**STATISTICAL ANALYSIS PLAN**

**Randomised double-blind controlled trial of connectivity guided theta burst transcranial magnetic stimulation versus repetitive transcranial magnetic stimulation for treatment resistant moderate to severe depression: evaluation of efficacy, cost effectiveness and mechanism of action.**

**(BRIGhTMIND)**

**SAP Version:** 2.0

**Date:** 27/09/2022

**Based on protocol:** BRIGhTMIND Trial Protocol

**Version:**6.0

**Date**:06/09/2021

**Trial registration:** 18/EM/0232

**ISRCTN:** 19674644

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| --- | --- |
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**Revision History**

| Version | Date | Author(s) and Role | Summary of Changes/Comments |
| --- | --- | --- | --- |
| 0.1 | 18/03/2019 | Ana Suazo Di Paola, Trial Statistician | Initial version |
| 0.2 | 08/05/2019 | Ana Suazo Di Paola, Trial StatisticianCassey Brookes, Principal Statistician | **Cover**Added Senior Statistician’s name.**Secondary Outcomes*** Corrected wording of the Sustained response outcome definition with CB’s suggestion.
* Included baseline time point in the definition of the BDI, THINC-IT, EuroQol-5D-5L, PHQ-9, GAD-7 and WSAS outcomes’ definition as per CB’s suggestion.

**Analysis Populations**Corrected wording of the definition of ITT and Safety populations with CB’s suggestions.**Analysis Software**Corrected wording and included the names of other software to be used. |
| 0.3 | 19/06/2019 | Ana Suazo Di Paola, Trial StatisticianCassey Brookes, Principal StatisticianShaun Barber, Senior Statistician | **Study Objectives**Removed Study objective related to Qualitative analysis.**Secondary Objectives**Removed Secondary Objective related to Economic and Qualitative analyses.**Secondary Outcomes*** Included definition of categories for the BDI, PHQ-9, GAD-7 and WSAS outcomes.
* Improved wording of definition of Sustained response, THINC-IT and EuroQol-5D-5L outcomes.

**Other variables to be summarised**Added this section.**Protocol Deviations**Corrected definition of Major and Minor Protocol Deviations with CB’s and SB’s suggestions.**Analysis Populations**Added Completers Population definition with CB’s suggestion.**General Issues for Statistical Analysis**Corrected definition of subsections with CB’s suggestions.**Statistical Methodology**Corrected definition of subsections with CB’s suggestions.**Internal Pilot**Corrected definition of subsections with CB’s and SB’s suggestions. |
| 0.4 | 05/07/2019 | Ana Suazo Di Paola, Trial StatisticianCassey Brookes, Principal Statistician | **Primary Outcome**Included two decimal points.**Secondary Outcomes**Improved wording of definition of Sustained response outcome with CB’s suggestion.**Analysis Populations**Slight improvement in wording of definition of Intention-to-treat population.**General Issues for Statistical Analysis**Further corrections in definition of subsections with CB’s suggestions.**Statistical Methodology**Further corrections in definition of subsections with CB’s suggestions.**Internal Pilot**Improved definition of subsections with CB’s suggestion. |
| 1.0 | 22/07/2019 | Ana Suazo Di Paola, Trial StatisticianCassey Brookes, Principal StatisticianShaun Barber, Senior Statistician | Final version |
| 1.1 | 13/12/2019 | Ana Suazo Di Paola, Trial StatisticianCassey Brookes, Principal StatisticianShaun Barber, Senior StatisticianRichard Morriss, Chief Investigator | **Secondary Objectives**Added statement about Health Economic data and Mechanistic Component objectives.**Randomisation and Blinding**Excluded text from the Protocol about labelling of TMS machine as per RM input related to it.**Primary Outcome**Clarification regarding derivation of HDRS-17 score from data.**Secondary Outcomes*** Correction in specification of time point.
* Added definition and measurement units of THINC-IT tool components.
* Added definition of the QIDS-SR16 outcome.

**Subgroups*** Stated 16 weeks as the time point of analysis as per RM suggestion.
* Included degree of childhood trauma as a moderator as per RM suggestion.

**Compliance*** Correction of wording.
* Included statement related to intake of Benzodiazepine, Diazepam, Zopiclone, Zolpidem or Zaleplon.

**Major Protocol Deviations*** Specification of medications not to be taken during the Trial.
* Included statement related to Psychotropic medications or Psychological interventions.
* Included statement related to daily prescription of Benzodiazepine, Diazepam, Zopiclone, Zolpidem and Zaleplon.

**Analysis Populations**Improved wording regarding definition of ITT population.**Other variables to be summarised**Improved wording regarding current medications taken.**Secondary Outcomes Analysis*** Changed specification of analysis to be performed for PHQ-9, GAD-7 and WSAS outcomes.
* Added the QIDS-SR16 to the list of continuous longitudinal outcomes.
* Added model residuals diagnostic for the continuous longitudinal outcomes.
* Improved wording regarding outcomes to be summarised descriptively (no hypothesis testing).

**Mechanistic Component outcomes** Added section to clarify that no details of their definition or analysis will be provided in the SAP.**Health Economic outcomes** Added section to clarify that no details of their definition or analysis will be provided in the SAP.**Adverse Events*** Improved wording.
* Added Syncope as an uncommon adverse effect as per RM suggestion.
 |
| 1.2 | 14/03/2022 | Ana Suazo Di Paola, Trial StatisticianProfessor Hamish McAllister-Williams, Principal Investigator (Newcastle) | **Subgroup Objectives*** Included 8, 16 and 26 weeks follow-up assessments for the exploration of moderators of depression response.
* Added clarification regarding each of the measures as moderators rather than mediators as stated in previous versions of the Protocol and the current version 6.0.

**Visit Schedule**The QIDS-SR16 outcome and the Arterial Spin Labelling were added to the table to reflect changes made in previous versions of the Protocol.**Outcomes*** Changes were made to the definition of the secondary outcomes for improvement of wording and accuracy.
* THINC-IT outcome: individual response times for correct responses were included under the definition of the Choice Reaction Time as outcomes that will be analysed in Newcastle site.

**Subgroups and/or interactions*** Included 8, 16 and 26 weeks follow-up assessments for the exploration of moderators of depression response.
* Added clarification regarding each of the measures as moderators rather than mediators as stated in previous versions of the Protocol and the current version 6.0.

