**WA HEALTH RESEARCH PROTOCOL**

**TEMPLATE FOR CLINICAL TRIALS**

**GUIDELINES**

This protocol template is provided as a guide for investigators who do not already have a protocol for their research project. It is a requirement of WA Health that a protocol is submitted with the ethics application. This template is based on the Therapeutic Goods Administration (TGA) [“Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95)” 2000.](http://www.tga.gov.au/industry/clinical-trials-note-ich13595.htm) To meet Good Clinical Practice Guidelines the Protocol should contain, but not be restricted to, the information contained within this template.

A clinical trial is a form of human research designed to find out the effects of an intervention, including a treatment or diagnostic procedure. A clinical trial can involve testing a drug, a surgical procedure, other therapeutic procedures and devices, a preventative procedure, or a diagnostic device or procedure.

Some Heath Service Providers provide access to statistical advice for investigators. Contact the relevant Research Governance Office for further advice; contact details are available on the Research Governance Service website.

NB: Further information on clinical trial protocol/study report formats can be found in the ICH Guideline [“Structure and Content of Clinical Study Reports” 1995](http://www.ich.org/products/guidelines/efficacy/efficacy-single/article/structure-and-content-of-clinical-study-reports.html) available on the ICH website.

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| **1. Trial Details** |

* 1. Trial Details.

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| **Protocol/Clinical Trial Title:** | Translation of preclinical findings: the effect of low intensity repetitive Transcranial Magnetic Stimulation (rTMS) on depression score and biomarkers in patients with major depression. | | |
| **Protocol Number (Version and Date):** | V125102018 | | |
| **Amendment**  **(Number and Date):** |  | | |
| **Trial Start Date:** | 01/04/2019 | **Trial Finish Date:** | 01/10/2021 |
| **Coordinating Principal Investigator Name:** | Assoc Professor Jennifer Rodger | | |
| **Coordinating Principal Investigator Contact Details:** | [jennifer.rodger@uwa.edu.au](mailto:jennifer.rodger@uwa.edu.au) | | |
| **Sponsor Name (if applicable):** | Perron Institute for Neurological and Translational Science | | |
| **Laboratory Name (if applicable):** |  | | |

* 1. **Trial Summary (less than 300 words) including background, objectives and trial plan.**

Depression is one of the most prevalent and costly medical conditions worldwide (WHO, 2012). Although antidepressant medication is effective for many patients, up to 40% remain drug-resistant. Non-invasive brain stimulation in the form of repetitive transcranial magnetic stimulation (rTMS) is an FDA-approved treatment for depression in drug resistant patients with response rates of up to 60%. However, outcomes are variable both within and between individuals, suggesting that treatment protocols remain suboptimal. This variability is not surprising because non-invasive brain stimulation techniques were first developed in humans with no systematic “bench-to-bedside” evaluation of protocols, resulting in poorly defined clinical guidelines. Our lab has compared a range of brain stimulation protocols in a preclinical model of treatment resistant depression, and has shown that rTMS delivered at a 50mT intensity (at cortex) matches the behavioural effects obtained with rTMS delivered at 1000mT equivalent to approximately 100% motor threshold (currently used in human patients). However the 50mT protocol has additional benefits: it causes structural changes in the brain, leading to long lasting improvements in mood and cognition. This project will test efficacy of our low intensity protocol (50mT; ~1%MT) as an add-on to the gold standard protocol (100%MT; 1000mT) in a patient cohort (40 participants), using psychiatric assessment to evaluate changes in mood and cognition, and detection of two novel blood biomarkers for predictive ability at the start of the trial, the end of treatment and 6 months following the end of treatment.

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| **2. Rationale / Background** |

* 1. **Summary of findings from previous clinical and non-clinical projects, relevant to this proposed trial. Include references to literature and data that are relevant to the trial and that provide background for the trial. *List references separately at the end of the protocol.***

Depression is one of the most prevalent and costly medical conditions worldwide (WHO, 2012). Although antidepressant medication is effective for many patients, up to 40% remain drug-resistant (Gaynes et al., 2014). Non-invasive brain stimulation in the form of repetitive transcranial magnetic stimulation (rTMS) is an FDA-approved treatment for patients with drug resistant depression with response rates of up to 60% (Gaynes et al., 2014; O’Reardon et al., 2007). However, outcomes are variable both within and between individuals, suggesting that treatment protocols remain suboptimal (Riddingand Ziemann, 2010). This variability is not surprising because non-invasive brain stimulation techniques were developed first in humans with no systematic “bench-to-bedside” evaluation of stimulation parameters (frequency, intensity, duration), resulting in poorly defined clinical guidelines. This lack of knowledge is compounded by the paucity of pre-clinical studies in animal models of depression on which to base evidence-based translational treatments for patients.

