NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Interventional Procedures Programme

Procedure Name:	**Transcranial magnetic stimulation for severe depression (346/2)**
Name of Specialist Advisor:	**Dr Andrea Malizia**
Specialist Society:	**Royal College of Psychiatrists**
Please complete and return to:	azeem.madari@nice.org.uk OR sally.compton@nice.org.uk

1 Do you have adequate knowledge of this procedure to provide advice?

Yes.

1.1 Does the title used above describe the procedure adequately?

No. If no, please enter any other titles below.

Comments:

There is no need to invoke severe depression (as defined by exceeding a specific score on a major depression rating scale_ in the title. The appropriate title should be: Transcranial magnetic stimulation for major depressive disorder and you may also wish to insert the word repetitive before TMS as this is a more accurate description

2 Your involvement in the procedure

2.1 Is this procedure relevant to your specialty?

Yes.

Is there any kind of inter-specialty controversy over the procedure? NO
Comments:

The next two questions are about whether you carry out the procedure, or refer patients for it. If you are in a specialty that normally carries out the procedure

please answer question 2.2.1. If you are in a specialty that normally selects or refers patients for the procedure please answer question 2.2.2.

2.2.1 If you are in a specialty which does this procedure, please indicate your experience with it:

I have never performed this procedure.

Comments:

The current level of evidence and the fact that TMS is only available privately or as part of a research study means that I am unlikely to select it as a routine tool in patients whom I see regularly in the NHS. Currently it would be very difficult to put together a business case to purchase the necessary equipment in the NHS and to fund the required expertise to carry TMS routinely

2.2.2 If your specialty is involved in patient selection or referral to another specialty for this procedure, please indicate your experience with it.

I have taken part in patient selection or referred a patient for this procedure at least once.

Comments:

2.3 Please indicate your research experience relating to this procedure (please choose one or more if relevant):

I have undertaken bibliographic research on this procedure.

3 Status of the procedure

3.1 Which of the following best describes the procedure (choose one):

Definitely novel and of uncertain safety and efficacy.

Comments:

There is a large body of literature on this procedure but it has been often carried out in groups of patients who could be treated with other well researched methods. In comparisons with ECT, it is much less effective although the numbers on which this knowledge is based is very low

3.2 What would be the comparator (standard practice) to this procedure?

Medication. Note that it is almost impossible to truly blind the procedure unless unsubstantiated assumptions are made

3.3 Please estimate the proportion of doctors in your specialty who are performing this procedure (choose one):

Far fewer than 10% of specialists engaged in this area of work. Virtually none

Comments:

There are no TMS machines available in Psychiatry in the NHS and there is little knowledge and no training

4 Safety and efficacy

4.1 What are the adverse effects of the procedure?

Please list adverse events and major risks (even if uncommon) and, if possible, estimate their incidence, as follows:

1. Theoretical adverse events

TMS is generally safe bu there is rare and mostly theoretical rik of inducing seizures

2. Anecdotal adverse events (known from experience)

Main risks are of pain and discomfort and unpleasant twitching in masseter and neck muscles. Headaches, mild confusion, problems with concentration and working memory and hearing loss are all transient.

3. Adverse events reported in the literature (if possible please cite literature)

As above

4.2 What are the key efficacy outcomes for this procedure?

Symptomatic improvement in symptoms of major depressive disorder

4.3 Are there uncertainties or concerns about the *efficacy* of this procedure? If so, what are they?

The difficulty in effective blinding and in a true placebo administration mean that efficacy studies carried out so far are unreliable

4.4 What training and facilities are required to undertake this procedure safely?

Training in administering TMS is relatively quick and straight forward if a machine is available

4.5 Are there any major trials or registries of this procedure currently in progress? If so, please list.

Current trials are mostly focused on evolutions in the way to administer TMS eg synchronised or multi coil.

4.6 Are you aware of any abstracts that have been *recently* presented/ published on this procedure that may not be listed in a standard literature search, e.g. PUBMED? (This can include your own work). If yes, please list.

Yes. There are too many to list and new work constantly coming up. Review of conference abstracts at Psychiatry and Psychopharmacology conferences will bring them up

4.7 Is there controversy, or important uncertainty, about any aspect of the way in which this procedure is currently being done or disseminated?

I am concerned that it is offered privately at vast cost to people who are very ill and would do a lot better trying ECT

5 Audit Criteria

Please suggest a minimum dataset of criteria by which this procedure could be audited.

5.1 Outcome measures of benefit (including commonly used clinical outcomes – both short and long-term; and quality of life measures):

Montgomery and Asberg Depression rating scale
Global assessment of function
Any instrument that can return QALYs

5.2 Adverse outcomes (including potential early and late complications):

Apart from above side effects a key parameter would be the peed of return of symptoms without concomitant medication changes

6 Trajectory of the procedure

6.1 In your opinion, what is the likely speed of diffusion of this procedure?

If the above issues were resolved and the evidence was good enough to recommend its use in primary care a choice after failure of initial treatment, its speed of diffusion would only be limited by purchase and training. The appropriate comparison to set up experimentally would be use of TMS by a practice nurse versus involvement of primary liaison care workers (from secondary care).

6.2 This procedure, if safe and efficacious, is likely to be carried out in (choose one):

Cannot predict at present.

Comments:

My view is that this procedure could be carried out in primary care or treatment centres if there was enough evidence to support its use and economic effectiveness. However economic effectiveness would have to be assessed against global rather than health care costs as major depressive disorder has it largest impact on benefit expenditure, loss of state revenue (tax) and loss of economic productivity.

6.3 The potential impact of this procedure on the NHS, in terms of numbers of patients eligible for treatment and use of resources, is:

☐ Major.

Comments:

Even if its economic effectiveness was limited to its use in secondary care its impact could be major

7 Other information

7.1 Is there any other information about this procedure that might assist NICE in assessing the possible need to investigate its use?

Choices of treatments in persistent major depressive disorders are limited and often not offered even when economic effectiveness has been determined because of patient choice, potential side effects and clinician prejudice (e.g. second generation antipsychotics, lithium and electroconvulsive therapy). So if TMS was found to be effective in a real world setting it would be a valuable and desirable addition because of it general acceptability in terms of side effect profile.

