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Final Decision Analytic Protocol (DAP) to guide the assessment of repetitive Transcranial Magnetic Stimulation as a treatment for major depression

January 2013

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Advice to the Applicants:

This DAP has described the use of rTMS in those with major depression with antidepressant-medication resistance, defined as having failed to response to at least two different classes of antidepressant medication, despite adequate dose, duration and compliance. Should the Applicants wish to broaden the indicated population to those who have failed at least two different treatments, one of which may be a psychological therapy, the intended purpose for the magnetic stimulator, as listed on the ARTG (item 148142), would first need to change. The Applicants would need to provide a clear description of how to define two different courses of treatment, to clarify whether concurrent antidepressant therapy and psychotherapy would be considered one or two courses of treatment.

MSAC and PASC

The Medical Services Advisory Committee (MSAC) is an independent expert committee appointed by the Australian Government Health Minister to strengthen the role of evidence in health financing decisions in Australia. MSAC advises the Commonwealth Minister for Health and Ageing 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.

The Protocol Advisory Sub-Committee (PASC) is a standing sub-committee of MSAC. Its primary objective is the determination of protocols to guide clinical and economic assessments of medical interventions proposed for public funding.

Purpose of this document

This document is intended to provide a draft decision analytic protocol (DAP) that will be used to guide the assessment of repeated Transcranial Magnetic Stimulation (rTMS) as a treatment for major depression. The draft protocol will be finalised after inviting relevant stakeholders to provide input. The final protocol will provide the basis for the assessment of the intervention.

The protocol guiding the assessment of the health intervention has been developed using the widely accepted "PICO" approach. The PICO approach involves a clear articulation of the following aspects of the research question that the assessment is intended to answer:

Patients – specification of the characteristics of the patients in whom the intervention is to be considered for use;
Intervention – specification of the proposed intervention;
Comparator – specification of the therapy most likely to be replaced by the proposed intervention; and
Outcomes – specification of the health outcomes and the healthcare resources likely to be affected by the introduction of the proposed intervention.

Purpose of application

An application requesting Medicare Benefits Schedule (MBS) listing of repetitive transcranial magnetic stimulation (rTMS) for the treatment of major depression was received from the Committee for Therapeutic Interventions and Evidence-Based Practice, Royal Australian and New Zealand College of Psychiatrists by the Department of Health and Ageing in February 2012.

Adelaide Health Technology Assessment (AHTA), in the School of Population Health, University of Adelaide, as part of its contract with the Department of Health and Ageing, has drafted this decision analytic protocol to guide the assessment of the safety, effectiveness and cost-effectiveness of the proposed intervention in order to inform MSAC's decision-making regarding public funding of the intervention.

Background

Current arrangements for public reimbursement

Repetitive transcranial magnetic stimulation (rTMS) currently receives no public reimbursement and the costs are not reimbursed by private health insurance. rTMS is currently available in a small number of hospitals in Australia, with the costs being met by either the organisation (such as at the Adelaide Clinic at Ramsay Health Care Mental Health Services in South Australia) or the patient (Galletly et al. 2010).

An assessment of rTMS for major depression was performed on behalf of MSAC in 2007 (Application 1101). rTMS was compared against electroconvulsive therapy (ECT), and the application was rejected due to insufficient evidence of effectiveness:

MSAC has considered the safety, effectiveness and cost-effectiveness of repetitive transcranial magnetic stimulation (rTMS) for moderate to severe refractory treatment resistant depression compared with electro convulsive therapy (ECT).

MSAC finds evidence that rTMS is safe and less invasive than ECT.

MSAC finds limited evidence that rTMS may be less effective than ECT.

The financial and resource implications will depend upon the mix of patients who have rTMS, including uptake amongst patients who would otherwise not have ECT.

At present, MSAC finds that there is insufficient evidence to support public funding.

The current application proposed that rTMS should be compared against antidepressant medication. PASC suggested that additional comparators of cognitive behavioural therapy (CBT), and ECT should be added.

Regulatory status

There are two items listed by the Therapeutic Goods Administration (TGA) which are classified as "Stimulator, magnetic". The magnetic stimulator manufactured by MagVenture, and sponsored by Sonoray Pty Ltd (Australian Register of Therapeutic Goods (ARTG) item 148142) was previously listed with the intended purpose: "To stimulate the Peripheral and Central Nervous System by the application of Magnetic waves". This has been now been amended to state the intended purpose as *"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."*

In the United States, the Food and Drug Administration has provided guidance that rTMS is intended to be used *"to treatment the symptoms of major depressive disorder (MDD) without inducing seizure in patients who have failed at least one antidepressant medication and are currently not on any antidepressant therapy"* (FDA 2011). This is different to the intended purpose as listed on the ARTG in both the number of antidepressant medications which must be tried before rTMS is used (≥1 or ≥2), and in the requirement for patients to cease antidepressant use prior to rTMS.

Intervention

Description

Major Depression (DSM IV) is a disorder of mood with features of depressed mood, loss of energy and interest, loss of pleasure, feelings of hopelessness and worthlessness, sleep and appetite disturbance and suicidal thoughts and behaviour. Accompanying disability can be severe and lead to social and occupational disruption.

In 2007, the 12-month prevalence of depressive episodes in Australia in people aged between 16 and 98 years was 4.1%, including severe, moderate and mild depressive episodes (ABS 2008). Lifetime prevalence was calculated at 11.6% of people aged between 16 and 85 years, with women having a significantly greater lifetime risk of having a depressive episode, compared to men (14.5% and 8.8%) (ABS 2008).