To address this knowledge gap, we examined the behavioural and neurobiological changes in a mouse model of treatment resistant depression (olfactory bulbectomy (OB) mice) following 4 weeks of daily (weekday) treatment with rTMS delivered at different intensities (Heath et al., 2018). Behavioural effects were assessed with forced swim test; neurobiological effects were assessed with brain levels of serotonin, brain-derived neurotrophic factor (BDNF), and neurogenesis. Peripheral metabolomic changes in blood serum induced by rTMS were monitored using ultrapressure liquid chromatography–driven targeted metabolomics. Both 150 mT rTMS (50mT at cortex) and 1000 mT rTMS attenuated psychomotor agitation but only 150 mT rTMS increased BDNF and neurogenesis levels. Both treatments normalized the plasma concentration of α-amino-n-butyric acid and 3-methylhistidine.

Our findings suggest that 150 mT rTMS (50mT at cortical surface) that will be tested in the current trial may have advantages over the currently used 100%MT; ~1000mT rTMS by inducing neurobiological changes that support long term stable improvements. Further, α-amino-n butyric acid and 3-methylhistidine may have utility as biomarkers to objectively monitor the response to rTMS treatment of depression (Heath et al., 2018)

* 1. **Name and description of the intervention or product(s) used in this trial, including investigational product(s) and comparator product/s (if applicable). Include status of product registration (i.e. registration on Australian Therapeutic Goods Registry, or equivalent).**

Medical Device Included Class IIa (Magstim super Rapid) using D70mm air film coil currently registered on the Australian Therapeutic goods register ARTG# 225208

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| **3. Trial Aims / Objectives / Hypotheses** |

* 1. **Detailed description of the specific primary and secondary objectives and the purpose of the trial. Describe any hypotheses that will be tested.**

This study will prospectively evaluate the antidepressant efficacy of a new rTMS parameter. Specifically we will translate an rTMS protocol that has been shown in a mouse model of depression to have longer lasting benefits compared to the FDA-approved protocol currently used in humans. Because of ethical considerations, and the need to retain the current clinical protocol, we propose a “head to head trial”, where 150 mT rTMS (50mT at cortex) is delivered as an add-on to the gold standard 100% MT; 1000 mT protocol (where 100% motor threshold is equivalent to ~1000mT). We also test the validity of blood biomarkers, including those identified in our animal studies to, objectively monitor patient response to rTMS treatment.

**Hypotheses**

\*Interleaving 150mT with the gold standard 100% MT (FDA-approved protocol) (delivered daily for 4 weeks) will be as effective at improving mood and cognition in patients with treatment resistant major depressive disorder

\*Interleaving 150mT with the gold standard 1000 mT (FDA-approved protocol) (delivered daily for 4 weeks) will have longer lasting effects compared to rTMS delivered at 1000 mT only.

\*Response to rTMS will be correlated to blood biomarker levels in serum.

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| **4. Trial Design** |

***The scientific integrity of the trial and the credibility of the trial data depend substantially on the trial design and methodology.***

* 1. Primary endpoints and the secondary endpoints, if any, to be measured during the trial and how they will be measured. *For further information refer to the TGA* [“Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95)” 2000.](http://www.tga.gov.au/industry/clinical-trials-note-ich13595.htm)

**Primary end point 1**

Outcome Name: Depression

Metric/method of measurement: The primary endpoint will be the percentage change in HAM-D-21) response (score) defined by a significant change from the initial score on the Hamilton Depression Scale (HAM-D-21)

**Time point:** directly following end of 4 week treatment period

**Secondary endpoint 1**: Number of respondents in remission defined by a HAM-D-21 score of <8 directly following 4 week treatment period and 6 months after;

**Time points:** Baseline, Immediately after end of 4 week rTMS treatment period and 6 months after treatment commencement.

**Secondary endpoint 2:** The change and presence of predictive markers of the therapeutic response: serum biomarkers

**Timepoints:** Baseline, Immediately after end of 4 week rTMS treatment period and 6 months after treatment commencement.