8 Data protection and conflicts of interest

8.1 Data protection statement

The Institute is committed to transparency. As part of this commitment your name and specialist society will be placed in the public domain, in future publications and on our website (www.nice.org.uk) and therefore viewable worldwide. This information may be passed to third parties connected with the work on interventional procedures.

A copy of the completed Specialist Adviser advice will be sent to the Specialist Society who nominated the Specialist Adviser.

Specialist Advisers should be aware that full implementation of the Freedom of Information Act 2000 may oblige us to release Specialist Advice from 2005. The Freedom of Information Act 2000 favours the disclosure of information however requests will be considered on a case by case basis. If information is made available, personal information will be removed in accordance with the Data Protection Act 1998. In light of this please ensure that you have not named or identified individuals in your comments.

8.2 **Declarations of interest by Specialist Advisers advising the NICE Interventional Procedures Advisory Committee**

Please state any potential conflicts of interest, or any involvements in disputes or complaints, relevant to this procedure. Please use the "Conflicts of Interest for Specialist Advisers" policy (attached) as a guide when declaring any conflicts of interest. Specialist Advisers should seek advice if required from the Associate Director – Interventional Procedures.

Do you or a member of your family[1] have a **personal pecuniary** interest? The main examples are as follows:

Consultancies or directorships attracting regular or occasional payments in cash or kind ☐ **NO**

Fee-paid work – any work commissioned by the healthcare industry **– this includes income earned in the course of private practice** ☐ **NO**

Shareholdings – any shareholding, or other beneficial interest, in shares of the healthcare industry ☐ **NO**

Expenses and hospitality – any expenses provided by a healthcare industry company beyond those reasonably required for accommodation, meals and travel to attend meetings and conferences ☐ **NO**

Investments – any funds which include investments in the healthcare industry ☐ **NO**

Do you have a **personal non-pecuniary** interest – eg have you made a public statement about the topic or do you hold an office in a professional organisation or advocacy group with a direct interest in the topic? ☐ **NO**

☐ **NO**

Do you have a **non-personal** interest? The main examples are as follows:

Fellowships endowed by the healthcare industry ☐ **NO**

Support by the healthcare industry or NICE that benefits his/her position or department, eg grants, sponsorship of posts ☐ **NO**

If you have answered YES to any of the above statements please describe the nature of the conflict(s) below.

Comments:

Thank you very much for your help.

Professor Bruce Campbell, Chairman, Interventional Procedures Advisory Committee

Professor Carole Longson, Director, Centre for Health Technology Evaluation.

[1] 'Family members' refers to a spouse or partner living in the same residence as the member or employee, children for whom the member or employee is legally responsible, and adults for whom the member or employee is legally responsible (for example, an adult whose full power of attorney is held by the individual).

February 2010

Conflicts of Interest for Specialist Advisers

1 Declarations of interest by Specialist Advisers advising the NICE Interventional Procedures Advisory Committee

1.1 Any conflicts of interest set out below should be declared on the questionnaire the Specialist Adviser completes for the procedure.

1.2 Specialist Advisers should seek advice if required from the Associate Director – Interventional Procedures.

2 Personal pecuniary interests

2.1 A personal pecuniary interest involves a current personal payment to a Specialist Adviser, which may either relate to the manufacturer or owner of a product or service being evaluated, in which case it is regarded as **'specific'** or to the industry or sector from which the product or service comes, in which case it is regarded as **'non-specific'**. The main examples are as follows.

2.1.1 **Consultancies** – any consultancy, directorship, position in or work for the healthcare industry that attracts regular or occasional payments in cash or kind (this includes both those which have been undertaken in the 12 months preceding the point at which the declaration is made and which are planned but have not taken place).

2.1.2 **Fee-paid work** – any work commissioned by the healthcare industry for which the member is paid in cash or in kind (this includes both those which have been undertaken in the 12 months preceding the point at which the declaration is made and which are planned but have not taken place).

2.1.3 **Shareholdings** – any shareholding, or other beneficial interest, in shares of the healthcare industry that are either held by the individual or for which the individual has legal responsibility (for example, children, or relatives whose full Power of Attorney is held by the individual). This does not include shareholdings through unit trusts, pensions funds, or other similar arrangements where the member has no influence on financial management.

2.1.4 **Expenses and hospitality** – any expenses provided by a healthcare industry company beyond that reasonably required for accommodation, meals and travel to attend meetings and conferences (this includes both those which have been undertaken in the 12 months preceding the point at which the declaration is made and which are planned but have not taken place.

2.1.5 **Investments** – any funds which include investments in the healthcare industry that are held in a portfolio over which individuals have the ability to instruct the fund manager as to the composition of the fund.

2.2 No personal interest exists in the case of:

2.2.1 assets over which individuals have no financial control (for example, wide portfolio unit trusts and occupational pension funds) and where

the fund manager has full discretion as to its composition (for example, the Universities Superannuation Scheme)

2.2.2 accrued pension rights from earlier employment in the healthcare industry.

3 Personal family interest

3.1 This relates to the personal interests of a family member and involves a **current payment** to the family member of the Specialist Adviser. The interest may relate to the manufacturer or owner of a product or service being evaluated, in which case it is regarded as '**specific**', or to the industry or sector from which the product or service comes, in which case it is regarded as '**non-specific**'. The main examples include the following.

3.1.1 Any consultancy, directorship, position in or work for a healthcare industry that attracts regular or occasional payments in cash or in kind.

3.1.2 Any fee-paid work commissioned by a healthcare industry for which the member is paid in cash or in kind.

3.1.3 Any shareholdings, or other beneficial interests, in a healthcare industry which are either held by the family member or for which an individual covered by this Code has legal responsibility (for example, children, or adults whose full Power of Attorney is held by the individual).

3.1.4 Expenses and hospitality provided by a healthcare industry company (except where they are provided to a general class of people such as attendees at an open conference)

3.1.5 Funds which include investments in the healthcare industry that are held in a portfolio over which individuals have the ability to instruct the fund manager as to the composition of the fund.