**Compliance**Changes were made to the wording of the variable to be derived for number of TMS sessions delivered within 6 weeks.**Other variables to be summarised*** BNF for medications related to physical and mental health were added to the list of variables.
* An addition was made to the description of the summary of Uncommon Side Effects.

 **Minor deviations**Excluded “Did not complete all outcome measures” from the non-compliance with randomised treatment deviations.**Analysis Populations**ITT: added wording in regards to method for dealing with missing data.Completers: added wording related to TMS treatment delivered as per MRI or as per changes allowed in the TMS SOP.**General Issues for Statistical Analysis, Derived/Computed Variables**Addition of variables to be derived as well as corrections were made for completeness purposes.**Statistical Methodology**Wording in relation to the addendum on estimands and sensitivity analysis as well as the extension to the CONSORT was included.Additions and corrections were also made in this section to the primary analysis of the primary and secondary outcomes. This also applies to sensitivity and subgroup analyses. |
| 1.3 | 30/03/2022 | Ana Suazo Di Paola, Trial Statistician | Changes, corrections and/or additions were made to the wording of the following sections in accordance with the feedback provided by the Chief Investigator, Principal Statistician and Senior Medical Statistician:* **Subgroup Objectives**
* **Definition of the cgiTBS arm**
* **Definition of the THINC-IT and EQ5D-5L secondary outcomes**
* **Exploratory Outcomes**
* **Definition of Intention-to-treat population**
* **Primary Analysis of the Primary Outcome**
* **Secondary Analyses of the Primary Outcome**
* **Sensitivity Analyses**
* **Primary Analysis of the THINC-IT outcome**
* **Subgroup Analyses**
* **Exploratory Analyses**
 |
| 1.4 | 07/06/2022 | Ana Suazo Di Paola, Trial Statistician | Changes, corrections and/or additions were made to the wording of the following sections in accordance with the feedback provided by the Chief Investigator and Principal Statistician:* **Randomisation and blinding**
* **Visit Schedule**
* **Other variables to be summarised**
* **Statistical Methodology**
 |
| 1.5 | 21/09/2022 | Ana Suazo Di Paola, Trial Statistician | Changes, corrections and/or additions were made to the wording of the following sections in accordance with the feedback provided by the Principal Statistician and Senior Statistician:* **Subgroups and/or interactions**
* **Protocol deviations**
* **Definition of Per-Protocol Population**
* **Derived/computed variables**
* **Statistical Methodology**
* **Safety and Adverse Events**
 |
| 1.6 | 22/09/2022 | Ana Suazo Di Paola, Trial Statistician | Changes, corrections and/or additions were made to the wording of the following sections in accordance with the feedback provided by the Principal Statistician and Senior Statistician:* **Subgroups and/or interactions**
* **Statistical Methodology**
* **Safety and Adverse Events**
 |
| 1.7 | 27/09/2022 | Ana Suazo Di Paola, Trial Statistician | Changes, corrections and/or additions were made to the wording of the following sections in accordance with the feedback provided by the Chief Investigator:* **Compliance**
* **Subgroup Objectives, Subgroups and/or interactions and Subgroup Analyses**
 |
| 2.0 | 27/09/2022 | Ana Suazo Di Paola, Trial Statistician | Final Amended version of SAP. |

**SAP approval for finalised version 2.0:**

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|  | **Signature** |  | **Date** |

LIST OF ABBREVIATIONS

|  |  |
| --- | --- |
| AE | Adverse Event |
| BDI | Beck Depression Inventory |
| CI | Chief Investigator |
| CRF | Case Report Form |
| CBT |  Cognitive Behavioural Therapy |
| CEACs | Cost Effectiveness Acceptability Curves |
| cgiTBS | Connectivity Guided Intermittent Theta Burst Stimulation |
| CTR | Clinical Trial Report |
| CTU | Clinical Trials Unit |
| DLPFC | Dorsolateral prefrontal cortex |
| DMPFC | Dorsomedial prefrontal cortex |
| DMEC | Data Monitoring Ethics Committee |
| EQ-5D | EuroQol five dimension scale  |
| FAS | Full Analysis Set |
| FC  | Functional Connectivity |
| eFC | Effective Functional Connectivity |
| fMRI | Functional Magnetic Resonance |
| GABA | Gamma-amino butyric acid |
| GCP | Good Clinical Practice |
| HRDS-17 | Hamilton Rating Scale for Depression |
| ICH GCP | The International Conference on Harmonisation Good Clinical Practice |
| ITBS | Intermittent theta-burst stimulation |
| LCTU | Leicester Clinical Trials Unit |
| MADRS | Montgomery-Asberg Depression Rating Scale |
| MDD | Major Depressive Disorder |
| MRS | Magnetic Resonance Spectroscopy |
| NHS HRA | National Health System Health Research Authority |
| NICE | The National Institute for Health and Care Excellence |
| NNT | Number Needed to Treat |
| PPI | Patient and Public Involvement |
| PPS | Per Protocol Set |
| QALY | Quality-Adjusted Life Year |
| QOL | Quality of Life |
| RCT | Randomised Controlled Trial |
| RsfMRI | Resting state (task-free) functional MRI |
| rTMS | Repetitive Transcranial Magnetic Stimulation |
| SAE | Serious Adverse Event |
| SAF | Safety Population |
| SAP | Statistical Analysis Plan |
| TMF | Trial Master File |
| TMS | Transcranial Magnetic Stimulation |
| TRD | Treatment resistant depression |
| TSC | Trial Steering Committee |

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# Introduction

This Statistical Analysis Plan (SAP) describes the planned analysis and reporting for the Trial Morriss\_16\_311\_TMS\_in\_Depression (Protocol V6.0). The structure and content of this SAP provides sufficient detail to meet the requirements identified by the FDA and International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH): Guidance on Statistical Principles in Clinical Trials. All work planned and reported for this SAP will follow internationally accepted guidelines, published by the American Statistical Association and the Royal Statistical Society for statistical practice.

The reader of this SAP is encouraged also to read the clinical trial protocol.