* 1. **Type (e.g. phase, pilot) and design (e.g. double-blind, placebo-controlled, parallel design) of the trial to be conducted and a schematic diagram of the trial design, procedures and stages (e.g. initial assessment, run-in, pre-randomisation assessment, randomisation, treatment phase, end-of-treatment assessment, washout, cross-over, alternative treatment, post-treatment assessments, trial exit).**

Head to head, interventional, randomised controlled trial.

* 1. **Measures taken to minimise/avoid bias, including randomisation and blinding.**

Masking/blinding will be used in this study for the following people

The people receiving the treatment/s

The people assessing the outcomes

The people analysing the results/data

The person doing assessment will be blind to treatment. The assessor is not in the treatment area so does not hear the treatment.

Scheduling will be used so that patients are not aware of the alternate treatment.

* 1. **Maintenance of any blinding records or randomisation codes and procedures for breaking codes.**

Hard copy case report forms will not be identifiable. A separate screening log will link participant identifiers to study numbers. This will be a separate electronic spreadsheet stored on the password protected network.

Codes will be broken only after all participants have completed the 6 month follow up assessment at the end of the study, after all data has been entered into a statistical analysis package.

* 1. **A description of the interventions or investigational product(s). For drug trials information regarding the dosage and dosage regimen, as well as a description of the dosage form, packaging, dispensing and labelling should be included.**

The study will consist of 4 weeks of treatment comprising 20 sessions (weekdays for 4 weeks) of rTMS to the left dorsolateral prefrontal cortex. Each stimulation session will last approximately 30 minutes. rTMS will be administered using a MagStim Super rapid2  with a D70mm air film coil.

The study will consist of 4 weeks of treatment comprising 20 sessions (weekdays for 4 weeks) of rTMS to the left dorsolateral prefrontal cortex. Patients will be randomly assigned to the standard protocol (100%MT; 1000mT) or add-on protocol (standard protocol+50mT) stimulation group.

Standard protocol: patients will receive 40 trains of rTMS at 10Hz at 100%MT equivilent to ~ 1000mT, with an inter-train interval of 30 seconds comprising of a total of 20 sessions (weekdays for 4 weeks)

Experimental protocol: patients will receive alternating trains during the session of standard protocol rTMS (10 trains of rTMS at 10Hz at 100%MT) followed by low intensity 50 mT rTMS (10 trains of rTMS at 10Hz at ~1%MT) with an inter-train interval of 15 seconds repeated till a total of 80 trains of 10Hz stimulation is provided comprising of a total of 20 sessions (weekdays for 4 weeks)

Standard Protocol will be the standard FDA-approved protocol of 40 trains of rTMS at 10Hz at 100%MT (~1000mT), with an inter-train interval of 30 seconds (Gaynes et al., 2014; O’Reardon et al., 2007)

* 1. **Accountability procedures for the investigational product(s) including the placebo(s) and comparator(s) (if applicable).**

Because there is an FDA-approved rTMS protocol for depression (referred to here as the Standard protocol), the control is an active control consisting of the standard protocol.

All patients will receive the standard protocol, ensuring that all patients receive at least the recommended treatment protocol, with the experimental protocol delivered as an add-on. There is no extant evidence, nor theoretical rationale, that the add-on stimuli will adversely affect the standard protocol.

* 1. **Expected duration of the trial and participant participation, including a description of the sequence and duration of all techniques or assessments to be performed, including follow-up (e.g. interventions, procedures, measurements, observations, laboratory investigations). Provide a schedule of assessments in a table if possible.**

It is expected that the trial will take up to two years to complete from first participant enrolment till data analysis is completed.

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| **Technique or assessment** | **Duration** |
| **Baseline assessment** |  |
| Patient interview | 1 hour |
| HAMD-21 | 15 minutes |
| Blood test | 15 minutes |
| **Treatment** |  |
| rTMS treatment \* | 30 minutes per day, week days for 4 weeks |
| Patient interview \* | 1 hour, once a week |
| HAMD-21 \* | 15 minutes, once a week |
| **Post-treatment assessment (immediate)** |  |
| Patient interview \* | 1 hour |
| HAMD-21 \* | 15 minutes |
| Blood test | 15 minutes |
| **Post-treatment assessment (6 months)** |  |
| Patient interview | 1 hour |
| HAMD-21 | 15 minutes |
| Blood test | 15 minutes |

\* Denotes a part of the existing clinical protocol.