3.2 No personal family interest exists in the case of:

3.2.1 assets over which individuals have no financial control (for example, wide portfolio unit trusts and occupational pension funds) and where the fund manager has full discretion as to its composition (for example, the Universities Superannuation Scheme)

3.2.2 accrued pension rights from earlier employment in the healthcare industry.

4 Personal non-pecuniary interests

These might include, but are not limited to:

4.1 a clear opinion, reached as the conclusion of a research project, about the clinical and/or cost effectiveness of an intervention under review

4.2 a public statement in which an individual covered by this Code has expressed a clear opinion about the matter under consideration, which could reasonably be interpreted as prejudicial to an objective interpretation of the evidence

4.3 holding office in a professional organisation or advocacy group with a direct interest in the matter under consideration

4.4 other reputational risks in relation to an intervention under review.

5 Non-personal interests

5.1 A non-personal interest involves payment that benefits a department or organisation for which a Specialist Advisor is responsible, but that is not received by the Specialist Advisor personally. This may either relate to the product or service being evaluated, in which case it is regarded as **'specific,'** or to the manufacturer or owner of the product or service, but is unrelated to the matter under consideration, in which case it is regarded as **'non-specific'**. The main examples are as follows.

5.1.1 **Fellowships** – the holding of a fellowship endowed by the healthcare industry.

5.1.2 **Support by the healthcare industry or NICE** – any payment, or other support by the healthcare industry or by NICE that does not convey any pecuniary or material benefit to a member personally but that does benefit his/her position or department. For example:

- a grant from a company for the running of a unit or department for which a Specialist Advisor is responsible
- a grant, fellowship or other payment to sponsor a post or member of staff in the unit for which a Specialist Adviser is responsible. This does not include financial assistance for students
- the commissioning of research or other work by, or advice from, staff who work in a unit for which the specialist advisor is responsible
- one or more contracts with, or grants from, NICE.

5.2 Specialist Advisers are under no obligation to seek out knowledge of work done for, or on behalf of, the healthcare industry within departments for which they are responsible if they would not normally expect to be informed.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Interventional Procedures Programme

Procedure Name:	**Transcranial magnetic stimulation for severe depression (346/2)**
Name of Specialist Advisor:	**Glyn Lewis**
Specialist Society:	**Royal College of Psychiatrists**
Please complete and return to:	azeem.madari@nice.org.uk OR sally.compton@nice.org.uk

1 Do you have adequate knowledge of this procedure to provide advice?

☒ Yes.

☐ No – please return the form/answer no more questions.

1.1 Does the title used above describe the procedure adequately?

☐ Yes.

☒ No. If no, please enter any other titles below.

Comments:

Usually called repetitive transcranial magnetic stimulation. There are also a variety of stimulation parameters and locations that might all affect its effectiveness.

2 Your involvement in the procedure

2.1 Is this procedure relevant to your specialty?

☒ Yes.

☐ Is there any kind of inter-specialty controversy over the procedure?

☒ No. If no, then answer no more questions, but please give any information you can about who is likely to be doing the procedure.

Comments:

The next two questions are about whether you carry out the procedure, or refer patients for it. If you are in a specialty that normally carries out the procedure please answer question 2.2.1. If you are in a specialty that normally selects or refers patients for the procedure please answer question 2.2.2.

2.2.1 If you are in a specialty which does this procedure, please indicate your experience with it:

☒ I have never performed this procedure.

☐ I have performed this procedure at least once.

☐ I perform this procedure regularly.

Comments:

I am currently applying to EME for a randomised trial that will examine the effectiveness of theta burst repetitive TMS in people with treatment resistant depression.

2.2.2 If your specialty is involved in patient selection or referral to another specialty for this procedure, please indicate your experience with it.

☒ I have never taken part in the selection or referral of a patient for this procedure.

☐ I have taken part in patient selection or referred a patient for this procedure at least once.

☐ I take part in patient selection or refer patients for this procedure regularly.

Comments:

2.3 Please indicate your research experience relating to this procedure (please choose one or more if relevant):

☒ I have undertaken bibliographic research on this procedure.

☐ I have undertaken research on this procedure in laboratory settings (e.g. device-related research).

☐ I have undertaken clinical research on this procedure involving patients or healthy volunteers.

☐ I have had no involvement in research on this procedure.

☐ Other (please comment)

Comments:

3 Status of the procedure

3.1 Which of the following best describes the procedure (choose one):

☐ Established practice and no longer new.

☐ A minor variation on an existing procedure, which is unlikely to alter that procedure's safety and efficacy.

☒ Definitely novel and of uncertain safety and efficacy.

☐ The first in a new class of procedure.

Comments:

It has been around for some time but is not routinely used in the NHS.

3.2 What would be the comparator (standard practice) to this procedure?

In RCTs one can compare with sham TMS to take account of any placebo like effects. If it were to be used in the NHS then it would be likely as an adjunctive treatment in people who had not responded to antidepressants.

3.3 Please estimate the proportion of doctors in your specialty who are performing this procedure (choose one):

☐ More than 50% of specialists engaged in this area of work.

☐ 10% to 50% of specialists engaged in this area of work.

☒ Fewer than 10% of specialists engaged in this area of work.

☐ Cannot give an estimate.

Comments:

Just a handful of people use it.

4 Safety and efficacy

4.1 What are the adverse effects of the procedure?

Please list adverse events and major risks (even if uncommon) and, if possible, estimate their incidence, as follows:

1. Theoretical adverse events

2. Anecdotal adverse events (known from experience)

3. Adverse events reported in the literature (if possible please cite literature)

Epileptic seizures. These are fairly rare and there is a literature on their occurrence.

Localised irritation and muscle twitching around the stimulation site is common. Headaches.

4.2 What are the key efficacy outcomes for this procedure?

Depressive symptoms and health related quality of life.

4.3 Are there uncertainties or concerns about the *efficacy* of this procedure? If so, what are they?

There are some fairly well conducted randomised clinical trials of the procedure. On balance they support its effectiveness but the effect size is modest. None have been carried out in the UK and the follow up period is short (maximum 6 weeks).