The purpose of this SAP is to outline the planned analyses that are to be performed on the data to support the completion of the Clinical Study Report (CSR). Additionally, this SAP also aims to outline the planned interim analysis on the data as to assess whether it is feasible to recruit the number of participants required to sufficiently power this Trial (refer to Section 7 for more details regarding the Internal Pilot).

The SAP will be amended if there are substantial changes to the planned analyses, and in any case will be finalized before the database lock for this study. Exploratory post-hoc or unplanned analyses not necessarily identified in this SAP may be performed on these data as required. These analyses will be clearly identified in the CSR.

**Throughout the document: Any verbatim text from the protocol is provided inside a box:**

Text from the protocol

## Study Objectives

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| The primary aim of this study is to examine the efficacy of connectivity guided, intermittent theta-burst Transcranial Magnetic Stimulation (cgiTBS) in comparison with NICE recommended standard rTMS, in treatment resistant moderate to severe MDD (TRD). We propose a multicentre RCT in patients with TRD who have not responded to treatment with at least two antidepressants in their current episode.A secondary aim of this current study is therefore to examine the mechanisms by which cgiTBS improves mood. This will be addressed by examining the hypothesised network regulatory effects of cgiTBS using FC and eFC analysis, and investigating how these effects are associated with clinical improvements.[…].Therefore another secondary aim of this study is to conduct qualitative interviews with patients to assess their general views of rTMS and cgiTBS, benefits from receiving, disadvantages from or dislikes about rTMS and cgiTBS, and a rating of acceptability on a scale of 1 to 5 (higher scores indicate more acceptability). |

### Primary Objectives

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| To determine the efficacy of cgiTBS compared with standard rTMS in reducing the HDRS-17 score over 26 weeks follow-up, in people with TRD. |

### Secondary Objectives

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| To explore secondary clinical outcomes of importance to patients and clinicians namely cognition, social function, quality of life and overall clinical improvement. |

The secondary objectives corresponding to the Health Economics analysis and the analysis of the Mechanistic Component of the Study are not included in this SAP as they will be addressed elsewhere.

### Subgroup Objectives

We will explore moderators of the continuous HDRS-17 score measured over 26 weeks at 8, 16 and 26 weeks such as:

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| […] severity of depression by baseline HDRS-17 score, degree of treatment resistance and age and number of TMS sessions attended as a (moderator\*) of outcome in exploratory sub-group analyses of the primary outcome. |

\* Protocol v6.0 states mediator of outcome, however, moderator is more appropriate as baseline variables will not be caused by the treatment arm.

**NB:** the number of TMS sessions that were attended, completed and delivered to the correct coordinates as per MRI data or as per changes allowed in the TMS SOP (10 or more, as per definition of Completers population) will be explored as a moderator of the primary outcome at each of the follow-up time points.

Additionally, the degree of childhood trauma measured at baseline as defined by the total score obtained on the Childhood Trauma Questionnaire (for participants with an overall score of 56 or more) and level of anxiety measured at baseline as defined by the total score obtained on the GAD-7 questionnaire (for participants with an overall score of 10 or more) will also be explored as moderators of the continuous HDRS-17 score measured over 26 weeks.

## Study Design

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| The study is a multicentre parallel group, double blind, randomised controlled trial of the efficacy of cgiTBS versus no connectivity guided standard rTMS in patients with a primary diagnosis of moderate to severe MDD who have failed to respond to adequate trials of at least 2 antidepressants in their current episode (TRD) (42). |

### Overview

### Participants

Adults aged 18 years old or above with Treatment Resistant Depression whose HDRS-17 score is of 16 or more and who have capacity to provide informed consent will be deemed as eligible participants. However, having either a history of bipolar disorder, neurological conditions or standard contraindications to MRI would make any potential participant ineligible to take part in the Study.

### Treatment groups

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| Participants will be randomly assigned in a 1:1 ratio into the rTMS and cgiTBS arms using blocks of varying size.  |

#### cgiTBS arm

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| **Individuals assigned to cgiTBS** will receive bursts of 3 pulses (80% motor threshold) at 50Hz applied at a frequency of 5 Hz (i.e. every 200 ms). Each 10 second cycle will consist of 10 bursts (consisting of 2 seconds of stimulation and 8 seconds rest) with a total of 20 cycles performed per run over a site determined from the assessment of maximal strength of connectivity between the anterior insula and the left dorsolateral prefrontal cortex (DLPFC) from fMRI and structural MRI using neuronavigation which computes the nearest location for TBS stimulus on the scalp from the same three fiducial points, the nasion, left preauricular and right preauricular sites. The pulses are repeated for a total of 5 runs with 5 minute rest intervals between runs. |

#### rTMS arm

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| **Individuals assigned to rTMS** will follow the standard US Food and Drug Administration (FDA) approved protocol. A single coil is placed over the left DLPFC. Stimulation is at 120% motor threshold with 75 x 4-second trains of 10Hz interspersed by 26-second intertrain intervals. The site of stimulation will be determined using a neuronavigation device which computes the F3 electrode site for TMS stimulation from just three fiducal points, the nasion, left preauricular and right preauricular sites. The change has been made because the neuronavigation has been made simple to use for nurses, will be more tolerable for patients, and provides more precise and reproducible site of stimulation over 20 TMS sessions. There is no need for patients to wear a cap or for a mark to be made on the skin; instead the neuronavigation device shines a green light onto the scalp and guides the nurse to the right site for stimulation.  |

### Sample size

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| A sample size of 266 participants gives 89.3% power to detect a mean difference of 3 points in the HDRS-17 over 26 weeks between the groups at the 5% two-sided significance level assuming a standard deviation of 8 (informed from both our Pilot Study and a multicentre randomised controlled trial in chronic persistent depressive disorder led by the chief investigator (Morriss et al, 2016), a correlation between follow-up measures of 0.7 (1 baseline measure with correlation of 0.27 to the follow-up measures) and 20% data loss/drop-out. NICE defined 3 points as a clinically important difference in outcome on the HDRS-17 in its NICE Clinical Guideline for Depression in 2004 and 2009. Therefore a target **total of** **266 participants will be recruited (133 per arm)**. The table below outlines the power for the targeted sample size as well as power if the recruitment occurs at a lower rate than expected, at the 5% significance level. Given the uncertainties of recruitment to the study in the current pandemic, we note that under the same assumptions, a sample size of 232 would reassuringly still yield >85% power (85.1%).