There are a range of different treatments available to treat major depressive disorders, including medication and psychological treatments. Unfortunately, 10 to 30 per cent of patients with major depression do not respond to antidepressant medication (Al-Harbi 2012). Repetitive transcranial magnetic stimulation (rTMS) is being proposed as a treatment for major depression (currently based on DSM IV rating), after treatment with two prior

antidepressants has failed, or the side effect profile has been unacceptable to the patient. It is estimated that between 9% and 24% of patients with the initial diagnosis of a major depressive episode will undergo a change in diagnosis over time, mostly to bipolar disorder (Angst & Preisig 1995). The implications for misdiagnosis are fairly limited[1]. In trials conducted to date patients with bipolar disorder have shown similar response rates to rTMS as patients with non bipolar depression.

Transcranial magnetic stimulation was first reported in 1985 as a non-invasive method of stimulating the motor cortex (Barker, Jalinous & Freeston 1985), and has been proposed as a treatment for depression since the mid 1990s (Fitzgerald 2011). However, the mode of action by which rTMS assists in depression is poorly understood (Schwarzkopf, Silvanto & Rees 2011). Transcranial magnetic stimulation induces a magnetic field using a coil held over the scalp, inducing an electrical field in superficial areas of the brain (Fitzgerald 2011). When pulses of magnetic stimulation are provided at sufficient intensity, the electrical field causes depolarisation of nerve cells. Repeated stimulation can progressively change the activity of nerve cells. High frequency stimulation can increase the cortical excitability, while low frequency stimulation can decrease the level of cortical excitability (Fitzgerald 2011).

There are several different companies which produce magnetic stimulators that may be used for rTMS. The proposed intervention may therefore be considered a generic intervention.

Delivery of the intervention

In order to receive treatment with rTMS, a patient would be required to see a psychiatrist, who would determine if the patient is eligible for treatment with rTMS (i.e. having treatment-resistant major depression). The psychiatrist would then provide a treatment prescription for rTMS, and perform a "mapping" procedure, locating the motor cortex on the patients scalp (to enable measurement to the dorsolateral prefrontal cortex), and prescribing the dose of rTMS as a proportion of the patient's motor threshold.

rTMS would be delivered by a physician, an allied health professional, a clinical care professional (honours level qualifications with relevant clinical experience) or a nurse (general or mental health). It is expected that treatment with rTMS would be provided at a public or private hospital outpatient clinic.

One session of rTMS takes around 45 minutes, and at present, a standard course of rTMS is five days per week for four weeks (a total of 20 treatments per patient). Based on the experience of the Applicants, approximately 20% of treated patients would return for a

[1] Expert opinion, Royal Australian and New Zealand College of Psychiatrists, public consultation submission.

second course within 2 years and approximately 10% follow on with maintenance treatments (usually one treatment a fortnight, i.e. a total of 26 treatments per year).

The Applicants have estimated that approximately 1,700 adults would be referred for rTMS annually. This is based on the current rate of referrals for rTMS among those with private health insurance in South Australia, which is 78 referrals from 754,600 privately insurance patients (i.e. 0.01% of those privately insured). Extrapolated to an adult population in Australia of approximately 16.6 million, this results in 1,716.

It is expected that this rate is likely to increase if there is public funding for rTMS, as more machines will potentially be purchased, thus making it more accessible, and making psychiatrists more willing to refer patients for rTMS treatment.

Prerequisites

rTMS is being proposed as a treatment option for patients with major depression who have failed to respond to two different classes of antidepressant medication, despite appropriate dose, duration and compliance. Other patient restrictions are listed under the section 'Proposed MBS listing' (page 14).

It is proposed that only psychiatrists may prescribe treatment with rTMS, determining whether the patient is eligible for rTMS treatment, and determining the appropriate magnetic dose. As outlined above in 'Delivery of the Intervention' (page 7), the delivery of rTMS may be provided by an allied health professional, a clinical care professional or a nurse. Training sessions, at least one day in duration, would be required for psychiatrists to prescribe rTMS treatment and for nurses or allied health staff to administer treatment (Galletly et al. 2010).

The Applicants proposed that treatment with rTMS should be restricted to approved hospitals, and have suggested that hospitals which provide electroconvulsive therapy (ECT) should be eligible. Expert clinical advice given to PASC was that rTMS could also be provided in a day clinic. Given the high safety record of rTMS, it was therefore decided that the restriction to an approved hospital was unnecessary.

Currently, there are only a small number of magnetic stimulators available in Australia which may be used for rTMS. In order to provide rTMS, facilities would be required to purchase a magnetic stimulator and dedicate space for a treatment room (Galletly et al. 2010).

Facilities providing rTMS would be credentialed by the Australian Council of Healthcare Standards. The applicants suggest that all rTMS facilities would have a record keeping protocol, recording adverse events and service level data such as number of patients, number of treatments and patient satisfaction data. An rTMS facility would be expected to undertake a quality assurance program including annual reviews. This will include

documentation regarding regular servicing of the machine and equipment and standards of staff training.

Co-administered and associated interventions

The Applicants proposed that rTMS would be used either as a replacement for, or in addition to, antidepressant medication. PASC expanded on this, suggesting that psychological therapies such as cognitive behavioural therapy (CBT) may also be used in conjunction with rTMS.

The Applicants suggest that if patients respond well to rTMS, then their use of antidepressant medication may cease, although antidepressant medication may still be required to prevent relapse.

Anti-depressant medications listed on the Pharmaceutical Benefits Schedule (PBS) are shown in Table 1. Anti-depressants are prescribed by either a psychiatrist or by a general practitioner. The Applicants suggest that use of these anti-depressants would reduce with the introduction of rTMS, although no data on the proportion of patients who would likely *replace* antidepressant use with rTMS, as opposed to *augment* antidepressant use with rTMS have been provided.

Dosage of antidepressants would vary between the different medications, and titrated to different amounts between patients, depending on how they tolerate the side effects.