4.4 What training and facilities are required to undertake this procedure safely?

Administering is not difficult to teach. Because of the risk of a seizure it probably needs to be given somewhere where a nurse is available to help if this occurs. The equipment is not mobile and quite heavy and currently expensive so the patient would have to come to an outpatient clinic or equivalent.

4.5 Are there any major trials or registries of this procedure currently in progress? If so, please list.

I am not aware of anyone doing a trial of active vs sham TMS for depression.

4.6 Are you aware of any abstracts that have been *recently* presented/ published on this procedure that may not be listed in a standard literature search, e.g. PUBMED? (This can include your own work). If yes, please list.

No. There is a group in Nottingham that are carrying out research on TMS.

4.7 Is there controversy, or important uncertainty, about any aspect of the way in which this procedure is currently being done or disseminated?

It is quite onerous for the patient. The current protocol is 37 mins rTMS, 5 days a week for 4 weeks.

5 Audit Criteria

Please suggest a minimum dataset of criteria by which this procedure could be audited.

5.1 Outcome measures of benefit (including commonly used clinical outcomes – both short and long-term; and quality of life measures):

I would use a depression symptom measure such as PHQ9 or Beck Depression Inventory.

Standard health related QoL measures such as SF36 would be useful.

5.2 Adverse outcomes (including potential early and late complications):

I am not sure of any standardised questions on this so would probably have to devise a bespoke questionnaire. It is possible the research studies have devised a useful set of questions.

6 Trajectory of the procedure

6.1 In your opinion, what is the likely speed of diffusion of this procedure?

If recommended, it could be easily implemented but would require NHS Trusts to set up dedicated facilities for its use. Also the acceptability to patients of having to attend regularly for 4 weeks might reduce the speed of adoption.

6.2 This procedure, if safe and efficacious, is likely to be carried out in (choose one):

☒ Most or all district general hospitals.

☐ A minority of hospitals, but at least 10 in the UK.

☐ Fewer than 10 specialist centres in the UK.

☐ Cannot predict at present.

Comments:

Treatment refractory depression is very common so it would need to be made available in a lot of centres if possible.

6.3 The potential impact of this procedure on the NHS, in terms of numbers of patients eligible for treatment and use of resources, is:

☐ Major.

☒ Moderate.

☐ Minor.

Comments:

Because it is such a common condition.

7 Other information

7.1 Is there any other information about this procedure that might assist NICE in assessing the possible need to investigate its use?

There is research investigating whether the stimulation parameters can be modified in order to shorten the treatment. There is now one smallish trial that suggests that theta burst stimulation (that only takes 2-3 mins per session) is effective. My own application to EME is planning to use theta burst as we think this will be much more acceptable to patients and more likely to be adopted if effective.

Your clinical question is about severe depression but the participants in the existing trial have not been particularly severe. It could have a place in treating relatively mild depression and in some cases might be preferred to medication (eg in pregnancy) because there is no systemic use of a medication. I think the question should be broadened from just severe depression.

8 Data protection and conflicts of interest

8.1 Data protection statement

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Do you or a member of your family[1] have a **personal pecuniary** interest? The main examples are as follows:

Consultancies or directorships attracting regular or occasional payments in cash or kind	☐	**YES**
	☒	**NO**
Fee-paid work – any work commissioned by the healthcare industry **– this includes income earned in the course of private practice**	☐	**YES**
	☒	**NO**
Shareholdings – any shareholding, or other beneficial interest, in shares of the healthcare industry	☐	**YES**
	☒	**NO**
Expenses and hospitality – any expenses provided by a healthcare industry company beyond those reasonably required for accommodation, meals and travel to attend meetings and conferences	☐	**YES**
	☒	**NO**
Investments – any funds which include investments in the healthcare industry	☐	**YES**
	☒	**NO**
Do you have a **personal non-pecuniary** interest – eg have you made a public statement about the topic or do you hold an office in a professional organisation or advocacy group with a direct interest in the topic?	☐	**YES**
	☒	**NO**

Do you have a **non-personal** interest? The main examples are as follows:

Fellowships endowed by the healthcare industry	☐	**YES**
	☒	**NO**
Support by the healthcare industry or NICE that benefits his/her position or department, eg grants, sponsorship of posts	☐	**YES**
	☒	**NO**

If you have answered YES to any of the above statements please describe the nature of the conflict(s) below.

Comments:

I have an application to EME to fund a TMS trial of depression. This has not been funded at present but if successful I would have to say "yes" to the last box.

[1] 'Family members' refers to a spouse or partner living in the same residence as the member or employee, children for whom the member or employee is legally responsible, and adults for whom the member or employee is legally responsible (for example, an adult whose full power of attorney is held by the individual).

Thank you very much for your help.

Professor Bruce Campbell, Chairman, Interventional Procedures Advisory Committee

Professor Carole Longson, Director, Centre for Health Technology Evaluation.

February 2010

Conflicts of Interest for Specialist Advisers

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2.1.1 **Consultancies** – any consultancy, directorship, position in or work for the healthcare industry that attracts regular or occasional payments in cash or kind (this includes both those which have been undertaken in the 12 months preceding the point at which the declaration is made and which are planned but have not taken place).

2.1.2 **Fee-paid work** – any work commissioned by the healthcare industry for which the member is paid in cash or in kind (this includes both those which have been undertaken in the 12 months preceding the point at which the declaration is made and which are planned but have not taken place).

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2.1.5 **Investments** – any funds which include investments in the healthcare industry that are held in a portfolio over which individuals have the ability to instruct the fund manager as to the composition of the fund.

2.2 No personal interest exists in the case of:

2.2.1 assets over which individuals have no financial control (for example, wide portfolio unit trusts and occupational pension funds) and where

the fund manager has full discretion as to its composition (for example, the Universities Superannuation Scheme)

2.2.2 accrued pension rights from earlier employment in the healthcare industry.

3 Personal family interest

3.1 This relates to the personal interests of a family member and involves a **current payment** to the family member of the Specialist Adviser. The interest may relate to the manufacturer or owner of a product or service being evaluated, in which case it is regarded as '**specific**', or to the industry or sector from which the product or service comes, in which case it is regarded as '**non-specific**'. The main examples include the following.