* 1. **Criteria for the termination of the trial. Description of the discontinuation criteria for individual participants, parts of the trial and entire trial.**

The trial will be terminated if there are concerns with patient safety, or evidence of unfeasibility of addressing the study hypotheses (e.g., poor patient intake, poor response to the protocol).

* 1. **The identification of any data to be recorded directly on the Case Report Forms (CRFs) (i.e. no prior written or electronic record of data), and to be considered to be source data.**

All data collected as part of the trial will be considered source data.

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| **5. Source and Selection of Participants** |

* 1. **Source of participants - research population, sample size, source, and sampling frame (if possible, split by site if multicentre trial).**

Participants (males and females, 18 years or over) will be recruited from patients diagnosed with Major Depression and referred to the Mental Health Unit at Sir Charles Gairdner Hospital due to non-responding to a previous treatment regime.

The sample size is 40 participants, 20 in each group.

* 1. **Participant inclusion criteria. Describe appropriate criteria for special risk populations (e.g. women of reproductive age, participants with disease states or organ impairment).**

ICD-10-AM diagnosis of major depression. Subsequent depression scale scores will act as a validation check (any discrepancies to be reviewed by PI), but initial inclusion will be purely by clinical diagnosis. Aged above 18 years.

Participants need not meet formal criteria for treatment resistance, but must have shown an unsatisfactory response to a previous treatment regime. The judgement to recommend a participant for this trial is, therefore, explicitly a clinical decision by the recruiting physician. However, we do require that the antidepressant medication regime be stable in type and dosage for 4 weeks prior to the rTMS trial.

* 1. **Participant exclusion criteria; May include conditions that increase the risk to the participant, that interfere with the participant’s ability to give informed consent or interfere with a participant’s ability to comply.**

Presence of cardiac pacemakers, medication pumps, cochlear implants or metal objects in the head or eyes that could be dangerous if heated or moved by the magnetic pulses.   
Significant medical illness, substantial risk of suicide, current psychosis, current substance dependence, a history of seizures, epilepsy, stroke or major head trauma, or a history of alcohol dependence.

* 1. **Participant withdrawal criteria (i.e. terminating investigational product/trial treatment) and procedures specifying:**

**(a) When and how to withdraw participants from the investigational product/trial treatment;**

**(b) The type and timing of the data to be collected for withdrawn participant(s);**

**(c) Whether and how participants are to be replaced; and**

**(d) The follow-up for participants withdrawn from the investigational product/trial treatment.**

1. Participants will be withdrawn if they show poor response to the protocol, however, a very low attrition rate is expected, below 5% because of the well-known high tolerance to rTMS (Rossi et al 2009). Participants are also able to withdraw consent voluntarily at any time with no consequences.
2. In case of withdrawal of consent, patients will not be included in final analysis – they will be replaced.
3. Data will be collected up to the date of withdrawal from the protocol
4. If patients withdraw consent from study they devolve to their clinician and will resume their standard treatment as decided by their clinician.

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| **6. Treatment of Participants** |

* 1. **Description and justification for the treatments, interventions or methods to be utilised (including product name(s), dose(s), dosing schedule(s), route/mode(s) of administration and treatment period(s)) and the follow-up period(s) for participants for each investigational product/trial treatment group/arm of the trial.**

rTMS is an approved treatment for patients with depression who have not responded to drug therapy and here we use the FDA-approved protocol for all patients (40 trains of rTMS at 10Hz at 100%MT (~1000mT), with an inter-train interval of 30 seconds (Gaynes et al., 2014; O’Reardon et al., 2007; Price et al., 2010)

The study will consist of 4 weeks of treatment comprising 20 sessions (weekdays for 4 weeks) of rTMS to the left dorsolateral prefrontal cortex as approved by the FDA (Gaynes et al., 2014; O’Reardon et al., 2007; Price et al., 2010). Patients will be randomly assigned to the standard protocol (100%MT; 1000mT) or add-on protocol (standard protocol+50mT) stimulation group.