Table 1 Anti-depressant medications listed on the Pharmaceutical Benefits Schedule (PBS) as at 15th June 2012

Class	Name	Item codes
Non-selective monoamine reuptake inhibitors	Imipramine Hydrochloride	2420J, 2421K
	Clomipramine Hydrochloride	1561E
	Amitriptyline Hydrochloride	2417F, 2418G, 2439W
	Doxepin Hydrochloride	1011F, 1012G, 1013H
	Dothiepin Hydrochloride	1357K, 1358L
	Nortiptyline Hydrochloride	2522R, 2523T
Selective serotonin reuptake inhibitors	Citalopram Hydrobromide	8220P, 8702B, 8703C
	Sertraline	2236Q, 2237R, 8836C, 8837D
	Fluoxetine	1434L, 8270G
	Fluovoxamine	8174F, 8512B
	Paroxetine	2242B, 9197C
	Escitalopram	8700X. 8701Y, 8849R, 9432K, 9433L
Monoamine oxidase inhibitors, non-selective	Phenelzine Sulfate	2856H
	Tranylcypromine sulphate	2444P
Monoamine oxidase type A inhibitors	Moclobemide	1900B, 8003F
Other antidepressants	Mianserin Hydrochloride	1627P, 1628Q
	Mirtazapine	8513C, 8855C, 8856D, 8857E, 8883M, 9365X
	Reboxetine Mesilate	8583R
	Duloxetine Hydrochloride	9155W, 9156X
	Desvenlafaxine succinate	9366Y, 9367B
	Venlafaxine Hydrochloride	8301X, 8302Y, 8868R
	Lithium carbonate	3059B, 8290H

There are a range of psychological therapies that are able to be claimed on the MBS. These specific focussed psychological strategies are:

1. Psycho-education including motivational interviewing
2. Cognitive-behavioural therapy (CBT) including:
    - Behavioural interventions
        - Behaviour modification
        - Exposure techniques
        - Activity scheduling
    - Cognitive interventions
        - Cognitive therapy
3. Relaxation strategies
    - Progressive muscle relaxation
    - Controlled breathing
4. Skills training
    - Problem solving skills and training

- Anger management
- Social skills training
- Communication training
- Stress management
- Parent management training

5. Interpersonal therapy (IPT)

MBS items that relate to these therapies (provided by a general practitioner or psychologist) are listed in Table 2.

Table 2: MBS item descriptors for provision of focused psychological strategies

Category 1 – professional attendances
MBS 2721 MEDICAL PRACTITIONER ATTENDANCE (INCLUDING A GENERAL PRACTITIONER, BUT NOT INCLUDING A SPECIALIST OR CONSULTANT PHYSICIAN) ASSOCIATED WITH PROVISION OF FOCUSSED PSYCHOLOGICAL STRATEGIES Note: These services may only be provided by a medical practitioner who is registered with Medicare Australia as having satisfied the requirements for higher level mental health skills for the provision of the service. Focussed psychological strategies are specific mental health care management strategies, derived from evidence based psychological therapies, that have been shown to integrate the best external evidence of clinical effectiveness with general practice clinical expertise. These strategies are required to be provided to patients by a credentialled medical practitioner and are time limited; being deliverable, in up to ten planned sessions per calendar year. In exceptional circumstances, following review by the practitioner managing the patient either under the GP Mental Health Treatment Plan or under the Psychiatric Assessment and Management Plan, up to a further 6 services may be approved from 1 March 2012 to 31 December 2012 to an individual patient. Medical practitioners must be notified to Medicare Australia by the General Practice Mental Health Standards Collaboration that they have met the required standards for higher level mental health skills. A session should last for a minimum of 30 minutes. FPS ATTENDANCE Professional attendance for the purpose of providing focussed psychological strategies (from the list included in the Explanatory Notes) for assessed mental disorders by a medical practitioner registered with Medicare Australia as meeting the credentialling requirements for provision of this service, and lasting at least 30 minutes to less than 40 minutes. SURGERY CONSULTATION (Professional attendance at consulting rooms) Fee: $89.25 Benefit: 100% = $89.25
MBS 2723 OUT-OF-SURGERY CONSULTATION (Professional attendance at a place other than consulting rooms) The fee for item 2721, plus $25.00 divided by the number of patients seen, up to a maximum of six patients. For seven or more patients - the fee for item 2721 plus $1.90 per patient.
MBS 2725 FPS EXTENDED ATTENDANCE Professional attendance for the purpose of providing focussed psychological strategies (from the list included in the Explanatory Notes) for assessed mental health disorders, by a medical practitioner registered with Medicare Australia as meeting the credentialling requirements for provision of this service, and lasting at least 40 minutes.