3.1.1 Any consultancy, directorship, position in or work for a healthcare industry that attracts regular or occasional payments in cash or in kind.

3.1.2 Any fee-paid work commissioned by a healthcare industry for which the member is paid in cash or in kind.

3.1.3 Any shareholdings, or other beneficial interests, in a healthcare industry which are either held by the family member or for which an individual covered by this Code has legal responsibility (for example, children, or adults whose full Power of Attorney is held by the individual).

3.1.4 Expenses and hospitality provided by a healthcare industry company (except where they are provided to a general class of people such as attendees at an open conference)

3.1.5 Funds which include investments in the healthcare industry that are held in a portfolio over which individuals have the ability to instruct the fund manager as to the composition of the fund.

3.2 No personal family interest exists in the case of:

3.2.1 assets over which individuals have no financial control (for example, wide portfolio unit trusts and occupational pension funds) and where the fund manager has full discretion as to its composition (for example, the Universities Superannuation Scheme)

3.2.2 accrued pension rights from earlier employment in the healthcare industry.

4 Personal non-pecuniary interests

These might include, but are not limited to:

4.1 a clear opinion, reached as the conclusion of a research project, about the clinical and/or cost effectiveness of an intervention under review

4.2 a public statement in which an individual covered by this Code has expressed a clear opinion about the matter under consideration, which could reasonably be interpreted as prejudicial to an objective interpretation of the evidence

4.3 holding office in a professional organisation or advocacy group with a direct interest in the matter under consideration

4.4 other reputational risks in relation to an intervention under review.

5 Non-personal interests

5.1 A non-personal interest involves payment that benefits a department or organisation for which a Specialist Advisor is responsible, but that is not received by the Specialist Advisor personally. This may either relate to the product or service being evaluated, in which case it is regarded as **'specific,'** or to the manufacturer or owner of the product or service, but is unrelated to the matter under consideration, in which case it is regarded as **'non-specific'**. The main examples are as follows.

5.1.1 **Fellowships** – the holding of a fellowship endowed by the healthcare industry.

5.1.2 **Support by the healthcare industry or NICE** – any payment, or other support by the healthcare industry or by NICE that does not convey any pecuniary or material benefit to a member personally but that does benefit his/her position or department. For example:

- a grant from a company for the running of a unit or department for which a Specialist Advisor is responsible
- a grant, fellowship or other payment to sponsor a post or member of staff in the unit for which a Specialist Adviser is responsible. This does not include financial assistance for students
- the commissioning of research or other work by, or advice from, staff who work in a unit for which the specialist advisor is responsible
- one or more contracts with, or grants from, NICE.

5.2 Specialist Advisers are under no obligation to seek out knowledge of work done for, or on behalf of, the healthcare industry within departments for which they are responsible if they would not normally expect to be informed.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Interventional Procedures Programme

Procedure Name:	**Transcranial magnetic stimulation for severe depression (346/2)**
Name of Specialist Advisor:	**Dr Rafael Euba**
Specialist Society:	**Royal College of Psychiatrists**
Please complete and return to:	azeem.madari@nice.org.uk OR sally.compton@nice.org.uk

1 Do you have adequate knowledge of this procedure to provide advice?

Yes.

1.1 Does the title used above describe the procedure adequately?

No (in my view)

Comments:

I believe "Transcranial magnetic stimulation for treatment-resistant depression" would be more relevant, as this is what rTMS is currently licensed for.

Your involvement in the procedure

1.2 Is this procedure relevant to your specialty?

Yes.

Is there any kind of inter-specialty controversy over the procedure?: No

Comments:

The next two questions are about whether you carry out the procedure, or refer patients for it. If you are in a specialty that normally carries out the procedure please answer question 2.2.1. If you are in a specialty that normally selects or refers patients for the procedure please answer question 2.2.2.

2.2.1 If you are in a specialty which does this procedure, please indicate your experience with it:

I perform this procedure regularly.

Comments:

I treat depressed patients with rTMS every week. I have been offering this treatment to my patients since 2012. We have treated over 100 patients so far.

2.2.2 If your specialty is involved in patient selection or referral to another specialty for this procedure, please indicate your experience with it.

I take part in patient selection or refer patients for this procedure regularly.

Comments:
I actually treat the patients with this procedure myself and also receive referrals from fellow psychiatrists, who have selected patients for this procedure.

1.3 **Please indicate your research experience relating to this procedure (please choose one or more if relevant):**

I have undertaken clinical research on this procedure involving patients or healthy volunteers.

Comments:
I have authored a naturalistic study, to be published in May this year, on the clinical outcomes of a set of depressed patients treated with rTMS.

2 Status of the procedure

2.1 **Which of the following best describes the procedure (choose one):**

Established practice and no longer new.

Comments:

The first reports on transcranial magnetic stimulation in connection with the treatment of major depressive disorders began to emerge in late 1995 [1]. A number of randomised placebo-controlled trials have compared real versus sham rTMS. These trials have consistently demonstrated the efficacy of this treatment against major depression. In fact, there have also been a number of meta-analyses of RCTs [2-4] and even meta-reviews of meta-analyses [5-6], all confirming the efficacy of rTMS in treatment-resistant major depression.

A large multi-site randomised placebo-controlled trial, using sham versus real rTMS with 301 medication-free patients, obtained positive results and led to FDA approval of this treatment in 2008 [7]. There are now hundreds of rTMS providers in the US that have been offering this treatment to the public for years, including institutions such as John Hopkins and the Mayo Clinic.

Naturalistic studies on rTMS in "real world" clinical settings have also shown positive results [8-10].

The value of rTMS in the management of treatment-resistant depression has therefore been systematically tested over many years and is now widely accepted.

Approval by the FDA in America and subsequent approval by European Union regulators has allowed a large number of mental health care providers in North America and Europe to offer rTMS to treatment-resistant depression sufferers. rTMS is therefore a well established treatment.