The experimental protocol is provided as an add-on to the standard treatment and has been through rigorous preclinical testing. Patients will receive alternating trains during the session of standard protocol rTMS (10 trains of rTMS at 10Hz at 100%MT) followed by 50 mT rTMS (10 trains of rTMS at 10Hz at ~1%MT;50mT) repeated till a total of 80 trains of 10Hz stimulation with an inter-train interval of 15 seconds is provided.

Follow up periods are standard for trials of depression and investigate acute response (immediately post treatment) and long term maintenance of treatment effects (6 months post treatment).

* 1. **The medications/treatments permitted (including rescue medication) and not permitted before and/or during the trial.**

No contraindications.

* 1. **The procedures for monitoring participant compliance.**

Not applicable: patients will receive treatment in the hospital and will be fully supervised throughout treatment and assessment procedures.

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| **7. Assessment of Efficacy** |

* 1. **Specification of the efficacy parameters.**

Outcome Measures

Patients will be assessed at baseline, 2 weeks, at the end of the intervention period (4 weeks) and 6 months post treatment using the following outcome measures –

HAMD-21

We will assess the percentage change in HAM-D-21 response (score), defined by a significant change from the initial score on the Hamilton Depression Scale (HAM-D-21).

We will also assess the number of respondents in remission defined by a HAM-D-21 score of <8 directly following 4 week treatment period and 6 months after;

Blood test

The change and presence of predictive markers of the therapeutic response: serum biomarkers

* 1. **The methods and timing for assessing, recording, and analysing efficacy parameters.**

Participants will complete the Hamilton Depression Scale (HAM-D-21) questionnaire at baseline, immediately after 4 week treatment regime and 6 months after treatment. Questionnaires will be scored by an investigator blinded to the treatment group of the participant and data recorded in a spreadsheet.

Participants will have blood taken to measure the change and presence of predictive markers of the therapeutic response: serum biomarkers at baseline, immediately after end of 4 week rTMS treatment period and 6 months after treatment commencement.

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| **8. Assessment of Safety** |

* 1. **Summary of known and potential risks and benefits, if any, to research participants.**

Recent studies have shown that the adverse effects of rTMS remain minor (slight headache, stiff neck), suggesting that rTMS is safe for human use under controlled conditions (Loo et al, 2008)

rTMS techniques will be performed following international, published guidelines for the safe use of rTMS. The international safety guidelines cover principles of TMS, safety concerns, side effects, considerations on patient selection, and considerations on dosing rTMS, and are regularly updated. The safety guidelines for participant selection include a screening questionnaire that will be used to exclude participants with potential contraindications to rTMS.

* 1. **The safety parameters and the methods and timing for assessing, recording, and analysing safety parameters. Include a description of emergency procedures if applicable.**

Safety parameters will be recorded at the initial patient recruitment.

* 1. **Details of the Data and Safety Monitoring Board, or equivalent. *For further information refer to the TGA*** [***“Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95)” 2000.***](http://www.tga.gov.au/industry/clinical-trials-note-ich13595.htm)

Patients will be monitored through hospital patient procedures. rTMS is safe and well tolerated. Investigators have extensive experience with these techniques and have been granted ethics approval for their use many times (Murdoch University (2014/247), the University of Western Australia (RA/4/1/2129), there have been no side effects reported following use of these techniques in any of the investigators’ experiences. Experiments were completed using rTMS at low intensity (<50mT) in healthy volunteers in 2015 and 2016 at UWA without any reports of adverse effects (RA/4/1/5467, CI Jennifer Rodger, coinvestigators Katherine Hankinson and Geoff Hammond).

* 1. **The procedures for eliciting reports of and for recording and reporting adverse events. Include definitions of adverse events. *For further information on adverse events refer to the TGA*** [***“The Australian Clinical Trial Handbook” 2006.***](http://www.tga.gov.au/industry/clinical-trials-handbook.htm)

Any adverse events will be reported in accordance with the Ethics Committee guidelines. All adverse events will be recorded on the Case Report Form and will be collected from the time the participant signs the consent form. A copy of these procedures is displayed in the laboratory and co-investigators applying TMS are aware of these clearly established procedures. In addition, investigators applying rTMS are trained in First Aid.

* 1. **The type and duration of the follow-up of participants after adverse events.**

Management of adverse events in rTMS follows the Health Department, NMHS, Incident management process.