SURGERY CONSULTATION (Professional attendance at consulting rooms) Fee: $127.70 Benefit: 100% = $127.70
MBS 2727 OUT-OF-SURGERY CONSULTATION (Professional attendance at a place other than consulting rooms) The fee for item 2725, plus $25.00 divided by the number of patients seen, up to a maximum of six patients. For seven or more patients - the fee for item 2725 plus $1.90 per patient.
Category 8 – Miscellaneous services
MBS 80000 Professional attendance for the purpose of providing psychological assessment and therapy for a mental disorder by a clinical psychologist registered with Medicare Australia as meeting the credentialing requirements for provision of this service, lasting more than 30 minutes but less than 50 minutes, where the patient is referred by a medical practitioner, as part of a GP Mental Health Treatment Plan; or referred by a medical practitioner (including a general practitioner, but not a specialist or consultant physician) who is managing the patient under a referred psychiatrist assessment and management plan; or referred by a specialist or consultant physician in the practice of his or her field of psychiatry or paediatrics. These therapies are time limited, being deliverable in up to ten planned sessions in a calendar year (including services to which items 2721 to 2727; 80000 to 80015; 80100 to 80115; 80125 to 80140; 80150 to 80165 apply). Claims for this service may exceed this maximum session limit, however, where exceptional circumstances apply (to a maximum total of 16 individual services per patient from 1 March 2012 to 31 December 2012). (Professional attendance at consulting rooms) Fee: $97.90 Benefit: 85% = $83.25
MBS 80005 Professional attendance at a place other than consulting rooms. As per the service requirements outlined for item 80000. Fee: $122.35 Benefit: 85% = $104.00
MBS 80010 Professional attendance for the purpose of providing psychological assessment and therapy for a mental disorder by a clinical psychologist registered with Medicare Australia as meeting the credentialing requirements for provision of this service, lasting at least 50 minutes, where the patient is referred by a medical practitioner, as part of a GP Mental Health Treatment Plan; or referred by a medical practitioner (including a general practitioner, but not a specialist or consultant physician) who is managing the patient under a referred psychiatrist assessment and management plan; or referred by a specialist or consultant physician in the practice of his or her field of psychiatry or paediatrics. These therapies are time limited, being deliverable in up to ten planned sessions in a calendar year (including services to which items 2721 to 2727; 80000 to 80015; 80100 to 80115; 80125 to 80140; 80150 to 80165 apply). Claims for this service may exceed this maximum session limit, however, where exceptional circumstances apply (to a maximum total of 16 individual services per patient from 1 March 2012 to 31 December 2012). (Professional attendance at consulting rooms) Fee: $143.70 Benefit: 85% = $122.15
MBS 80015 Professional attendance at a place other than consulting rooms As per the service requirements outlined for item 80010. Fee: $168.15 Benefit: 85% = $142.95
MBS 80100

Professional attendance for the purpose of providing focussed psychological strategies services for an assessed mental disorder by a psychologist registered with Medicare Australia as meeting the credentialing requirements for provision of this service - lasting more than 20 minutes, but not more than 50 minutes - where the patient is referred by a medical practitioner, as part of a GP Mental Health Treatment Plan; or referred by a medical practitioner (including a general practitioner, but not a specialist or consultant physician) who is managing the patient under a referred psychiatrist assessment and management plan; or referred by a specialist or consultant physician in the practice of his or her field of psychiatry or paediatrics.

These services are time limited, being deliverable in up to ten planned sessions in a calendar year (including services to which items 2721 to 2727; 80000 to 80015; 80100 to 80115; 80125 to 80140; 80150 to 80165 apply).

Claims for this service may exceed this maximum session limit, however, where exceptional circumstances apply (to a maximum total of 16 individual services per patient from 1 March 2012 to 31 December 2012).

(Professional attendance at consulting rooms)

Fee: $69.35 Benefit: 85% = $58.95

MBS 80105

Professional attendance at a place other than consulting rooms.

As per the psychologist service requirements outlined for item 80100.

Fee: $94.35 Benefit: 85% = $80.20

MBS 80110

Professional attendance for the purpose of providing focussed psychological strategies services for an assessed mental disorder by a psychologist registered with Medicare Australia as meeting the credentialing requirements for provision of this service - lasting more than 50 minutes - where the patient is referred by a medical practitioner, as part of a GP Mental Health Treatment Plan; or referred by a medical practitioner (including a general practitioner, but not a specialist or consultant physician) who is managing the patient under a referred psychiatrist assessment and management plan; or referred by a specialist or consultant physician in the practice of his or her field of psychiatry or paediatrics.

These services are time limited, being deliverable in up to ten planned sessions in a calendar year (including services to which items 2721 to 2727; 80000 to 80015; 80100 to 80115; 80125 to 80140; 80150 to 80165 apply).

Claims for this service may exceed this maximum session limit, however, where exceptional circumstances apply (to a maximum total of 16 individual services per patient from 1 March 2012 to 31 December 2012).

(Professional attendance at consulting rooms)

Fee: $97.90 Benefit: 85% = $83.25

MBS 80115

Professional attendance at a place other than consulting rooms.

As per the psychologist service requirements outlined for item 80110.

Fee: $122.95 Benefit: 85% = $104.55

MBS 80120

Professional attendance for the purpose of providing focussed psychological strategies services for an assessed mental disorder by a psychologist registered with Medicare Australia as meeting the credentialing requirements for provision of this service, lasting for at least 60 minutes duration where the patients are referred by a medical practitioner, as part of a GP Mental Health Treatment Plan; or referred by a medical practitioner (including a general practitioner, but not a specialist or consultant physician) who is managing the patient under a referred psychiatrist assessment and management plan; or referred by a specialist or consultant physician in the practice of his or her field of psychiatry or paediatrics.

These therapies are time limited, being deliverable in up to ten planned sessions in a calendar year (including services to which items 80020, 80145 and 80170 apply).

GROUP THERAPY with a group of 6 to 10 patients, EACH PATIENT

Fee: $25.00 Benefit: 85% = $21.25

Listing proposed and options for MSAC consideration

Proposed MBS listing

The proposed MBS item listings for rTMS prescription and treatment are shown in Table 3. The first proposed item may be an alternative to psychiatric risk assessment, MBS item number 296. The second proposed item most closely resembles is MBS item 14224, for electroconvulsive therapy (Table 4).

Eligibility for treatment with rTMS relies on patients meeting the criteria for major depression (DSM IV rating) with antidepressant medication resistance, defined as "depression that has not remitted after at least two trials with antidepressants from different pharmacologic classes with adequate dose, duration, and compliance". This is consistent with the listed purpose on the ARTG: 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.

Patients must be 18 years of age or older and satisfy the safety requirements, which are:

- 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
- Not be pregnant or planning to become pregnant during the treatment course.

