumption only, it was based on the uptake of ECT following its listing on the PBS in 1999 and took into consideration the safety profile of rTMS. A sensitivity analysis in which the uptake of rTMS increases by 15% and 20% per year is presented in Table 3.

Table 33: Sensitivity analysis – Gradual uptake rate of rTMS

	Year 1 2015	Year 2 2016	Year 3 2017	Year 4 2018	Year 5 2019
Gradual uptake = 10%/year (base case)	$13,007,201	$14,437,236	$15,932,570	$17,450,607	$19,025,011
Gradual uptake = 15%/year	$13,611,351	$15,666,526	$17,808,185	$19,993,830	$22,256,636
Gradual uptake = 20%/year	$14,215,501	$16,895,815	$19,683,800	$22,537,052	$25,488,262

Source: Excel spreadsheet (rTMS Section E.xls)

rTMS = repetitive Transcranial Magnetic Stimulation

Increasing the gradual uptake rate of rTMS to 15% and 20% per year results in a predicted expenditure in Year 5 is which is $2.2 and $4.5 million respectively more than the base-case estimate.

The average number of rTMS treatments per course

In the base case analysis, the average number of treatments per course of rTMS is 28.3 (SD = 10.1) (Carpenter 2012). As there is limited information available on what is the optimal number of treatments and on compliance rates (rTMS requires regularly attending a clinic/hospital for treatment sessions), and as the application states that '<u>most</u> patients would undergo a course treatment of between 20 and 30 treatments' a sensitivity analysis in which the number of treatments equals 15, 25 and 35 is presented below in Table 3.

Table 34: Sensitivity analysis – Average number of rTMS treatments

	Year 1 2015	Year 2 2016	Year 3 2017	Year 4 2018	Year 5 2019
15 rTMS treatments/course	$7,540,631	$8,370,114	$9,246,930	$10,128,608	$11,050,215
25 rTMS treatments/course	$11,650,834	$12,931,860	$14,273,727	$15,633,870	$17,046,302
28.3 rTMS treatments/course (base case)	$13,007,201	$14,437,236	$15,932,570	$17,450,607	$19,025,011
35 rTMS treatments/course	$15,761,037	$17,493,606	$19,300,525	$21,139,133	$23,042,389

Source: Excel spreadsheet (rTMS Section E.xls)

rTMS = repetitive Transcranial Magnetic Stimulation

If the average number of rTMS treatments per course is increased to 35, the impact to the Governments health care budget is expected to increase to $93.7 million over the next five years. If the average number of treatments is actually 25 per course, the impact to the five year budget of rTMS is $71.5 million.

The reduced rates of antidepressant and ECT use

That 20% of rTMS users would reduce their antidepressant use was an assumption. A sensitivity analysis using values of 10% and 30% is presented in Table 34.

Table 35: Sensitivity analysis – Rate of reduction in antidepressant use following rTMS therapy

	Year 1 2015	Year 2 2016	Year 3 2017	Year 4 2018	Year 5 2019
10% reduction in patients using antidepressants	$13,154,941	$14,601,207	$16,113,258	$17,648,493	$19,240,539
20% reduction in patients using antidepressants (base case)	$13,007,201	$14,437,236	$15,932,570	$17,450,607	$19,025,011
30% reduction in patients using antidepressants	$12,859,461	$14,273,265	$15,751,883	$17,252,722	$18,809,483

Source: Excel spreadsheet (rTMS Section E.xls)

ECT = electroconvulsive therapy; rTMS = repetitive Transcranial Magnetic Stimulation

Altering the assumptions surrounding the estimated extent of substitution if rTMS is available on the MBS results in changes to predicted Government expenditures. If 10% of rTMS users reduce their use of antidepressants, the impact to the health budget is estimated to be an extra $0.9 million over five years. On the other hand, if 30% of patients reduce their use of antidepressants, the impact to the healthcare budget is estimated to be approximately $78.9 million, a decrease of $0.9 million over five years.

Table 36 below presents the sensitivity analysis for when the percentage of patients opting for rTMS instead of ECT is varied to 15% and 20%.

Table 36: Sensitivity analysis – Rate of reduction in ECT use following rTMS therapy

	Year 1 2015	Year 2 2016	Year 3 2017	Year 4 2018	Year 5 2019
10% of ECT patients are eligible and opt for rTMS (base case)	$13,007,201	$14,437,236	$15,932,570	$17,450,607	$19,025,011
15% of ECT patients are eligible and opt for rTMS	$12,865,149	$14,280,117	$15,771,192	$17,274,631	$18,842,640
20% of ECT patients are eligible and opt for rTMS	$12,723,097	$14,122,998	$15,609,813	$17,098,656	$18,660,268

Source: Excel spreadsheet (rTMS Section E.xls)

ECT = electroconvulsive therapy; rTMS = repetitive Transcranial Magnetic Stimulation

Increasing the number of patients who opt to receive rTMS rather than ECT has a minimal impact on the overall healthcare budget. If 15% of eligible ECT patients opt for rTMS treatment there is an overall saving of 0$0.8 million over five years, if this increases to 20% the saving is $1.6 million.

Discussion

Is it safe?