|  |  |  |
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|  **Average number of participants recruited per month from April 2021 until end of recruitment (January 2022)** | **N** | **Power (%)** |
| 4.7 | 232 | 85.1 |
| 6.8 | 253 | 87.8 |
| 8.1 | 266 | 89.3 |

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### Randomisation and blinding

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| Randomisation will take place immediately prior to the start of the first treatment session. Randomisation will be conducted via a web-based randomisation system by a named nurse and health care assistant delivering TMS at each centre who will remain un-blinded. Participants will be randomly assigned in a 1:1 ratio into the rTMS and cgiTBS arms using blocks of varying size. Randomisation will be stratified by centre and minimised on baseline depression and treatment resistance.Patients, referring clinical teams and the outcomes assessor will be kept blind with respect to the treatment protocol assigned and administered. Allocation to treatment will be performed at the first TMS treatment session by the nurse leading the TMS or a doctor whose only role is to deliver TMS.Following steps will be taken to ensure participants are blinded to the treatment:-* Will not recruit participants who have received TMS treatment prior to their participation into the study.
* Every participant will receive an MRI Imaging Scan.
* All treatment sessions will be similar in length of time.
* TMS machine will not indicate which treatment is being delivered. It will marked only as Treatment A or Treatment B.
* Research staff will not be based in the same building as the TMS suite.
* Research staff will play no role in image analysis until all follow up is complete.
* Research staff will be advised to disregard any statement by the participant about which treatment they have received as this will be based on guess work. We will record if any statements are made by the participant as potential attempts to unblind.

Any unintended unblinding will be recorded and another assessor will complete all further assessments for that participant. At each assessment, the outcomes assessor will be asked to guess the treatment allocation of the participant. |

It is important to note that while the TMS machine was not marked as treatment A or treatment B, all participants were blinded to the treatment allocation by turning the TMS machine settings away from them prior to the delivery of their TMS session in accordance with the guidance provided in the TMS SOP.

## Visit schedule

|  |  |  |  |  |  |  |  |
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| **Outcome measures** | **Baseline Assessment. (Consent to the study)** | **Baseline****MRI Scan** | **Treatment Mon- Fri for 4 weeks** | **8 Week Follow up Assessment** | **16 Week Follow Up Assessment** | **16 Week MRI Scan** | **26 Week Follow Up****Assessment** |
| Visit Window |  | Within 14 days of Baseline Assessment | + 14 days of MRI Scan  | +/- 1 week from Randomisation | +/- 1 weekfrom Randomisation | Within 14 days of 16 Week Follow Up Assessment | +/- 1 week from Randomisation |
| HDRS-17 | ✓ |  | ✓Only if Baseline assessment exceeds 4 weeks  | ✓ | ✓ |  | ✓ |
| MGH | ✓ |  | ✓ Only if Baseline assessment exceeds 4 weeks |  |  |  |  |
| BDI-2  | ✓ |  |  | ✓ | ✓ |  | ✓ |
| PHQ-9  | ✓ |  |  | ✓ | ✓ |  | ✓ |
| WSAS  | ✓ |  |  | ✓ | ✓ |  | ✓ |
| GAD7  | ✓ |  |  | ✓ | ✓ |  | ✓ |
| EQ-5D-5L | ✓ |  |  | ✓ | ✓ | ✓ | ✓ |
| THINC-it | ✓ | ✓(When completed at a separate visit whilst COVID-19 mitigation restrictions in place) |  |  ✓(Not completed whilst COVID-19 mitigation restrictions in place) | ✓ | ✓(When completed at a separate visit whilst COVID-19 mitigation restrictions in place) |  ✓(Not completed whilst COVID-19 mitigation restrictions in place) |
| QIDS--SR16 | ✓ |  |  | ✓ | ✓ |  |  |
| SCID Research Interviews | ✓ |  |  |  |  |  |  |
| CTQ (Replaces PSTD section in SCID Questionnaire.) | ✓ |  |  |  |  |  |  |
| Client Resource Questionnaire | ✓ |  |  |  | ✓ |  | ✓ |
| Patient Acceptability  |  |  | ✓ | ✓ | ✓ |  | ✓ |
| Side Effects Checklist ( Adverse Events) |  |  | ✓ | ✓ |  |  |  |
| **MRI** |
| rsfMRI  |  | ✓ |  |  |  | ✓(Not in London) |  |
| MRS (Not in London & Oldham) |  | ✓ |  |  |  | ✓ |  |
| Diffusion weighted imaging |  | ✓ |  |  |  | ✓(Not in London) |  |
| Arterial Spin Labelling (Not in London & Newcastle) |  | ✓ |  |  |  | ✓ |  |

# Outcomes and other variables

## Primary Outcome

### Definition and Derivation of Primary Outcome

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| Hamilton Depression Rating Scale (HDRS-17) measured over 26 weeks at 8, 16 and 26 week assessments. |

The HDRS-17 score is defined as a continuous outcome that will be measured at baseline, 8 weeks, 16 weeks and 26 weeks.

The score is derived from a scale which is comprised of a list of 17 items with each item being measured either on a five-point (0-4) or three-point scale (0-2). HDRS-17 scores range from 0 to 52 (inclusive)(Sharp, 2015).

### Hypothesis to be investigated

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| Our primary hypothesis is that cgiTBS is more efficacious in reducing the mean HDRS-17 score over 26 weeks compared to standard rTMS in patients with TRD. |

## Secondary Outcomes

### Definition and Derivation of Secondary Outcomes

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| --- |
| 1. HDRS-17 score measured separately at each assessment at 8, 16 and 26 weeks
 |

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| 1. Response rate at 8, 16 and 26 weeks measured using HDRS-17 (defined as a 50% or greater reduction in HDRS-17 score at each of the specified time points from Baseline).
 |

The HDRS-17 score measured at baseline as well as 8, 16 and 26 weeks will be used to derive three binary variables of responder or non-responder that will represent this Secondary Outcome. Participants observed to have a 50% or greater reduction in their HDRS-17 score from baseline to each of the mentioned assessment time points will be classed as responders.