Table 3: Proposed MBS item descriptors for rTMS as a treatment for major depression

Category 3 – Therapeutic procedures
MBS [proposed MBS item number] REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION treatment prescription by a psychiatrist Fee: $312.90 This item enables a psychiatrist to prescribe rTMS, to determine if the patient is eligible to have the treatment, to do the "mapping" procedure whereby the location of the motor cortex on the patients scalp is determined (enabling measurement forward to the dorsolateral prefrontal cortex) and to prescribe the dose of rTMS as a proportion of the motor threshold.
MBS [proposed MBS item number] REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION treatment provided by a nurse or allied health professional Fee: $150 This item enables a nurse or allied health professional to provide rTMS treatment to a patient, under medical supervision. The rTMS treatment must be prescribed by a psychiatrist (as described above) and be given in a setting where immediate medical assistance is available if required.

The fee for rTMS as suggested by the Applicant covers the professional component ($81) and practice costs ($69). The professional component includes 10 minutes of setting up, 45 minutes of getting the patient seated 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, checking 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).

Clinical place for proposed intervention

The Applicants proposed a simple management algorithm, showing antidepressants as the sole comparator for rTMS. PASC determined that this algorithm was too simplistic, and that patients may also receive psychological therapies in addition to both rTMS and antidepressants, and ECT. In those patients where ECT is clearly indicated (i.e. where a rapid and definitive response is required because of psychosis or suicide risk), rTMS should not be used as a substitute. The exception that may be considered is where the patient refuses ECT. ECT may also be considered after other treatments have failed (i.e. it may be considered a comparator to rTMS in those with antidepressant-treatment resistance). ECT is commonly used in combination with antidepressant medication with the expectation that the continuing antidepressant medication will assist remission after the course of ECT is completed. ECT can have temporary effects on memory and learning, so psychotherapy is generally not undertaken in combination with ECT. However, supportive psychotherapy may be given during ECT, and psychotherapy may be given during maintenance ECT (treatments spaced after an acute ECT treatment course to prevent relapse)[2].

Figure 1 shows a management algorithm incorporating the comparators of antidepressant medication ± psychological therapies or ECT ± antidepressant medication. After third line treatment with rTMS or its comparators, possible outcomes are that the patient:

1. Does not respond (in which case another form of treatment or adjunctive treatments would be trialled);

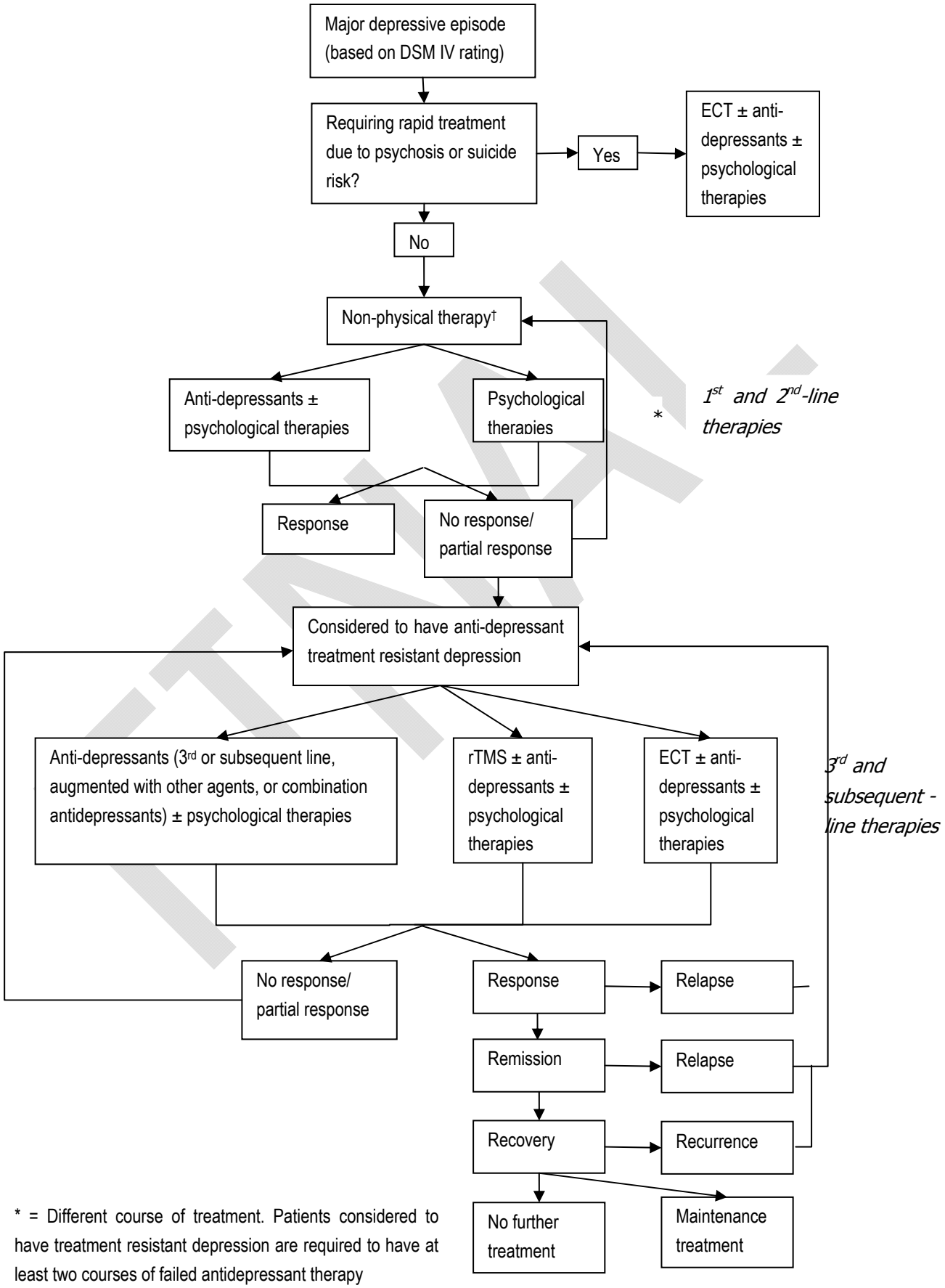
2. Responds but then relapses, with requiring retreatment; or

3. Responds and recovers, with no retreatment required (although maintenance treatment may be used).

The submission of evidence should provide information on how many cycles of rTMS would be contemplated if the patient responds, but then relapses.