NeuroStar rTMS has a unique safety profile among depression treatments in that it is non-systemic and non-invasive. The ability of NeuroStar rTMS to non-invasively enter the brain, positively impact neurobiological function and exit without leaving negative residual effects is a significant medical innovation. The primary side effect of the use of NeuroStar rTMS is discomfort or pain at the site of stimulation during active treatment. This is due to the brief activation of motor and sensory nerves in the scalp.

A major recognized strength of NeuroStar rTMS Therapy in clinical use is its safety and tolerability. The early experience with rTMS reported in the published literature has established a predictable and clinically benign safety and tolerability profile for rTMS in therapeutic use in patients with major depression.

This prior research and the clinical studies conducted using the NeuroStar rTMS Therapy System underscore the fact that rTMS can be safely administered in an outpatient clinical setting (Janicak, 2008).

The strength of the evidence for the NeuroStar system in RCTs and post-market review trials indicates that rTMS is safe with few harmful effects (e.g. 7 seizures reported for 14,000 patients since 2008). The sham trials consistently support this. There were no seizures or deaths and little suicidal ideation in the NeuroStar trials.

There is no direct comparative evidence of safety outcomes from trial evidence for either antidepressants or ECT. The available evidence shows that with all three treatments, there are different toxicity profiles. rTMS however, has the least serious effects of all three options.

An important advantage of rTMS over antidepressants is the very low discontinuation rate once therapy has begun. In Janicak *et al.* (2008) and George *et al.* (2010), discontinuation rates were less than 5%. This reflects the very high acceptability of this form of antidepressant treatment and high safety profile relative to antidepressants and ECT.

Is it effective?

There is a large body of evidence for TMS against sham TMS but relatively less for rTMS against ECT and none versus antidepressants.

Level II evidence strongly supports the efficacy of rTMS against sham. However this is not the comparator appropriate for the proposed MBS target population since there are other options available (antidepressants or ECT). There this is lack of evidence directly comparing rTMS with either antidepressants or ECT and indirect comparisons were necessary here. These indicate in general, that rTMS is effective in terms of higher response rates than antidepressants but has similar effectiveness compared with ECT.

In order to properly understand the scientific evidence base for the use of TMS therapy as an antidepressant, it is important to consider the temporal evolution of the literature

on the technology of rTMS itself, and to examine the early generation of clinical trial data separately from the more recently completed multi-site randomized controlled clinical trials. In the earlier generation of studies, a major focus of scientific interest was placed on establishing a clear dose-effect relationship, understanding the optimal method of targeting the brain regions of interest, and then clarifying the appropriate duration of treatment exposure. For example, one of the earliest meta-analyses conducted came from the Cochrane Library (Martin, et al 2003). While this meta-analysis was authoritative at the time that it was published, it should be noted that this report was published at a time when only 13 small, exploratory studies had been conducted and reported in the scientific literature. Since that time, significant improvements in the field's understanding of dose selection, study design, treatment duration, and site of stimulation have been addressed. In fact, later meta-analyses have clearly demonstrated a secular trend of improved and more consistent results in rTMS studies over time. For example, the more recent meta-analysis by Gross and colleagues (2007) compared the conclusions of the Cochrane review report to the results of studies conducted in the subsequent years and found that the more recently completed TMS trials showed consistently larger treatment effects than the first generation of exploratory studies.

The review summarises the extensive body of research evaluating the efficacy of rTMS, predominately compared to sham or placebo treatment. It is notable that this includes a number of large multisite trials are summarised in the report but also greater than 30 single site studies summarised in multiple positive meta-analyses. The evidence clearly indicates superior or equivalent efficacy to antidepressant medication, despite rTMS treatment trials having predominately been performed in patients who are medication resistant and who would typically be was expected to respond at very low rates to further trials of medication therapy.

The effectiveness of rTMS does not appear to be dependent on the individual machine being used for administration with positive clinical trials using the Neuro Star device quoted in the application, but also using a range of other commercially available systems. There appears to be no difference in efficacy or safety related to the type of rTMS equipment utilised.

A secondary efficacy comparison has been made between rTMS and ECT. In clinical practice, these are highly unlikely to be comparable therapeutic options for patients at an equivalent illness stage. Due to the side-effects and stigma associated with ECT, it is typically reserved for patients who are either acutely and severely unwell or for those who are significantly treatment resistant. Treatment resistant patients referred for ECT will most typically have undergone a significantly greater number of antidepressant treatment trials compared to those being considered for rTMS given the more favourable safety profile of rTMS treatment.

Consideration is given to structured psychotherapy as a potential comparator. It is clear that there are no direct studies comparing rTMS treatment to structured psychotherapy. What is perhaps slightly less clear is a significant absence of substantive evidence for the efficacy of psychotherapy in this clinical population. In particular, no studies have compared the use of a structured form of psychotherapy to a control therapy in patients who have failed to respond to two or more antidepressant medication treatments as it is typically the case with rTMS trials. A small number of trials have compared efficacy of structured psychotherapy to a control condition in patients who have failed one antidepressant medication. However, in these studies, the level of depression has typically

been mild and hence not comparable to the clinical population where rTMS is being utilised. The vast majority of rTMS treatment studies have been conducted in patients with moderate or severe depression.