References:

1. George, M. S., Wassermann, E. M., Williams, W. A., Callahan, A., Ketter, T. A., Basser, P., Hallett M., Post, R. M. Daily repetitive transcranial magnetic stimulation (rTMS) improves mood in depression. Neuroreport 6(14), 1853-1856 (1995)

2. Slotema CW, Blom JD, Hoek HW et al. "Should We Expand the Toolbox of Psychiatric Treatment Methods to Include Repetitive Transcranial Magnetic Stimulation (rTMS)?". J Clin Psychiat 71(7), 873–884 (2010).

3. Lefaucheur JP; André-Obadia, N, Antal A et al. Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS). Clin Neurophysiol. In Press (2014).

4. Marangell, LB, Martinez, M, Jurdi RA et al. "Neurostimulation therapies in depression: a review of new modalities". Acta Psychiat Scand 116(3), 174–181 (2007).

5. Dell'Osso B. Meta-Review of Metanalytic Studies with Repetitive Transcranial Magnetic Stimulation (rTMS) for the Treatment of Major Depression. Clin Pract Epidemiol Ment Health 7, 167–177 (2011).

6. Hovington CL, McGirr A, Lepage M et al. Repetitive transcranial magnetic stimulation (rTMS) for treating major depression and schizophrenia: a systematic review of recent meta-analyses. Ann Med. 45(4), 308-21 (2013).

7. O'Reardon JP, Solvason HB, Janicak PG et al. Efficacy and safety of transcranial magnetic stimulation in the acute treatment of major depression: a multisite randomized controlled trial. Biol Psychiatry 62(11), 1208-16 (2007).

8. Carpenter LL, Janicak PG, Aaronson ST et al. Transcranial magnetic stimulation (TMS) for major depression: a multisite, naturalistic, observational study of acute treatment outcomes in clinical practice. Depress Anxiety 29(7), 587–596 (2012). Good quality naturalistic study on the effectiveness of rTMS in clinical settings.

9. Connolly RK, Helmer A, Cristancho MA et al. Effectiveness of transcranial magnetic stimulation in clinical practice post-FDA approval in the United States: results observed with the first 100 consecutive cases of depression at an academic medical center. J Clin Psychiatry 73(4), 567–573 (2012).

10. Euba R., Panihhidina I, Zamar A. Treatment-resistant depression: the experience of the first rTMS Clinic in the UK. Future Neurology. In press.

2.2 **What would be the comparator (standard practice) to this procedure?**

Other antidepressant interventions, such as antidepressant tablets, or ECT. rTMS is licensed for those who have not responded to adequate trials of antidepressant medication, so rTMS is designed for those cases in which antidepressants have already failed.

As far as ECT is concerned, this remains the gold standard of antidepressant treatments [1], but only for very severe and psychotic depressions. It is also very invasive. A recently published study compared rTMS to ECT and concluded that rTMS is as effective as ECT in non-psychotic depression, but unlike ECT, rTMS did not produce any cognitive side-effects [2].

References

1. UK ECT Review Group. Efficacy and safety of electroconvulsive therapy in depressive disorders: a systematic review and meta-analysis. Lancet 2003; 361: 799–808.

2. Ren et al. Repetitive transcranial magnetic stimulation versus electroconvulsive therapy for major depression: A systematic review and meta-analysis. Progress in Neuro-Psychopharmacology & Biological Psychiatry 2014; 181-189.

2.3 **Please estimate the proportion of doctors in your specialty who are performing this procedure (choose one):**

Fewer than 10% of specialists engaged in this area of work.

Comments:
rTMS is very well established in the US and Canada, as well as in certain areas of the European continent, but not in the UK. This is to a large extent due, in my view, to the fact that it is not yet recommended by NICE.

Safety and efficacy

2.4 **What are the adverse effects of the procedure?**

Please list adverse events and major risks (even if uncommon) and, if possible, estimate their incidence, as follows:

1. Theoretical adverse events

An extremely low risk of seizures. By December 2008, only 16 cases had been reported in the literature, after many thousands of patients had been treated worldwide, only 4 of which occurred with rTMS parameters considered safe according to the 1998 safety guidelines. Three of these four instances of seizures occurred in patients taking pro-epileptogenic medications or following sleep-deprivation, and one of the four cases may represent a non-epileptic event [1].

Scalp pain and mild headache occur rarely.

Treatment-emergent mania. The risk is low, and even below natural switch rates in patients with bipolar disorders receiving mood stabilizers [2].

References:

1. Rossi et al (the Safety of TMS Consensus Group). Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. Clin Neurophysiol. 2009 Dec; 120(12): 2008–2039.

2. Xia G, Gajwani P, Muzina DJ, Kemp DE, Gao K, Ganocy SJ, et al. Treatment-emergent mania in unipolar and bipolar depression: focus on repetitive transcranial magnetic stimulation. Int J Neuropsychopharmacol 2008;11:119–30.

2. Anecdotal adverse events (known from experience)

Potential worsening of psychomotor agitation in cases of Mixed Affective Disorders.

3. Adverse events reported in the literature (if possible please cite literature)

Please see above (2.4.1). Also syncope and transient increases in auditory thresholds, both very rare. Patients should be encouraged to wear ear plugs [1, above].

Overall, rTMS is considered a very safe treatment, particularly in comparison with the invasive and potentially toxic alternatives, like ECT, or complex combination pharmacological therapies.

2.5 What are the key efficacy outcomes for this procedure?

Achieving remission in treatment-resistant depression. This will be expressed in terms of absence of significant symptoms of depression or anxiety and improved functioning.

2.6 Are there uncertainties or concerns about the *efficacy* of this procedure? If so, what are they?

I believe there are no significant uncertainties or concerns about the efficacy of this procedure. It is not recommended for psychotic depression.

2.7 What training and facilities are required to undertake this procedure safely?

rTMS can be undertaken in a standard out-patient clinic, as it is not invasive and it does not require sedation or an anaesthetic. The treatment needs to be supervised by a health professional trained in the procedure.

The prescriber, who has an overall supervising role, should be a fully trained psychiatrist who has also undertaken specific training in rTMS. This training should be both theoretical and practical. Training requirements would be comparable in length and complexity to those undertaken by ECT practitioners.

2.8 Are there any major trials or registries of this procedure currently in progress? If so, please list.

I believe that this large Chinese trial is till recruiting:

"Efficacy of repetitive transcranial magnetic stimulation in the prevention of relapse of depression: study protocol for a randomized controlled trial."