[2] Royal Australian and New Zealand College of Psychiatrists, public consultation submission

Figure 1 Management algorithm for patients with major depression



* = Different course of treatment. Patients considered to have treatment resistant depression are required to have at least two courses of failed antidepressant therapy

† Physical therapies = ECT and rTMS

Comparator

There are two comparators being considered for rTMS, which may also be used in combination with each other, and/or in addition to psychological therapies:

- Antidepressants and
- Electroconvulsive therapy (ECT)

The current application proposed that rTMS would be used in addition to, or as a replacement for, being switched to a third-line antidepressant, or continued antidepressant medication augmented with another agent such as lithium, thyroid hormones, pindolol, psychostimulants, atypical antipsychotics, sex hormones, anticonvulsants/mood stabilizers, and dopamine agonists. These medication augmentations are not antidepressants, but may assist the effectiveness of antidepressant medication (Al-Harbi 2012). Another option is combination antidepressant therapies (adding one antidepressant to another antidepressant). Antidepressant medications are prescribed by psychiatrists and general practitioners. Those listed on the PBS are outlined in Table 1, on page 10. Antidepressants may be used either with or without concurrent psychological therapies.

Psychological therapies are commonly used in the treatment of depression, and may be used after antidepressant medication failure (McPherson et al. 2005). They are also increasingly being seen as being useful in augmenting antidepressant medication, and may be used to try to prevent relapse/recurrence of depression (McPherson et al. 2005). The types of psychological therapies funded on the MBS are listed on page 10. For moderate to severe depression, the Royal Australian and New Zealand College of Psychiatrists recommend in their clinical practice guidelines that CBT or interpersonal psychotherapy (IPT) are equally effective (Ellis 2004).

ECT is considered either for patients requiring a rapid and definitive response (because of psychosis or suicide risk) or for those patients who do not respond to antidepressant medication, and meet the criteria for antidepressant treatment resistance. It is considered the main established treatment for treatment-resistant depression (Fitzgerald 2012), with expert advice to PASC indicating superiority in terms of treatment response and timeliness of effect in patients who suffer from severe depression and better outcomes in older patients. Therefore, when rTMS assessed by MSAC in 2007, it was proposed as a replacement for electroconvulsive therapy (ECT) (Cameron & Pekarsky 2007). The MBS items for ECT are shown in Table 4. In the current application, the Applicants stated that in their experience, rates of ECT have not decreased with the introduction of rTMS, and suggested that therefore ECT should not a comparator. However, PASC considered that there would likely be some patients with treatment-resistant depression who would try rTMS as an alternative to ECT, and thus, ECT should also be considered a comparator.

Table 4: MBS item descriptor for electroconvulsive therapy

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: $ 69.05 Benefit: 75% = $51.80 85% = $58.70
MBS 20104 INITIATION OF MANAGEMENT OF ANAESTHESIA for electroconvulsive therapy (4 basic units) Fee: $77.80 Benefit: 75% = $58.35 85% = $66.15

Outcomes for safety and effectiveness evaluation

The health outcomes, upon which the comparative clinical performance of rTMS ± antidepressant medication ± psychological therapy will be measured versus the comparators of antidepressant medication (by itself, augmented antidepressants, or combined antidepressants) ± psychological therapy, and ECT ± antidepressant medication, are:

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 early discontinuation, rate of hospital admission

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 (Berk & Parker 2009).

Summary of PICO to be used for assessment of evidence (systematic review)

Table 5 provides a summary of the PICO used to:

(1) define the question for public funding,

(2) select the evidence to assess the safety and effectiveness of rTMS for treating major depression in treatment-resistant patients, and

(3) provide the evidence-based inputs for any decision-analytical modelling to determine the cost-effectiveness of rTMS for treating major depression in treatment-resistant patients.

Table 5 Summary of PICO to define research questions that assessment will investigate

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	<u>Safety</u> 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. <u>Effectiveness</u> 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 <u>Cost-effectiveness</u> Cost, cost per relevant health outcome (eg LYG, QALY)
<u>Questions</u> 1. Is rTMS ± antidepressant medication ± psychological therapy as safe, effective and cost-effective as antidepressant medication ± psychological therapy, or ECT ± antidepressant medication?			

LYG = life-year gained; QALY = quality adjusted life-year.

Clinical claim

The primary comparator is envisaged to be antidepressant medication with/without concurrent psychological therapy. The Royal Australian and New Zealand College of Psychiatrists state that their experience, along with a large multinational trial (Lisanby et al. 2009) and two meta-analyses (Schutter 2009; Slotema et al. 2010) demonstrates that rTMS has an effect size similar to that of antidepressants, without the side effects associated with

antidepressants. They claim that rTMS is suitable for patients who fail to respond to antidepressant medication, who cannot tolerate the side effects of mediation or refuse to take medication. The Applicants state that rTMS has been shown to be cost effective in treatment resistant depression, compared with switching of antidepressant medication, with benefits in resumption of work and reduction of medical costs resulting in social and economic benefits (Simpson et al. 2009).

It is therefore expected that the submission of evidence would show non-inferior efficacy and superior safety of rTMS ± antidepressant medication versus antidepressant medication alone, in patients with treatment resistant major depression. As shown in the highlighted box in Table 6, a cost-effectiveness analysis or a cost-utility analysis would therefore be required.