Long term rTMS vs sham

In summary, there are now three independent studies of the long term outcomes following acute treatment with the NeuroStar TMS Therapy System. Over increasing intervals of time through 12 months of follow-up, these studies are consistent in demonstrating that the acute treatment benefits are durable, and can be maintained with a reduced burden of antidepressant medication as maintenance treatment. Additionally, these reports demonstrate a modest need for reintroduction of rTMS over the 12 months following acute treatment.

rTMS vs Antidepressant

Patients in the NeuroStar rTMS registration trial had failed a prior "adequate antidepressant drug trial." The word "adequate" has a very specific research meaning that is stricter than that often used by treating physicians. For example, an adequate drug trial is defined by the Antidepressant Treatment History Form (ATHF) (Sackeim, 2001), a rigorous and validated methodology for establishing antidepressant treatment resistance in research settings. The ATHF assigns each drug therapy an antidepressant resistance rating from 1 to 5 (1 being the lowest and 5 being the highest), based on the dosage and length of treatment. Generally, drug therapy must last at least four weeks in duration to be considered of an adequate duration with this methodology. An antidepressant resistance rating of 3 or greater indicates an adequate trial, in both duration and dosage. In many instances, patients receive multiple trials of drug therapy, most of which do not achieve treatment adequacy as defined by the ATHF, usually because of intolerance to adverse effects of the treatment, or general non-adherence to recommended therapy. These patients were screened out of the NeuroStar rTMS trials because they had not received an adequate drug trial.

In summary, outcomes in this naturalistic study showed clinical response and adherence rates under conditions of general clinical use were similar to those reported in open-label clinical trials in research study populations. These data validate that the acute and long-term durability of effect of NeuroStar rTMS Therapy efficacy in real-world clinical treatment is similar to the outcomes reported in published controlled clinical trials conducted in research populations, and further support the use NeuroStar rTMS Therapy as an effective and well tolerated treatment for those who have failed to benefit from initial treatment with antidepressant medication.

The AHRQ 2011 review is an important document because of the level of rigor and independence of this review group. In particular, this report arrives at conclusions regarding the safety and effectiveness of rTMS that are consistent with the data reviewed in the sections above. Among the analyses included in that document was a synthesis of the available peer-reviewed clinical research literature concerning the efficacy and safety of the use of rTMS therapy as an antidepressant treatment for patients with major depression who have failed to benefit from initial antidepressant medications.

Overall, the Panel concluded that there is a substantial and well-replicated body of evidence from randomized, sham-controlled clinical trials that provide a "high strength of evidence" that TMS produces significantly greater decreases in depression severity, response rate and remission rate when compared to a

sham treatment condition in the majority of peer-reviewed published clinical trials (for example, see Table A, Page ES-4 of the Executive Summary, and also Table 97 on Page 150 of the Overview of Main Findings). Of specific note is the general conclusion articulated in the Overview of Main Findings on Page 155, where the Panel summarizes that in the most stringent subset of studies (i.e. Tier 1 studies) for the patients meeting the strict definition of treatment resistant depression (TRD, i.e. two or more antidepressant failures of prior treatment with medications):

"Specifically, TMS averaged a decrease in depressive severity measured by the Hamilton Rating Scale for Depression (HAM-D) of more than 5 points relative to sham control, and this change meets the minimum threshold of the 3-point HAM-D difference that is considered clinically meaningful. Response rates were greater with TMS than sham (also high strength of evidence); those receiving TMS were more than three times as likely to achieve a depressive response as patients receiving sham procedure. Finally, TMS was also more likely to produce remission than the control procedure (moderate strength of evidence); patients receiving TMS were more than 6 times as likely to achieve remission as those receiving the sham…"

In attempting to position the evidence for the various non-pharmacologic treatments in comparison to the outcomes expected for medication treatment as an alternative, the AHRQ report also summarizes for the reader the likelihood of patient benefit from the standard pharmacologic 'next-step' options. On Page 156, they note for example, that the likelihood of achieving remission in patient with a routine pharmacologic "switch" to next best medication only averaged 22.3% (95% CI: 16.2, 28.4). With augmentation, the likelihood of achieving remission was similar, averaging 27.2% (95% CI: 20.4, 34.0). These numbers highlight the diminishing benefit with increasing levels of treatment resistance with standard pharmacologic options, and compare reasonably well with the clinician-rated remission rates observed in Neuronetics' Outcomes Study 37.1% (95% CI: 31.9, 42.7).

These conclusions are significant for several reasons. First, they are a rigorously conducted, unbiased assessment of the available scientific evidence. Secondly, they stand in a unique and authoritative position as a statement on the favourable scientific and clinical conclusions that can be drawn from the peer-reviewed, published literature on the use of TMS in depression. Finally, they are consistent with the prevailing conclusions in the broader scientific literature regarding the safety and efficacy of the use of TMS in treatment resistant depression.

What are the economic considerations?

Subject to the data limitations to fully inform the economic model, rTMS treatment for patients with major depression who have failed at least two adequate courses of antidepressants is cost-effective compared to an antidepressant strategy. Compared to ECT, rTMS has lower costs but slightly lower effectiveness in terms of QALY gains.

The financial cost to MBS of rTMS is expected to be around $13 million per year including savings expected for the reduction of antidepressant costs incurred by MBS. The costs to MBS will also decrease from a reduction in ECT where some patients with non-psychotic depression will choose rTMS over ECT.

Financial estimates are highly dependent on the proportion of patients that will receive rTMS. This is uncertain in the face of limited knowledge on this estimate. Further research is required on the uptake rate with the current machines available in Australia and the willingness of clinicians to refer clients to this option. Our assessment on the reduction of antidepressant-related costs (including any healthcare costs for adverse events) may be conservative if the high patient and clinician acceptability is realised.