2.9 **Are you aware of any abstracts that have been *recently* presented/ published on this procedure that may not be listed in a standard literature search, e.g. PUBMED? (This can include your own work). If yes, please list.**

Our own study is yet to be published in Future Neurology. It is a naturalistic report of the clinical outcomes of rTMS in resistant depression in a "real world" clinical setting, confirming the clinical effectiveness of this treatment, as shown in previous studies:

Euba R, Panihhidina I, Zamar A. Treatment-resistant depression: the experience of the first rTMS Clinic in the UK. Future Neurology. In press.

2.10 **Is there controversy, or important uncertainty, about any aspect of the way in which this procedure is currently being done or disseminated?**

I am not aware of any controversies.

5 Audit Criteria

Please suggest a minimum dataset of criteria by which this procedure could be audited.

5.1 Outcome measures of benefit (including commonly used clinical outcomes – both short and long-term; and quality of life measures):

Remission: This is, in my view, a more clinically significant outcome measure than treatment response (normally defined by a drop of at least 50% in a depression scale), as remission is associated with a much better prognosis. Remission can be detected with a number of depression inventories, such as Beck's (BDI-II) [1], or the Hamilton's depression scale [2]. Improvements in anxiety can also be measured with a rating scale, such as the BAI [3]. Recovery in terms of improved functioning can be measured with the Sheehan Disability Scale [4].

References:

1. Beck AT, Steer RA and Brown GK (1996) "Manual for the Beck Depression Inventory-II". San Antonio, TX: Psychological Corporation

2. Hamilton, M (1980) Rating depressive patients. Journal of Clinical Psychiatry. 41: 21-24 PMID 7440521

3. Beck AT, Steer RA (1993). Beck Anxiety Inventory Manual. San Antonio: Harcourt Brace and Company.

4. Sheehan, D V; Harnett-Sheehan, K; Raj, B A. The measurement of disability. International Clinical Psychopharmacology: Volume 11. June 1996

5.2 Adverse outcomes (including potential early and late complications):

Incidence of adverse effects described above. Percentage of drop-outs in treatment cohorts.

6 Trajectory of the procedure

6.1 In your opinion, what is the likely speed of diffusion of this procedure?

My opinion is that rTMS will spread relatively quickly once NICE approves it and clinicians become more familiar with the treatment as a result.

6.2 This procedure, if safe and efficacious, is likely to be carried out in (choose one):

A minority of hospitals, but at least 10 in the UK.

Comments:

I believe that he diffusion of the treatment will be encouraged by its safety, tolerability and effectiveness. It will remain, however, a specialist treatment, mainly delivered by specialist psychiatric centres.

There is a trend at the moment towards the development of new rTMS modalities, in which the treatment can be delivered in much shorter sessions. This will make it progressively more affordable and more cost-effective.

6.3 The potential impact of this procedure on the NHS, in terms of numbers of patients eligible for treatment and use of resources, is:

Moderate.

Comments:

The potential impact on the NHS would be offset by the effectiveness of rTMS in treatment-resistant depression, a condition that consumes large amounts of very expensive resources and often demands intensive supervision and complex treatment regimes delivered by Community Mental Health Teams, psychotherapists and psychiatrists over prolonged periods of time.

7 Other information

7.1 Is there any other information about this procedure that might assist NICE in assessing the possible need to investigate its use?

rTMS compares very favourably with other interventions in treatment-resistant depression. Sequenced treatments paradigms, like the one described in the STAR*D Study [1], involve complex pharmacological regimes that require far longer treatment periods and carry a very substantial risk of side-effects and patient disengagement.

I am not aware of any direct comparison between rTMS and sequenced pharmacological interventions in treatment-resistant depression in terms of clinical effectiveness, but the outcome figures for rTMS available in the psychiatric literature compare favourably with the pharmacological alternatives.

rTMS is much faster than drugs in treatment-resistant depression. It also constitutes a much more tolerable and acceptable intervention for the sufferer.

Reference:

1. Rush AJ, Trivedi MH, Wisniewski SR et al. Acute and Longer-Term Outcomes in Depressed Outpatients Requiring One or Several Treatment Steps: A STAR*D Report. Am J Psychiatry 163(11), 1905-17 (2006).

8 Data protection and conflicts of interest

8.1 Data protection statement

The Institute is committed to transparency. As part of this commitment your name and specialist society will be placed in the public domain, in future publications and on our website (www.nice.org.uk) and therefore viewable worldwide. This information may be passed to third parties connected with the work on interventional procedures.

A copy of the completed Specialist Adviser advice will be sent to the Specialist Society who nominated the Specialist Adviser.

Specialist Advisers should be aware that full implementation of the Freedom of Information Act 2000 may oblige us to release Specialist Advice from 2005. The Freedom of Information Act 2000 favours the disclosure of information however requests will be considered on a case by case basis. If information is made available, personal information will be removed in accordance with the Data Protection Act 1998. In light of this please ensure that you have not named or identified individuals in your comments.

8.2 Declarations of interest by Specialist Advisers advising the NICE Interventional Procedures Advisory Committee

Please state any potential conflicts of interest, or any involvements in disputes or complaints, relevant to this procedure. Please use the "Conflicts of Interest for Specialist Advisers" policy (attached) as a guide when declaring any conflicts of interest. Specialist Advisers should seek advice if required from the Associate Director – Interventional Procedures.

Do you or a member of your family have a **personal pecuniary** interest? The main examples are as follows:

Consultancies or directorships attracting regular or occasional payments in cash or kind **NO**

Fee-paid work – any work commissioned by the healthcare industry – **this includes income earned in the course of private practice** **YES**

Shareholdings – any shareholding, or other beneficial interest, in shares of the healthcare industry **NO**

Expenses and hospitality – **any expenses provided by a healthcare industry company beyond those reasonably required for accommodation, meals and travel to attend meetings and conferences** **NO**

Investments – **any funds which include investments in the healthcare industry** **NO**

Do you have a personal non-pecuniary interest – **eg have you made a public statement about the topic or do you hold an office in a professional organisation or advocacy group with a direct interest in the topic?** **NO**

I have written on the topic in my capacity as a private rTMS practitioner, already declared above.