The Applicants have not made any claim regarding the comparative effectiveness or safety of treatment with rTMS against treatment with ECT.

The submission of evidence will be required to estimate the proportion of patients likely to receive all the different treatment combination options.

Table 6: Classification of rTMS versus antidepressant medication for determination of economic evaluation to be presented

<table>
<tr><td colspan="2" rowspan="2"></td><td colspan="5">Comparative effectiveness versus comparator</td></tr>
<tr><td colspan="2">Superior</td><td>Non-inferior</td><td colspan="2">Inferior</td></tr>
<tr><td rowspan="6">Comparative safety versus comparator</td><td rowspan="3">Superior</td><td colspan="2" rowspan="3">CEA/CUA</td><td rowspan="3">CEA/CUA</td><td>Net clinical benefit</td><td>CEA/CUA</td></tr>
<tr><td>Neutral benefit</td><td>CEA/CUA*</td></tr>
<tr><td>Net harms</td><td>None^</td></tr>
<tr><td>Non-inferior</td><td colspan="2">CEA/CUA</td><td>CEA/CUA*</td><td colspan="2">None^</td></tr>
<tr><td rowspan="3">Inferior</td><td>Net clinical benefit</td><td>CEA/CUA</td><td rowspan="3">None^</td><td colspan="2" rowspan="3">None^</td></tr>
<tr><td>Neutral benefit</td><td>CEA/CUA*</td></tr>
<tr><td>Net harms</td><td>None^</td></tr>
</table>

Abbreviations: CEA = cost-effectiveness analysis; CUA = cost-utility analysis

* May be reduced to cost-minimisation analysis. Cost-minimisation analysis should only be presented when the proposed service has been indisputably demonstrated to be no worse than its main comparator(s) in terms of both effectiveness and safety, so the difference between the service and the appropriate comparator can be reduced to a comparison of costs. In most cases, there will be some uncertainty around such a conclusion (i.e., the conclusion is often not indisputable). Therefore, when an assessment concludes that an intervention was no worse than a comparator, an assessment of the uncertainty around this conclusion should be provided by presentation of cost-effectiveness and/or cost-utility analyses.

^ No economic evaluation needs to be presented; MSAC is unlikely to recommend government subsidy of this intervention

Outcomes and health care resources affected by introduction of proposed intervention

Outcomes for economic evaluation

The Applicants claim that rTMS is equally effective to antidepressant medications, with fewer side effects. It is expected that quality of life would therefore be improved by rTMS, and the appropriate outcome for economic evaluation would be quality-adjusted life-years gained. PASC suggest that the outcomes for the decision analytic should include response, remission, recovery and relapse, and should evaluate depression free days (i.e. time spent in remission and recovery states), as well as time to events (such as relapse or recurrence) for alternative interventions over a long period of time.

Response is defined as a significant (50% or greater) reduction in symptoms from baseline. Remission is a period where patients are symptom-free, or have minimal symptoms. Recovery is defined as at least 6 months without symptoms. Relapse is defined as a flare up of the depressive episode, which occurs after remission. Lastly, recurrence is a new depressive episode which occurs after recovery (Haji Ali Afzali, Karnon & Gray 2012).

Health care resources

A list of healthcare resources which will need to be incorporated into the economic evaluation are shown in Table 7. The economic evaluation will need to incorporate the costs associated with third-line treatment (i.e. rTMS ± psychotherapy ± antidepressants versus the comparative treatments), treatment for any side effects, as well as subsequent treatments as required due to lack of response, relapse or recurrence.

Table 7: List of resources to be considered in the economic analysis

	Provider of resource	Setting in which resource is provided	Proportion of patients receiving resource	Number of units of resource per relevant time horizon per patient receiving resource	Disaggregated unit cost					
					MBS	Safety nets*	Other govt budget	Private health insurer	Patient	Total cost
Resources provided to identify eligible population for rTMS										
- Psychiatric risk assessment	Psychiatrist	Outpatient	100%	1	$312.90					$312.90
Resources provided to deliver rTMS										
- Delivery of rTMS (setting up, monitoring treatment, remove coils – 1 hour)	Allied health professional or nurse	Outpatient	100%	20	$81					$1620
- Consumables/	Facility	Outpatient	100%	20	$38					$760

	Provider of resource	Setting in which resource is provided	Proportion of patients receiving resource	Number of units of resource per relevant time horizon per patient receiving resource	Disaggregated unit cost					
					MBS	Safety nets*	Other govt budget	Private health insurer	Patient	Total cost
miscellaneous										
- Capital equipment	Facility	Outpatient	100%	20	$14					$280
- Indirect costs (overhead facility costs)	Facility	Outpatient	100%	20	$17					$340
Resources provided in association with rTMS										
- Follow-up	Psychiatrist	Outpatient	100%							
- Repeat rTMS	Allied health professional or nurse	Outpatient	20% within 2 years	20						
- Maintenance rTMS	Allied health professional or nurse	Outpatient	10%	26 per annum						
Resources provided in the event of adverse event after proposed intervention (e.g. a seizure)										
- Hospital stay	Hospital	Inpatient	<2%							
Resources provided to identify eligible population for switched or augmented or combined antidepressants										
- Psychiatric consultation	Psychiatrist	Outpatient	TBD	1						
- General Practitioner consultation	General Practitioner	Outpatient	TBD	1						
Resources provided to deliver switched or augmented or combined antidepressants										
- Antidepressant	Pharmacist	Outpatient	100%							
- Augmentation	Pharmacist	Outpatient	TBD							
Resources provided in association with switched or augmented or combined antidepressants (e.g, resources used to monitor or in follow-up, resources used in management of adverse events, resources used for treatment of down-stream conditions)										
- Psychiatric consultation	Psychiatrist	Outpatient	TBD	1						
- General Practitioner consultation	General Practitioner	Outpatient	TBD	1						
Resources provided to identify eligible population for psychotherapy										
- GP Mental Health Treatment Plan	General Practitioner	Outpatient	100%	1	$69 - $129					$69 - $129
Resources provided in association with psychotherapy										
- General Practitioner consultation	General practitioner	Outpatient	TBD	≤10 per year						
- Psychologist consultation	Psychologist	Outpatient	TBD	≤10 per year						
Resources provided to identify eligible population for ECT										
- Psychiatric risk assessment	Psychiatrist	Outpatient	100%	1	$312.90					$312.90
Resources provided to deliver ECT										
- ECT delivery	Psychiatrist	Inpatient	100%	10	$69					
- Anaesthesia	Anaesthetist	Inpatient	100%	10	$78					