Conclusions

Safety

rTMS is non-systematic and non-invasive. It is widely believed to have a superior profile on safety relative to ECT and antidepressants. The most serious safety issues are pain at the site of administration which is usually mild and transient and seizures, which are extremely rare. Post-market surveillance on rTMS shows very low levels of serious toxicitiy (0.1% per patient) in 14,000 patients worldwide since 2008.

Effectiveness

rTMS is superior to sham using direct RCT level I evidence. Indirectly comparing the evidence on remission and response rates on the HAM-D instruments shows that rTMS is also at least equivalent or more effective than antidepressants depending on the agent. However, indirect comparisons with ECT are less consistent and evidence shows rTMS may be equivalent at best to ECT or inferior.

Economic considerations

Cost effectiveness

The proposed use of rTMS is cost-effective compared with antidepressants producing cost-savings and higher QALYs (dominant). This result is reasonably stable when most model inputs are altered in sensitivity analyses. This result is subject to the assumptions made in the model until further evidence is available. When rTMS is compared with ECT, it produced cost-savings but also fewer QALYs and the incremental cost-effectiveness ratio is $75,844 per QALY gained. The likelihood that rTMS is cost-effective compared with antidepressants was 70.5% and for ECT was 38.8% at a willingness-to-pay threshold of $50,000 per QALY.

Financial implications

The expected uptake of rTMS is estimated at 82,777 separate treatments for 2012 patients in Year 1 to 120,757 treatments for 2935 patients by Year 5.

The listing of rTMS therapy is expected to have a net cost to the MBS of approximately $13.303 million in Year 1, increasing to $19.456 million in Year 5. Over the next 5 years, rTMS treatment and psychiatrist consults would cost the MBS approximately $81.664 million, after cost-offsets are taken into account.

Appendix A Health Expert Standing Panel Members and Evaluators

Health Expert Standing Panel Members

Member	Nomination / Expertise or Affiliation
Perminder Sachev	Professor in Psychiatry UNSW, Psychiatrist

Evaluators

Name	Organisation
Louisa Gordon	Griffith University
Emilie Bettington	Griffith University
Kim Nguyen	Griffith University

The above evaluators completed the following sections: Background, What are the economic considerations? Discussion, Conclusions, Appendix A, C, D, and Executive Summary.

Appendix B Search strategies

Searches were undertaken utilising Scopus, Pubmed and the Cochrane library. Search terms included rTMS, TMS, transcranial magnetic stimulation, ECT, electroconvulsive therapy, antidepressant, depression, mood disorder, treatment resistant.

In addition the RANZCP group are extensively involved in Neurostimulation research and attend international conferences and meetings where the most recent rTMS data is presented.

Appendix C Existing Systematic Reviews and HTA reports

Comparative Effectiveness Review No. 33. (Prepared by RTI International-University of North Caroline (RTI-UNC) Evidence-based Practice Center under Contract No. 290-02-00161.) AHRQ Publication No. 11-EHC056-EF. Rockville, MD: Agency for Healthcare Research and Quality. September 2011. Available from: www.effectivehealthcare.ahrq.gov/reports/final.cfm