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| 1. Remission rate at 8, 16 and 26 weeks measured using HDRS-17 (defined as a score of 8 or less on the HDRS-17)
 |

The HDRS-17 score measured at 8, 16 and 26 weeks will be used to derive three binary variables of remitters or non-remitters that will represent this Secondary Outcome. Participants whose HDRS-17 score at each of the mentioned assessment time points is 8 or less will be classed as remitters.

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| 1. Sustained response at 16 and 26 weeks (defined as a continuing response as defined above following a response at the previous time point)
 |

The binary variables of responder or non-responder at 8, 16 and 26 weeks will be used to derive this Secondary Outcome. Participants who have two consecutive assessments of response will be classed as having a sustained response. At 16 weeks, participants will be defined as sustained responders (50% reduction in HDRS-17 score from baseline) having already responded at 8 weeks. Similarly, at 26 weeks, participants will be defined as sustained responders having responded at 16 weeks alone, or 8 and 16 weeks. Participants who have a response at 8 weeks, but not at 16 weeks (i.e. HDRS-17 score increased between 8 and 16 weeks such that the definition of response is not met at 16 weeks) will be classed as non-sustained responders at 26 weeks. Likewise, participants who only have a response at 26 weeks (and not at 8 and 16 weeks) will be classed as not having a sustained response.

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| 1. Beck Depression Inventory (BDI) at 8, 16 and 26 weeks
 |

The BDI score is defined as a continuous outcome that will be measured at baseline, 8 weeks, 16 weeks and 26 weeks.

The score is derived from a scale which is comprised of a list of 21 items with each item being measured on a four-point scale (0-3). BDI scores range from 0 to 63 (inclusive).

The levels of depression based on BDI cut off scores are defined as follows: “None” or “Minimal” for scores between 0-9, “Mild” for scores between 10-18, “Moderate” for scores between 19-29 and “Severe” for scores between 30-63 (Beck et al, 1988).

This Secondary Outcome will be derived as a categorical variable at baseline, 8 weeks, 16 weeks and 26 weeks.

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| 1. THINC Integrated Tool (THINCIT), at 8, 16 and 26 weeks
 |

The THINC Integrated Tool is defined as an outcome that will be measured at baseline, 8 weeks, 16 weeks and 26 weeks.

The THINC-IT is comprised of five components, which are described as follows:

1. Choice Reaction Time:
* Total number correct
* Overall reaction time

The total number correct is defined as a discrete outcome that ranges from 0 to 80 (inclusive).

The overall reaction time is defined as a continuous outcome that is measured in milliseconds (values are rounded to one decimal place).

Individual response times for correct responses for each participant will also be analysed using an ex-Gaussian analysis returning three variables:

* Mu – the mean of the Gaussian component of the distribution of response times
* Sigma – the standard deviation of the Gaussian component of the distribution of response times
* Tau – the time constant of the exponential component of the distribution

All three of the above are continuous variables measured in milliseconds (rounded to one decimal place). “Goodness of fit” of the ex-Gaussian function to the response times for each participant will also be reported.

It is important to note that the analysis described above will be conducted by Newcastle University, therefore it does not fall under the LCTU remit.

1. One-back Test (NBack):
* Total number correct
* Average reaction time

The total number correct is defined as a discrete outcome that ranges from 0 to 40 (inclusive).

The average reaction time is defined as a continuous outcome that is measured in milliseconds (values are rounded to one decimal place).

1. Digit Symbol Substitution Test (DSST):
* Trials administered
* Number of Errors

The number of trials administered as well as the number of errors are defined as discrete outcomes.

1. Trail Making Test (TMT):
* Total time(s) taken to complete
* Number of Errors

Total time(s) taken to complete is defined as a continuous outcome that is measured in seconds (values are rounded to one decimal place).

The number of errors is defined as a discrete outcome.

1. Questionnaire:
* Questionnaire Score

The questionnaire score is defined as a continuous outcome that ranges from 0 to 20 (inclusive).

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| 1. EuroQol-5D-5L at 8, 16 and 26 weeks
 |

The EQ-5D-5L is defined as a continuous outcome that was designed to measure health-related quality of life across five domains: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each domain or dimension has 5 levels of response: no difficulties, slight difficulties, moderate difficulties, severe difficulties and extreme difficulties scored on a scale from 1 to 5. Responses recorded for these domains using the EQ-5D-5L questionnaire will be used to map (or cross-walk) the 5L descriptive system data onto the 3L value set in accordance with new guidance published by NICE in January 2022 (Hernández-Alava et al, 2022).

Each of the five components of this Secondary Outcome will be derived as a categorical variable at baseline, 8 weeks, 16 weeks and 26 weeks.

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| 1. Patient Health Questionnaire (PHQ-9) at 8, 16 and 26 weeks
 |

The PHQ-9 score is defined as a continuous outcome that will be measured at baseline, 8 weeks, 16 weeks and 26 weeks.

The score is derived from a scale which is comprised of a list of 9 items with each item being measured on a four-point scale (0-3). PHQ-9 scores range from 0 to 27 (inclusive).

The levels of depression based on the PHQ-9 cut off scores are defined as follows: “Minimal” for scores between 0-4, “Mild” for scores between 5-9, “Moderate” for scores between 10-14, “Moderately Severe” for scores between 15-19 and “Severe” for scores between 20-27 (Kroenke et al, 2001).

This Secondary Outcome will be derived as a categorical variable at baseline, 8 weeks, 16 weeks and 26 weeks.

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| 1. Generalised Anxiety Disorder Assessment (GAD-7) at 8, 16 and 26 weeks
 |

The GAD-7 score is defined as a continuous outcome that will be measured at baseline, 8 weeks, 16 weeks and 26 weeks.

The score is derived from a scale which is comprised of a list of 7 items with each item being measured on a four-point scale (0-3). GAD-7 scores range from 0 to 21 (inclusive).

The levels of anxiety based on the GAD-7 cut off scores are defined as follows: “Minimal” for scores between 0-4, “Mild” for scores between 5-9, “Moderate” for scores between 10-14 and “Severe” for scores between 15-21 (Spitzer et al, 2006).

This Secondary Outcome will be derived as a categorical variable at baseline, 8 weeks, 16 weeks and 26 weeks.