	Provider of resource	Setting in which resource is provided	Proportion of patients receiving resource	Number of units of resource per relevant time horizon per patient receiving resource	Disaggregated unit cost					
					MBS	Safety nets*	Other govt budget	Private health insurer	Patient	Total cost
- Hospital accommodation	Hospital		TBD							

* Include costs relating to both the standard and extended safety net; TBD=to be determined

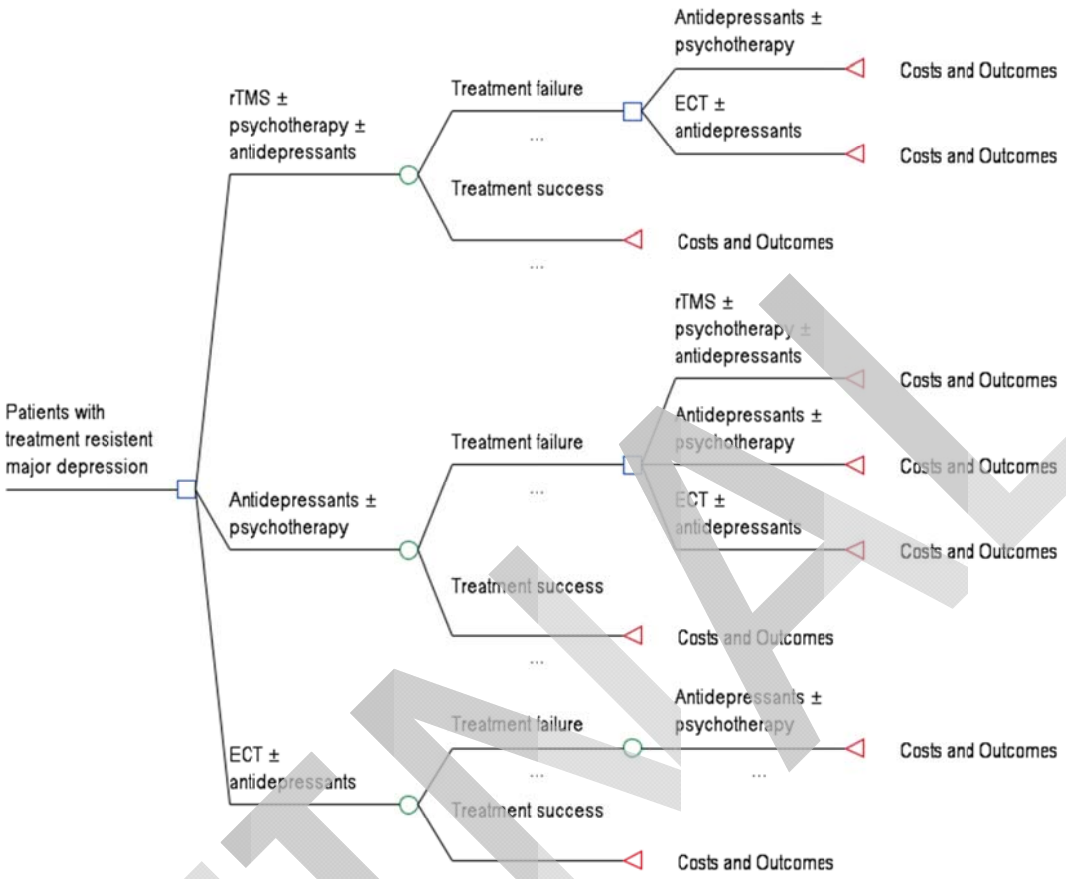
Proposed structure of economic evaluation (decision-analytic)

A draft decision analytic is shown in Figure 2, which incorporates the treatment choices and potential outcomes for patients with treatment-resistant major depression (excluding those who are psychotic and suicidal, as these patients would not be considered for rTMS).

It is proposed that the time period would be at least two years, to enable the economic analyses to incorporate the rate of retreatment with rTMS, or other alternative fourth or fifth-line treatments, plus the rates of relapse and recurrence. The economic evaluation should incorporate depression free days (i.e. time spent in remission and recovery states) as well as time to events (such as relapse or recurrence).

Treatment success can be defined as remission and recovery. Treatment failure (which requires a change in treatment plan) can be defined as no or partial response, relapse, recurrence or an unacceptable side effect profile.

It is assumed that the majority of patients would be receiving maintenance therapy (either antidepressants, psychotherapy, rTMS or some combination of these) for at least 2 years after acute treatment.


Patients with treatment resistent major depression
rTMS ± psychotherapy ± antidepressants
Antidepressants ± psychotherapy
ECT ± antidepressants
Treatment failure
Treatment success
Antidepressants ± psychotherapy
ECT ± antidepressants
Costs and Outcomes
rTMS ± psychotherapy ± antidepressants
Antidepressants ± psychotherapy
ECT ± antidepressants
Costs and Outcomes

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