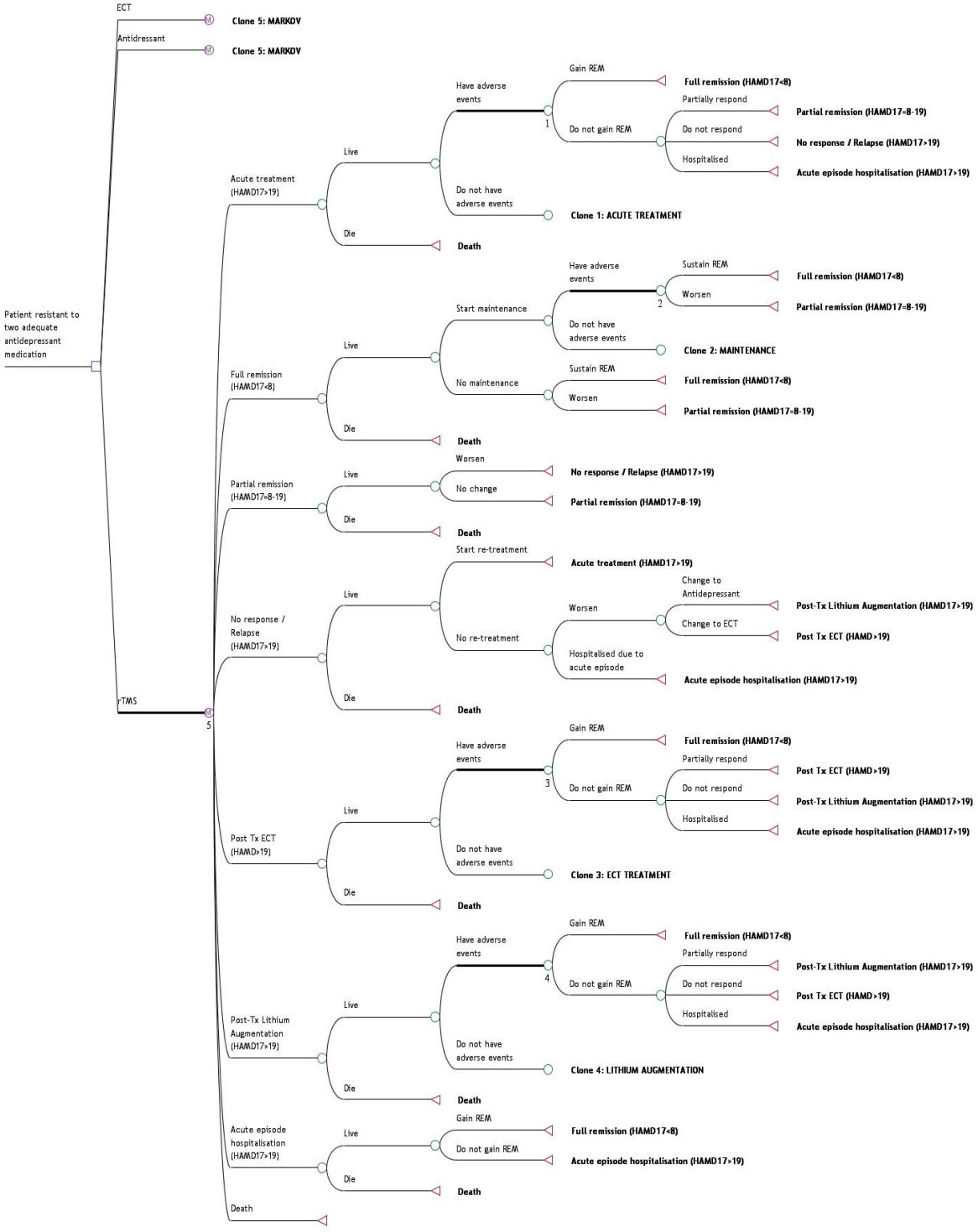
McLoughlin DM, Mogg A, et al. The clinical effectiveness and cost of repetitive transcranial magnetic stimulation versus electroconvulsive therapy in severe depression: a multicentre pragmatic randomised controlled trial and economic analysis. HTA 2007 Vol 11: No.24

MSAC 1101, 2007 Assessment Report, Repetitive Transcranial Magnetic Stimulation http://www.msac.gov.au/internet/msac/publishing.nsf/Content/115CC907F00447B3CA2575AD0082FD6C/$File/1101%20-%20Repetitive%20transcranial%20magnetic%20stimulation%20Report.pdf

Appendix D Additional tables for the economic evaluation

Structure of the economic model

Figure 9: Structure of the Markov model (3-year duration 1-month cycle)