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| 1. Work and Social Adjustment Scale (WSAS) 8, 16 and 26 weeks
 |

The WSAS is defined as a continuous outcome that will be measured at baseline, 8 weeks, 16 weeks and 26 weeks.

The score is derived from a scale which is comprised of a list of 5 items with each item being measured on a nine-point scale (0-8). WSAS scores range from 0 to 40 (inclusive).

WSAS scores above 20 suggest a “Moderately severe or Worse” Psychopathology. WSAS scores between 10 and 20 are associated with “Significant functional impairment”. Scores below 10 are associated with “Subclinical populations” (Pedersen et al, 2017).

This Secondary Outcome will be derived as a categorical variable at baseline, 8 weeks, 16 weeks and 26 weeks.

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| 1. Quick Inventory of Depressive Symptomology (QIDS-SR16) at baseline, 8 weeks and 16 weeks
 |

 The QIDS-SR16 score is defined as a continuous outcome that will be measured at baseline, 8 weeks and 16 weeks.

The score is derived from a scale which is comprised of a list of 16 items with each item being measured on a four-point scale (0-3). Scores on the QIDS-SR16 range from 0 to 27 (inclusive). The scoring system for the QIDS converts responses to the mentioned 16 items into the nine DSM-IV symptom criterion domains. The nine domains include: 1) sad mood, 2) concentration, 3) self-criticism, 4) suicidal ideation, 5) interest, 6) energy/fatigue, 7) sleep disturbance (initial, middle and late insomnia or hypersomnia), 8) decrease/increase in appetite/weight and 9) psychomotor agitation/retardation

According to Rush et al (2003), the severity of depression can be estimated based on the following QIDS16 score thresholds: mild depression (for scores ranging between 6-10), moderate depression (for scores ranging between 11-15), severe depression (for scores between 16-20) and very severe depression (for scores between 21-27).

|  |
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| 1. Patient acceptability (0-5 scale). After each TMS session and at 8, 16 and 26 weeks
 |

The Patient Acceptability is defined as a categorical outcome. The values associated to the categories of this Secondary Outcome range from 0 to 5 (inclusive), where the lowest and highest categories indicate “Much Worse” and “Much better” acceptability, respectively.

|  |
| --- |
| 1. Adverse Event checklist after each TMS session
 |

The detailed specification regarding the definition and derivation of this Secondary Outcome will be covered in Section 6 of this SAP.

### Hypotheses to be investigated

All Secondary Outcomes are hypothesised to benefit from the Intervention.

## Mechanistic Component Outcomes

Details regarding the definition and analysis of the Mechanistic Component outcomes are not provided in this SAP.

## Health Economic Outcomes

Details regarding the definition and analysis of the Health Economic outcomes are not provided in this SAP.

## Subgroups and/or interactions

We will explore moderators of the continuous HDRS-17 score measured over 26 weeks at 8, 16 and 26 weeks such as:

|  |
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| […] severity of depression by baseline HDRS-17 score, degree of treatment resistance and age and number of TMS sessions attended as a (moderator\*) of outcome in exploratory sub-group analyses of the primary outcome.  |

\* Protocol v6.0 states mediator of outcome, however, moderator is more appropriate as baseline variables will not be caused by treatment arm.

Additionally, the degree of childhood trauma measured at baseline as defined by the total score obtained on the Childhood Trauma Questionnaire (for participants with an overall score of 56 or more) and the level of anxiety measured at baseline as defined by the total score obtained on the GAD-7 questionnaire (for participants with an overall score of 10 or more) will also be explored as moderators of the continuous HDRS-17 score measured over 26 weeks.

The number of TMS sessions that were attended, completed and delivered to the correct coordinates as per MRI data or as per changes allowed in the TMS SOP (10 or more as per definition of Completers population) will be explored as a moderator of the primary outcome at each of the follow-up time points.

Moderators such as the overall GAD-7 score, number of TMS sessions and the overall CTQ score will be included in the subgroup analysis of the primary outcome model as categorical variables, whereas age, the overall HDRS-17 score and the Degree of Treatment Resistant Depression will be included as continuous variables. Please refer to section 5.5 for details on the models that will be fitted for the moderators described in this section.

## Exploratory outcomes

### Definition and Derivation of Exploratory Outcomes

The HDRS-6 score is defined as a continuous outcome that measures the core symptoms of depression. The HDRS-6 comprises 6 of the 17 items from the HDRS-17 questionnaire: depressed mood, work and interests (pleasure), general somatic (tiredness), psychic anxiety, guilty feelings and psychomotor retardation. Each of the items on the HDRS-6 are therefore scored using the same scales as in the HDRS-17 questionnaire (Nixon et al, 2020).

## Compliance

**The following variables will be used to measure compliance with the treatments:**

1. Number of TMS sessions delivered (as per Protocol or as per changes allowed in the TMS SOP) within 6 weeks after randomisation.
2. The number of breaks between TMS sessions of more than 4 days as well as the average break length between TMS sessions of more than 4 days (measured in days).
3. Number of existing psychotropic medications or psychological interventions kept stable for 16 weeks for the duration of the Trial, except for those at risk to themselves or others.
4. Dose and frequency of intake of Benzodiazepine, Diazepam equivalentsa, Zopiclone, Zolpidem or Zaleplon from baseline assessment to the end of TMS treatment.

a The following medications are defined as Diazepam equivalents: Zopiclone, Zolpidem and Zaleplon as well as Benzodiazepines.

## Other variables to be summarised

We will summarise medications data collected at all time points by using BNF categories for Physical and Mental Health medications.

We will report the number and proportion of individuals with at least one medication from a BNF category for each BNF category at each time point. The denominator at each time point will be the number of participants who attended each visit.

Number of current medications taken at 8, 16 and 26 weeks will be summarised as a total count.

1. *Common Side Effects Yes/No*
	1. Headaches Yes/No
	2. Neck pain Yes/No
	3. Scalp discomfort Yes/No
	4. Tinnitus Yes/No
	5. Dizziness Yes/No
	6. Jaw ache Yes/No
	7. Nausea Yes/No
	8. Watering eyes Yes/No

The number and proportion of participants who had any of the common side effects listed above will be summarised by treatment arm and overall using data collected at 8, 16 and 26 weeks as well as at each TMS treatment session.