Do you have a **non-personal** interest? The main examples are as follows:

Fellowships endowed by the healthcare industry **NO**

Support by the healthcare industry or NICE that benefits his/her position or department, eg grants, sponsorship of posts **NO**

If you have answered YES to any of the above statements please describe the nature of the conflict(s) below.

Comments:

I have been providing rTMS as a private Consultant Psychiatrist in the independent sector since 2012.

Thank you very much for your help.

Professor Bruce Campbell, Chairman, Interventional Procedures Advisory Committee

Professor Carole Longson, Director, Centre for Health Technology Evaluation.

February 2010

Conflicts of Interest for Specialist Advisers

1 **Declarations of interest by Specialist Advisers advising the NICE Interventional Procedures Advisory Committee**

1.1 Any conflicts of interest set out below should be declared on the questionnaire the Specialist Adviser completes for the procedure.

1.2 Specialist Advisers should seek advice if required from the Associate Director – Interventional Procedures.

2 **Personal pecuniary interests**

2.1 A personal pecuniary interest involves a current personal payment to a Specialist Adviser, which may either relate to the manufacturer or owner of a product or service being evaluated, in which case it is regarded as **'specific'** or to the industry or sector from which the product or service comes, in which case it is regarded as **'non-specific'**. The main examples are as follows.

2.1.1 **Consultancies** – any consultancy, directorship, position in or work for the healthcare industry that attracts regular or occasional payments in cash or kind (this includes both those which have been undertaken in the 12 months preceding the point at which the declaration is made and which are planned but have not taken place).

2.1.2 **Fee-paid work** – any work commissioned by the healthcare industry for which the member is paid in cash or in kind (this includes both those which have been undertaken in the 12 months preceding the point at which the declaration is made and which are planned but have not taken place).

2.1.3 **Shareholdings** – any shareholding, or other beneficial interest, in shares of the healthcare industry that are either held by the individual or for which the individual has legal responsibility (for example, children, or relatives whose full Power of Attorney is held by the individual). This does not include shareholdings through unit trusts, pensions funds, or other similar arrangements where the member has no influence on financial management.

2.1.4 Expenses and hospitality – any expenses provided by a healthcare industry company beyond that reasonably required for accommodation, meals and travel to attend meetings and conferences (this includes both those which have been undertaken in the 12 months preceding the point at which the declaration is made and which are planned but have not taken place.

2.1.5 Investments – any funds which include investments in the healthcare industry that are held in a portfolio over which individuals have the ability to instruct the fund manager as to the composition of the fund.

2.2 No personal interest exists in the case of:

2.2.1 **assets over which individuals have no financial control (for example, wide portfolio unit trusts and occupational pension funds) and where the fund manager has full discretion as to its composition (for example, the Universities Superannuation Scheme)**

2.2.2 **accrued pension rights from earlier employment in the healthcare industry.**

3 Personal family interest

3.1 **This relates to the personal interests of a family member and involves a current payment to the family member of the Specialist Adviser. The interest may relate to the manufacturer or owner of a product or service being evaluated, in which case it is regarded as 'specific', or to the industry or sector from which the product or service comes, in which case it is regarded as 'non-specific'. The main examples include the following.**

3.1.1 **Any consultancy, directorship, position in or work for a healthcare industry that attracts regular or occasional payments in cash or in kind.**

3.1.2 **Any fee-paid work commissioned by a healthcare industry for which the member is paid in cash or in kind.**

3.1.3 **Any shareholdings, or other beneficial interests, in a healthcare industry which are either held by the family member or for which an individual covered by this Code has legal responsibility (for example, children, or adults whose full Power of Attorney is held by the individual).**

3.1.4 **Expenses and hospitality provided by a healthcare industry company (except where they are provided to a general class of people such as attendees at an open conference)**

3.1.5 **Funds which include investments in the healthcare industry that are held in a portfolio over which individuals have the ability to instruct the fund manager as to the composition of the fund.**

3.2 **No personal family interest exists in the case of:**

3.2.1 **assets over which individuals have no financial control (for example, wide portfolio unit trusts and occupational pension funds) and where the fund manager has full discretion as to its composition (for example, the Universities Superannuation Scheme)**

3.2.2 **accrued pension rights from earlier employment in the healthcare industry.**

4 Personal non-pecuniary interests

These might include, but are not limited to:

4.1 **a clear opinion, reached as the conclusion of a research project, about the clinical and/or cost effectiveness of an intervention under review**

4.2 **a public statement in which an individual covered by this Code has expressed a clear opinion about the matter under consideration, which could reasonably be interpreted as prejudicial to an objective interpretation of the evidence**

4.3 **holding office in a professional organisation or advocacy group with a direct interest in the matter under consideration**

4.4 **other reputational risks in relation to an intervention under review.**

5 **Non-personal interests**

5.1 A non-personal interest involves payment that benefits a department or organisation for which a Specialist Advisor is responsible, but that is not received by the Specialist Advisor personally. This may either relate to the product or service being evaluated, in which case it is regarded as **'specific,'** or to the manufacturer or owner of the product or service, but is unrelated to the matter under consideration, in which case it is regarded as **'non-specific'**. The main examples are as follows.

5.1.1 **Fellowships** – the holding of a fellowship endowed by the healthcare industry.

5.1.2 **Support by the healthcare industry or NICE** – any payment, or other support by the healthcare industry or by NICE that does not convey any pecuniary or material benefit to a member personally but that does benefit his/her position or department. For example:

- **a grant from a company for the running of a unit or department for which a Specialist Advisor is responsible**
- **a grant, fellowship or other payment to sponsor a post or member of staff in the unit for which a Specialist Adviser is responsible. This does not include financial assistance for students**
- **the commissioning of research or other work by, or advice from, staff who work in a unit for which the specialist advisor is responsible**
- **one or more contracts with, or grants from, NICE.**

5.2 Specialist Advisers are under no obligation to seek out knowledge of work done for, or on behalf of, the healthcare industry within departments for which they are responsible if they would not normally expect to be informed.