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| **9. Data Management, Statistical Analysis and Record Keeping** |

* 1. **Description of the statistical methods to be employed, including timing of any planned interim analysis.**

**All statistical tests will be two-sided, and tested at a 5% level of significance.**

A descriptive analysis of the data collected during each patient evaluation will be carried out up until the final evaluation. Specific time points for analysis are: end of rTMS sessions and at 6 months after the treatment course. Continuous variables will be described using median and range; and qualitative variables using frequencies and percentages.

The therapeutic response rates (proportion of responders) in each group will be compared using a chi-squared test (or Fisher’s exact test, if appropriate). Estimates of absolute and relative differences (via the odds ratio or relative risk) in terms of efficacy will be provided with their corresponding 95% confidence intervals. The format of the outcome data used for each participant for analysis will be changes from baseline.

The therapeutic effect of rTMS on % change in HAMD-21 will be analysed using random effect models that take into account the repeated measurements. Main effects of Time (baseline, 1 month, 6 months) and group (Standard or Add-on protocol) as well as an interactions will be estimated and tested. The analysis and comparison between groups of the onset of relapse of depression at 6 months will be carried out using a logistic regression model and testing factors linked to the therapeutic response (neuropsychological tests, dimensional scales, blood biomarkers).

* 1. **The number of participants planned to be enrolled (if possible, include number at each site). Document the reason for choice of sample size, including reflections on (or calculations of) the power of the trial and clinical justification.**

40 participants in total will be recruited. Power analysis based on our published LI-rTMS data in preclinical models indicates that 16 individuals/group for behaviour (equivalent of behavioural changes in humans), or 8 individuals per group for biochemical/neurological changes (equivalent for blood samples in humans), will provide 0.8 power to detect changes of 20%.

* 1. **The level of significance to be used.**

p=0.05

* 1. **Procedures for reporting any deviation(s) from the original statistical plan (any deviation(s) from the original statistical plan should be described and justified in the protocol and/or in the final report, as appropriate).**

Any deviation from the original statistical plan will be described and justified in the final report

* 1. **The selection of participants to be included in the analyses (e.g. all randomised participants, all dosed participants, all eligible participants, or all evaluable participants).**

All evaluable participants will be included in the analysis

Withdrawals will not be subject to Intention to treat analysis, as there is no adverse difference in the add-on.

* 1. **Information on how data will be managed, including coding for computer analysis and data handling (collection, storage, maintenance, security and archiving). Include details regarding these processes if the data is sent off-site (e.g. encryption). *Clinical trial records should be retained for a minimum of 15 years from the completion of the trial.***

Data will be stored for a minimum of 15 years after publication or project completion, whichever is the later.  
  
This project will utilise the CHIC Code of Practice for the Use of Name Identified Data, as implemented at the Centre for Clinical Research in Neuropsychiatry.

Specifically, participants are assigned a unique identification number which is used to identify all computer and paper data. Access to the master files (hard copy) that link participant’s names to their identification number is restricted to authorised project personnel, and the files are kept in a locked steel cabinet. “Staff only” areas. Data for analysis will be stored and archived only on the secure health and university networks and shared with co-investigators via these networks, or via password- encoded folders on portable memory devices.  
  
Administrative records will be managed using the Department of Health “Retention and Disposal Schedule for Administrative and Functional Records 2007” and electronic records will be managed according to the Department of Health “Long Term Management of Electronic Records Policy” 2004.

It is intended that the results of the study will be published in a scientific journal.

* 1. **Procedure for accounting for missing, unused, and spurious (*false*) data.**

Missing data will be described in terms of frequencies and percentage for each group. Imbalances will be evaluated by the chi-squared test (or Fisher’s exact test). Comparison of missing data onset during follow-up will be realised with a log-rank test for longitudinal data. Each dropout will be described as follows: arm, exit date, exit reason, characteristics at inclusion and last data collected. In case of missing data, a multiple imputation analysis will be performed.

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| **10. Monitoring / Audit** |

* 1. **Statement that the trial investigators/institutions will permit trial-related monitoring, audits, and regulatory inspections, providing direct access to source data/documents. This may include, but not limited to, review by external sponsors, Human Research Ethics Committees and institutional governance review bodies.**

We confirm that we will permit trial-related monitoring, audits, and regulatory inspections, providing direct access to source data/documents. This may include, but not limited to, review by external sponsors, Human Research Ethics Committees and institutional governance review bodies.