1. *Uncommon Side Effects Yes/No*

The proportion of participants who had any uncommon side effects will be summarised by treatment arm and overall using data collected at 8, 16 and 26 weeks as well as at each TMS treatment session. Uncommon side effects will be listed in a table by treatment arm and overall.

The overall proportion of participants with any side effects in addition to the frequency of all side effects will also be reported by treatment arm and overall.

# Analysis Sets/Populations

## Protocol deviations

### Major deviations

* Ineligibility post-randomisation.
* Non-compliance with the randomised treatment:
	+ Not receiving the protocolised treatment defined as receiving less than 20 sessions over a period of 4-6 weeks.
	+ Receiving wrong treatment as per randomised allocation (e.g.: delivery of TMS treatment to the incorrect coordinates as opposed to as per MRI data).
	+ Session stopped part way through treatment.
	+ Time between the first and last session exceeds 6 weeks.
	+ Break between treatment sessions of more than 4 days.
* Missing primary outcome data (including loss to follow-up) defined as the failure to provide the HDRS-17 score at all of the assessment time points: 8, 16 and 26 weeks.
* Receiving concomitant medications that should not be taken while receiving treatment (i.e. Lamotrigine, Pregabalin or Gabapentin).
* Psychotropic medications or psychological interventions not kept stable for 16 weeks for the duration of the Trial (except for those at risk to themselves or others).
* Daily prescription of Benzodiazepine above 5mg, Diazepam equivalents, Zopiclone above 7.5mg, Zolpidem above 10mg or Zaleplon above 10mg from baseline assessment to the end of TMS treatment.

### Minor deviations

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| Time windows for assessing outcomes will be at the following time points post randomisation date. 8 week Follow up will be 7 to 9 weeks, 16 weeks follow up will be 15 to 18 weeks and 26 weeks follow up from 25-27 weeks.Assessments completed outside these time frames will still be collected, however, will be treated as a protocol deviation and noted as such on a deviation CRF. |

* Time window deviations.
* Non-compliance with randomised treatment:
* Treatment adjusted as participant could not tolerate.
* Visit/assessment not performed as per Protocol:
* Did not attend/unsuccessful contact.
* Attended/contacted out of time frame.
* Component of assessment/procedure not done.
* Missing Secondary Outcome data assessments

The number and proportion of protocol deviations by type as well as the number and proportion of participants affected per deviation type will be reported by treatment arm and overall. Additionally, the number and proportion of participants who completed at least half (n=10) the number of TMS sessions adequately as stated in the Protocol will also be reported by treatment arm and overall.

## Intention-to-treat Population

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| --- |
| The primary analysis will test the null hypothesis that treatment with cgiTBS does not change the mean HDRS-17 score over 26 weeks when compared to rTMS on an intention to treat population.Provision of HDRS-17 at follow-up visits is expected to be very high, where this expectation isn’t met imputation methods will be utilised to account for missing data and maintain the intention to treat principle. |

The full Intention-To-Treat (ITT) population will consist of all participants who were randomised into the Trial. Participants will be analysed in the treatment arm to which they were randomly allocated, regardless of the treatment they received or any Protocol Deviations.

We will use multiple imputation technique to handle missing data in the primary analysis of the primary outcome in the event a participant is missing any of the HDRS-17 scores. This technique will also be used in the following variables: the outcome variable, predictors included in the final analysis model and any additional auxiliary variables in the imputation model under the assumption that data are missing at random (MAR), although we do not expect any missing data at Baseline.

Details on how the technique will be implemented in the primary analysis of the primary outcome can be found in section 5.3.

* 1.
	2.

## Per-protocol Population

The Per-Protocol population will consist of all participants randomised into the Trial who had their randomised treatment administered and who do not have any of the major Protocol deviations outlined in the Protocol Deviations section 3.1.

No imputation methods will be utilised for missing data in this population.

Changes in psychotropic medications were captured under the “Other Deviation” category and they will be adjudicated by the Chief Investigator as to determine whether or not they are this type of medication.

* 1.

## Safety Population

The Safety population will consist of all participants randomised into the Trial who had treatment administered. Participants will be considered to be in the treatment arm corresponding to the intervention they received the majority of the time, regardless of their randomised allocation.

## Other Analysis Populations

## Completers Population

The Completers population will comprise all participants randomised into the Trial who had 10 or more sessions of rTMS or cgiTBS delivered at the correct coordinates as per MRI data, and who were assessed at baseline and 16 weeks. Participants whose TMS site of stimulation was moved away from the coordinates to improve comfort, in accordance with the TMS SOP, will also be included in this population.

# General Issues for Statistical Analysis

Continuous Outcome data with symmetric distribution will be described with summary statistics such as the mean and standard deviation (SD). Determination of symmetry will be made informally by visualisation, taking into account sample size for each variable, the nature of potential outliers, and similarity between mean and median values (recognising formal statistics to test for normality often lead to spurious results).

Skewed continuous Outcome data will be summarised in terms of the median and interquartile range (IQR).

Categorical Outcome data will be summarised with frequency count and percentages.

In the case of the Patient Acceptability outcome, the value associated to each of the outcome’s categories will be treated as a score. The Patient Acceptability scores measured after each TMS session as well as those measured at each follow-up time point will be described by using a stacked bar chart.

Summary tables for both continuous and categorical Outcome data will be presented by treatment arm and overall in the intention to treat population.

Treatment comparison estimates will be presented alongside 95% Confidence Intervals (95% CI).

## Derived/ Computed Variables

1. *Number of TMS sessions delivered as per Protocol or as per changes allowed in the TMS SOP within 6 weeks of randomisation*

The TMS session number, session completion status and the number of sessions completed as originally planned or as per changes allowed in the TMS SOP will be used to derive a variable for the number of TMS sessions that were attended, completed and delivered to the correct coordinates as per MRI data or as per changes allowed in the TMS SOP within 6 weeks of randomisation.

1. *Number of breaks and average break length between TMS sessions*

The TMS session completion status and the session dates will be used to derive a variable that measures time since last completed session (or randomisation if first session) as to estimate both the number of breaks of more than 4 days as well as the average break length (measured in days) between TMS sessions.