Meta-analysis of the efficacy of rTMS and ECT

Figure 6: Remission rate rTMS vs. Sham

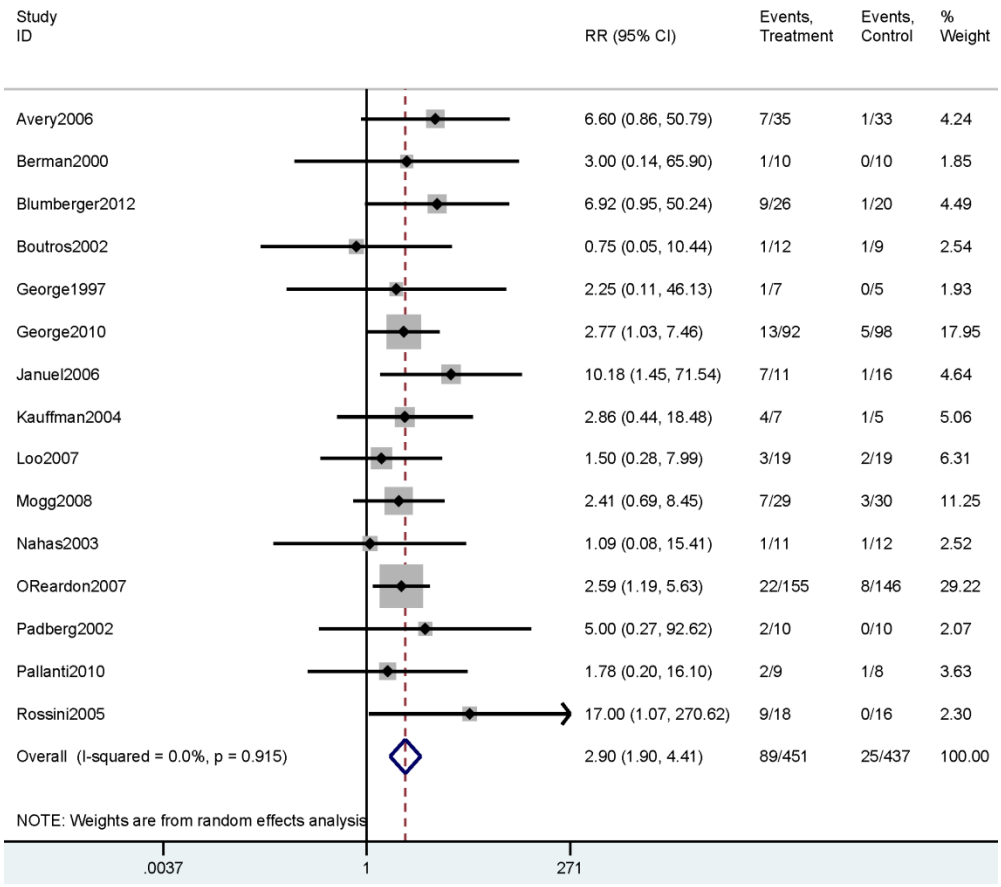


Figure 7: Remission rate rTMS vs. ECT

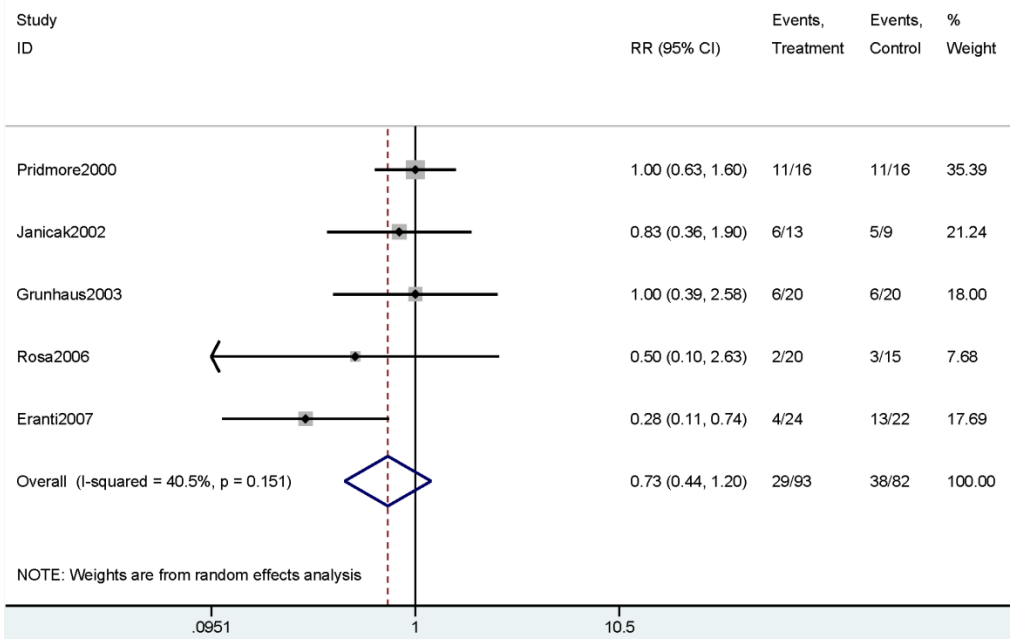


Figure 8: Response rate rTMS vs. Sham

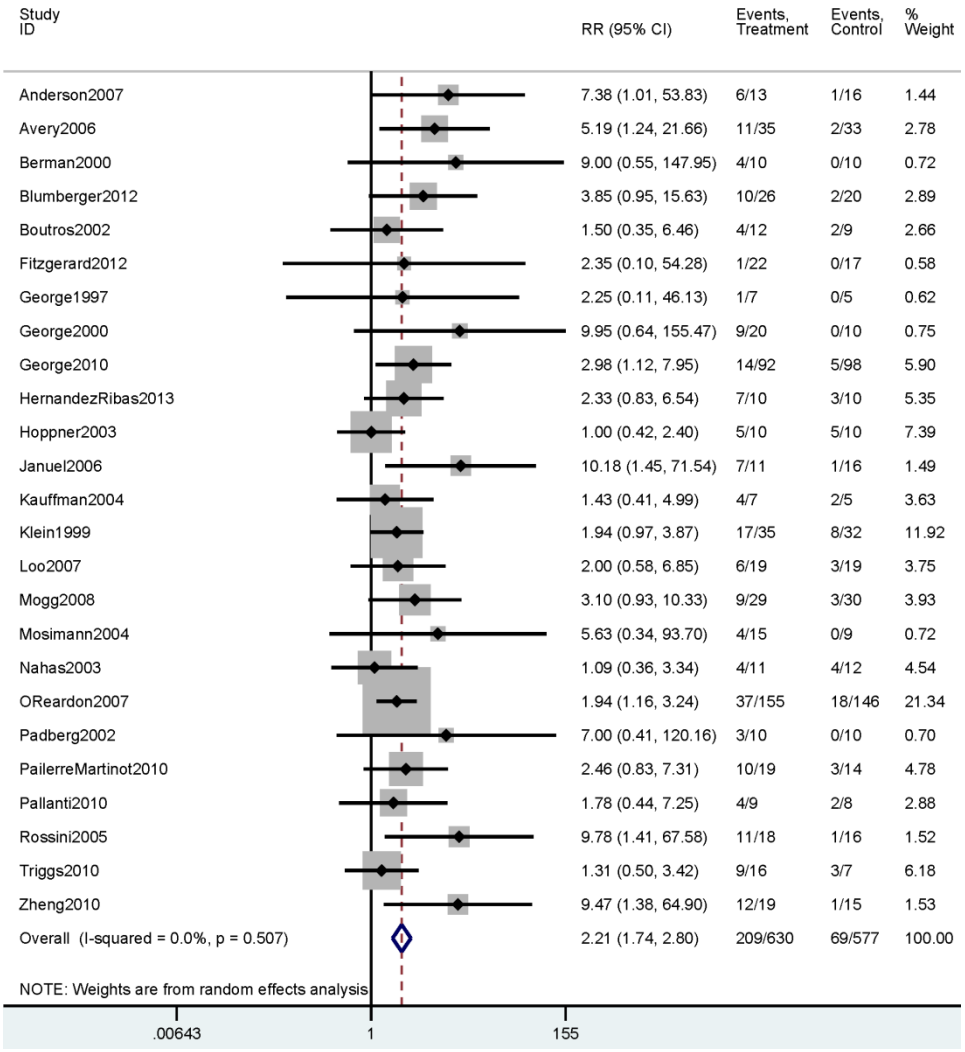
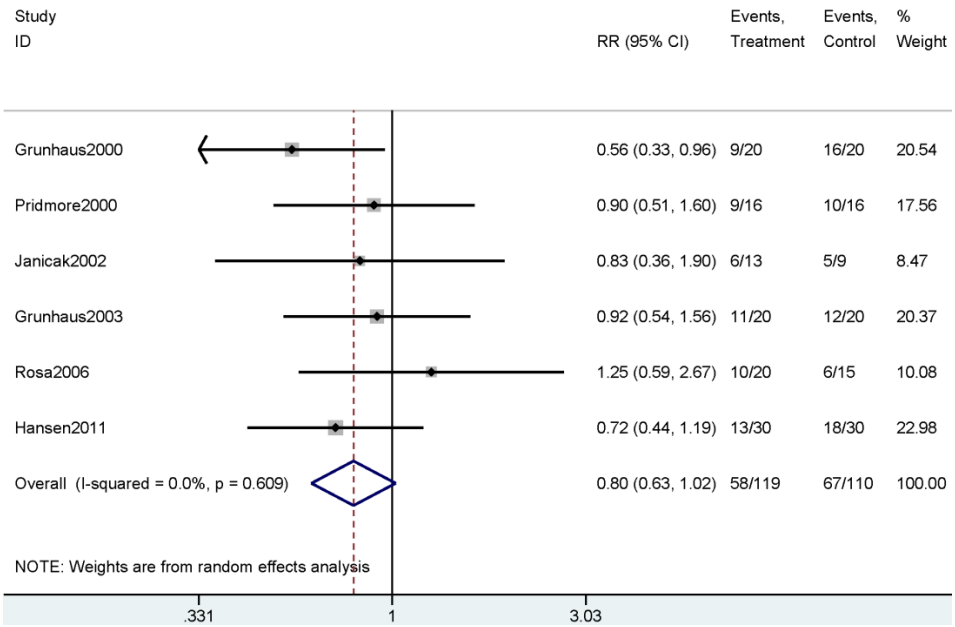