* 1. **Description of the procedures for monitoring and auditing. The clinical trial sponsor may nominate the form of monitoring and auditing and will indicate the times of audit visits.**

The Perron Institute for Neurological and Translational Science requires annual reports on project progress and will audit the trial procedures annually at annual review meetings to be scheduled with the investigators.

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| **11. Quality Control and Quality Assurance** |

* 1. **Statement that the trial will be conducted in compliance with the protocol, Good Clinical Practice and the application regulatory requirements.**

This clinical trial will be conducted in compliance with all stipulation of this protocol, the conditions of the ethics committee approval, the NHMRC National Statement on ethical Conduct in Human Research (2007 and all updates), the Integrated Addendum to ICH E6 (R1): Guideline for Good Clinical Practice E6 (R2), dated 9 November 2016 annotated with TGA comments and the NHMRC guidance Safety monitoring and reporting in clinical trials involving therapeutic goods (EH59, 2016).

* 1. **Quality control & quality assurance measures to ensure quality of data.**

The trial will be conducted in compliance with the protocol, Good Clinical Practice and the application regulatory requirements.

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| **12. Ethics** |

* 1. **Description of ethical considerations related to the trial with particular reference to participant consent (including Participant Information and Consent Forms).**

Participants are given a participant information form and are required to sign a consent form (both forms are attached)

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| **13. Budget, Financing, Indemnity and Insurance** |

* 1. **Budget, financing, indemnity and insurance, if not addressed in a separate agreement.**

These will be addressed in the SSA and related Governance forms on the RGS site once ethics has been approved.

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| **14. Publication** |

* 1. **Publication and dissemination of trial results (including any limitations), if not addressed in a separate agreement. *In accordance with the Declaration of Helsinki (2008) every clinical trial must be registered in a publicly accessible database before recruitment of the first participant.***

The trial is currently under preliminary registration with the Australian and New Zealand Clinical Trials registry (ANZCTR) Registration #ACTRN12618001889246p.

Data is expected to be published on completion of the trial in a relevant peer reviewed scientific journal.

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| **15. References** |

* 1. **A list of articles from the literature pertinent to the evaluation of the trial. Include references that have been cited in the protocol.**

O'Reardon JP, Solvason HB, Janicak PG, Sampson S, Isenberg KE, Nahas Z, McDonald WM, Avery D, Fitzgerald PB, Loo C, Demitrack MA, George MS, Sackeim HA (2007) Efficacy and safety of transcranial magnetic stimulation in the acute treatment of major depression: a multisite randomized controlled trial. Biol Psychiatry **62**:1208-1216.

Gaynes BN, Lloyd SW, Lux L, Gartlehner G, Hansen RA, Brode S, Jonas DE, Swinson Evans T, Viswanathan M, Lohr KN. (2014) Repetitive transcranial magnetic stimulation for treatment-resistant depression: a systematic review and meta-analysis. J Clin Psychiatry. **75**:477-89.

Heath E,Lindberg DR, Makowiecki K, Gray A, Asp AJ, **Rodger** J\*, Choi DS\*, Croarkin PE\*. Medium- and High-Intensity rTMS Reduces Psychomotor Agitation with Distinct Neurobiologic Mechanisms. Translational Psychiatry *in press*. \* indicates equal contribution.

Loo CK, McFarquhar TF, Mitchell PB. (2008) A review of the safety of repetitive transcranial magnetic stimulation as a clinical treatment for depression

International Journal of Neuropsychopharmacology, **11(1)**:31-147.

Ridding MC, Ziemann U. (2010) Determinants of the induction of cortical plasticity by non-invasive brain stimulation in healthy subjects. J Physiol, **588:**2291-2304.

Rossi S, Hallett M, Rossini PM, Pascual-Leone A, Safety of TMS Consensus Group. (2009) Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. Clin Neurophysiol. **120(12):**2008-2039.

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| **16. Appendices** |

* 1. **List all appendices. Including an Investigator’s Brochure or Device Manual (if applicable).** All ***trials involving unregistered drugs must be accompanied by an investigator’s brochure which is a compilation of the clinical and non-clinical data available on the experimental products intended for use in the trial. Clinical investigations involving devices should include an Investigator’s Brochure or Device Manual.***

*FDA Guidance Brochure*

*Peer review*

*Participant Consent Form*

*Participant Information Sheet*

*Research Protocol*

*TMS Safety Screening Questionnaire*