Figure 9: Response rate rTMS vs. ECT



Quality of life measurement

A systematic literature review was conducted in February-March 2014 to review the utility values relevant for the economic model where patients with MDD are treated with antidepressants, ECT and rTMS. The search databases include PubMed/MEDLINE, EMBASE and the CEA registry.

The choice of utilities is influenced by the health states defined in the economic model. Quality of life estimated from research undertaken within the past ten years is likely to represent current patient profiles and medical practice. Therefore, the search was limited to publications after January 2000.

All publications found were screened and duplicates were removed. Only full-text publications in English language were included. Abstracts, followed by full-texts of potentially relevant papers, were screened for inclusion. All studies that measured quality of life in patients with MDD were included. Qualitative studies or studies that established the correlation between different QoL measurements were not included.

All cost-effectiveness and cost-utility studies that included patient with MDD were reviewed, regardless of treatment therapies. This includes health technology assessments, systematic reviews, and individual studies. This process results into 14 studies, one systematic review (Zimovetz et al 2012) and one quality of life (EQ-5D) study (Sapin *et al.* 2004) that provide relevant utility measures. The reported utilities are summarised in Table 14 below.

Table 14: Utility weights for MDD reported in the literature

Health states	Utilities	Sources
Well / in remission		
Well - in antidepressant	0.750	Aziz 2005
Well - after ECT	0.900	Aziz 2005
Well	0.860	Sobocki 2008
Well - remission	0.860	Hawthorne 2009
No depression (MARDS 0)	0.830	Simpson 2009
Remitted depression	0.890	Valenstein 2001
Remitted depression	0.880	Olgiati 2012
Remission	0.810	Sobocki 2008
Remitters	0.790	Benedict 2010
Staying in remission	0.860	Benedict 2010
Treated depression	0.848	Sullivan 2004; Amstrong 2008
In remission with treatment SSRI	0.800	Nuijten 2001; Sado 2008; Simon 2006
In remission with treatment TCA	0.720	Nuijten 2001
In remission off treatment	0.860	Nuijten 2001; Sado 2008; Simon 2006
Responder - remitter	0.850	Sapin 2004
Responder	0.680	Benedict 2010
Responder – non remitter	0.720	Sapin 2004
Recovered - not on treatment	0.880	Perlis 2009
Recovered - on treatment	0.840	Perlis 2009

Health states	Utilities	Sources
In depression		
Minor depression	0.710	Hawthorne 2009
Non-responders	0.550	Benedict 2010
Non-responder	0.580	Sapin 2004
Partial depression - treated with antidepressant	0.550	Aziz 2005
Partial depression - treated with ECT	0.660	Aziz 2005
Depression on treatment SSRI	0.700	Nuijten 2001
Depression on treatment TCA	0.670	Nuijten 2001
Depression - treated with antidepressant	0.430	Aziz 2005
Depression - treated with ECT	0.520	Aziz 2005
Depressed - on treatment	0.590	Perlis 2009
Depressed - not on treatment	0.630	Perlis 2009
Untreated depression	0.580	Sullivan 2004; Amstrong 2008
Moderate depression (MARDS 2)	0.630	Simpson 2009; Sado 2008, Simon 2006
Depressive episode	0.570	Sobocki 2008
Significant depressive symptoms	0.700	Valenstein 2001
Severe depression (MARDS 3)	0.300	Simpson 2009; Sado 2008, Simon 2006; Nuijten 2001
Non-remission or acute	0.400	Olgiati 2012
Major depression	0.630	Valenstein 2001
Major depression	0.540	Hawthorne 2009
Hospitalisation	0.090	Simpson 2009

Of these studies, Hawthorne et al (2009) estimated the utility weights for Australia (using AQoL) in a costing study for South Australia. These utility values fall within the range reported in the literature. These values are used in the economic model.

There is limited information on disutility of the adverse events associated with each treatment. The most relevant study for this topic is Sullivan et al (2004) on the cost effectiveness of serotonin reuptake inhibitors (SSRIs) and associated adverse drug reactions in the US. Censored least absolute deviations (CLAD) regression analysis was used to obtain utility estimates for relevant adverse events. Utility is derived from the EuroQol EQ-5D scores for 14,888 adults in 2000 Medical Expenditure Panel Survey (MEPS).

In this assessment report, the disulilities (and costs) associated with treatment adverse events are calculated as the weighted average of the disutilities (and costs) of adverse events relevant to each treatment (see Table 14). The utility values are taken directly from Sullivan et al (2004) and the weights are the probabilities of getting each adverse event. The individual adverse event costs were sourced from cost of medication and health resource using the PBS and MBS.

Table 15: Disutility and cost associated with adverse events

Adverse events	Disutility [a]	Cost [b]	rTMS [c]	Antidepressants [d]	ECT [e]
Excitation	-0.012	$65		16.4	
Gastrointestinal disorder	-0.065	$78		24.1	
Headache	-0.115	$114	48.4%	5.3	18%
Sedation/drowsiness	-0.085	$0		9.5	18%

Adverse events	Disutility [a]	Cost [b]	rTMS [c]	Antidepressants [d]	ECT [e]
Sexual dysfunctional	-0.049	$107		11.2	
Others	-0.085	$100	24.4%	33.5	
Mild pain	-0.085	$10	23.6%		18%
Mania	-0.115	$0	4.3%		
Memory loss	-0.115	$109			46%
Weighted disutility			-0.101	-0.066	-0.100
Weighted cost			$81.79	$80.95	$72.53

a Disutility values are sourced from Sullivan et al 2004

b Costs are sourced from Sullivan et al 2004, PBS and MBS online

c Adverse event rates associated with rTMS are sourced from

d Adverse event rates associated with antidepressant are sourced from

e There is no quantitative information on adverse event rates with ECT. Most trials reported no adverse event while observational studies discuss side effects without reporting rates. Here, the adverse event rates are assumed.

Table 16: Summary of utility weights used in the economic model

Health states	Description	Utility	Value ranges in the literature
Remission	HAMD 17 < 8	0.860	0.75 – 0.90
Partial remission	HAMD 17 >=8 & <20 (mild/moderate)	0.710	0.65 – 0.82
No response	HAMD 17 >=20 (severe/very severe)	0.520	0.25 – 0.58
Treatment AntiDep	Dis-utility: weighted average	-0.066	-0.04 – -0.10
Treatment rTMS	Dis-utility: weighted average	-0.101	Not available
Treatment ECT	Dis-utility: weighted average	-0.104	Not available
Hospitalisation	HAMD 17>=20 with treat of suicide?	0.300	0.09 – 0.4

Source: Table 14 and Table 15

Glossary and abbreviations

AHRQ	Agency for Healthcare Research and Quality
AIHW	Australian Institute of Health and Welfare
ARTG	Australian Register of Therapeutic Goods
ATHF	Antidepressant Treatment History Form
CBT	Cognitive Behavioural Therapy
CEPAC	Comparative Effectiveness and Public Advisory Council
CGI-S	Clinical Global Impression – Severity scale;
CI	confidence interval
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, 4th Ed
HAM-D	Hamilton Depression Scale
HESP	Health Expert Standing
HRQoL	health-related quality of life
HTA	health technology assessment
ICER	incremental cost-effectiveness ratio
IDS-SR	Inventory of Depressive Symptomatology – self-report;
MADRS	Montgomery-Asberg depression rating scale;
MBS	Medical Benefits Schedule
MD	mean difference
MDD	major depressive disorder
MRI	magnetic resonance imaging
MSAC	Medical Services Advisory Committee
NHMRC	National Health and Medical Research Council
NHS	National Health Service
NIH	National Institutes of Health;
NIMH	National Institute of Mental Health
PHQ-9	patient health questionnaire;
QOL	quality of life;
RANZCP	Royal Australian and New Zealand College of Practitioners
RAPiD	Regional Adaptation for Payer Policy Decisions
RCT	randomised controlled trial;
rTMS	repetitive transcranial magnetic stimulation
STAR*D	Sequenced Treatment Alternative to Reduce Depression
TRD	treatment resistant depression
VAS	visual analogue scale

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