1. *Number of existing psychotropic medications or psychological interventions kept stable for 16 weeks for the duration of the Trial*

Medication data collected at Baseline, 8 weeks and 16 weeks will be used to derive a variable that will count the number of psychotropic medications or psychological interventions that were kept stable for each participant from Baseline until the follow-up assessment carried out at 16 weeks.

Changes in psychotropic medications were captured under the “Other Deviation” category and they will be adjudicated by the Chief Investigator as to determine whether or not they are this type of medication.

## Multiple Testing

No corrections for multiple testing will be made when analysing the primary and secondary outcomes.

## Analysis Software

All clinical data will be extracted from a MACRO database.

The statistical analysis will be performed using a current version of either SAS, Stata or R (for graphical illustrations).

# Statistical Methodology

The specification of the interim analysis to be performed for the Feasibility Study will be detailed in section 7 of this SAP.

The statistical analysis of the main Trial will be based on external guidelines (e.g. ICH E3 and E9) as well as the addendum on estimands and sensitivity analysis in clinical trials (ICH E9 (R1)).

The date of data extraction will be included in each Statistical Report.

## Disposition

Disposition of participants will be presented on the ITT population with respect to number of randomised participants, completion status, reason for non-completion, intervention compliance, protocol deviations, length of stay in the Trial and blinding status. Results will be tabulated and summarised over time by treatment arm and overall.

A CONSORT diagram will display the flow of participants through the Trial including the eligibility, reasons for exclusion, numbers randomised to each treatment arm, number of participants who completed/did not complete their assessment at each of the follow-up time points, number of participants who were lost to follow-up and number of participants analysed in each population.

A graph of cumulative recruitment will be presented in addition to summaries of recruitment (e.g. start and end date) by site and overall.

Data completeness (i.e. CRF return rate) will also be summarised by treatment arm and overall for each CRF.

In light of the impact of the COVID-19 pandemic, the following impacts and mitigating strategies are listed below in accordance with the extension to the CONSORT for trials that were modified due to the pandemic (Orkin et al, 2021):

Extenuating circumstances: COVID-19 and its effects on recruitment and Study processes.

Impacts: pause to recruitment for 6 months (from 18th March until 31st August 2020), changes to methods for obtaining consent, outcome assessment (ie. conducting face-to-face follow-up assessments by telephone/video call) and the collection of outcome data (THINC-IT assessment same day as MRI Scan).

Mitigating strategies: please refer to the Appendix section 1 of this SAP for more details regarding the mitigating strategies that have been implemented to address the impacts on the Trial.

Responsible parties: proposals for modifications were planned by the Trial Management Group. These were then presented to the Trial Steering Committee for review and approval. Upon receiving approval from the committee, the proposals were then submitted to the Research Ethics Committee for approval.

Interim data: assessment completion rates pre and during COVID-19 are reported to the blinded and unblinded members of the Data Monitoring and Ethics Committee (DMEC) for their review and recommendations.

|  |
| --- |
| **CONSERVE-SPIRIT Extension: 14/03/2022** |
| **SPIRIT Item and Number** |  |
| No Change | Impact\* | Mitigating Strategy\*\* |
| 1 | Title | 🗸 |  |  |
| 2 | Trial registration | 🗸 |  |  |
| 3 | Protocol version |  |  | 🗸 |
| 4 | Funding |  |  | 🗸 |
| 5 | Roles and responsibilities | 🗸 |  |  |
| 6 | Background and rationale | 🗸 |  |  |
| 7 | Objectives |  |  | 🗸 |
| 8 | Trial design | 🗸 |  |  |
| 9 | Study setting | 🗸 |  |  |
| 10 | Eligibility criteria | 🗸 |  |  |
| 11 | Interventions | 🗸 |  |  |
| 12 | Outcomes |  |  | 🗸 |
| 13 | Participant timeline | 🗸 |  |  |
| 14 | Sample size |  |  | 🗸 |
| 15 | Recruitment |  | 🗸 |  |
| 16 | Allocation | 🗸 |  |  |
| 17 | Blinding (masking) | 🗸 |  |  |
| 18 | Data collection methods |  |  | 🗸 |
| 19 | Data management | 🗸 |  |  |
| 20 | Statistical methods |  |  | 🗸 |
| 21 | Data monitoring | 🗸 |  |  |
| 22 | Harms | 🗸 |  |  |
| 23 | Auditing | 🗸 |  |  |
| 24 | Research ethics approval | 🗸 |  |  |
| 25 | Protocol amendments | 🗸 |  |  |
| 26 | Consent or assent | 🗸 |  |  |
| 27 | Confidentiality | 🗸 |  |  |
| 28 | Declaration of interests | 🗸 |  |  |
| 29 | Access to data | 🗸 |  |  |
| 30 | Ancillary and post-trial care | 🗸 |  |  |
| 31 | Dissemination policy | 🗸 |  |  |
| 32 | Informed consent materials |  |  | 🗸 |
| 33 | Biological specimens | 🗸 |  |  |
| \*Aspects of the trial that are directly affected or changed by the extenuating circumstance and are not under the control of investigators, sponsor or funder. \*\*Aspects of the trial that are modified by the study investigators, sponsor or funder to respond to the extenuating circumstance or manage the direct impacts on the trial. The CONSERVE-SPIRIT Checklist is licensed by the CONSERVE Group under the Creative Commons Attribution-NonCommercial-NoDerivs 4.0 International license. |

Please refer to the Appendices sections 1 and 2 of this SAP for more details regarding the mitigating strategies that have been implemented and the Protocol Amendments that have been made.

## Demographic and Baseline Characteristics

Demographics and baseline characteristics will be summarised by treatment arm and overall for each centre, which is the only stratification variable in the main Trial.

Frequency (with percentages) will be presented to summarise categorical and ordinal variables. Means (and standard deviations) will be reported for continuous data that are approximately normally distributed. Normality will be evaluated by using histograms. Medians (with lower and upper quartiles) will be used to summarise skewed continuous variables.

There will be no tests of statistical significance nor confidence intervals for differences between randomised groups on any baseline variable.

## Primary Outcome Analysis

### Primary Analysis of Primary Outcomes

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| The primary analysis of the primary outcome will be a mixed effects model with participant as random effect to account for repeated measures over time. Each participant will contribute up to 3 repeated outcome measures to the model in addition to the baseline HDRS-17 score. The model will be adjusted for the stratification and minimisation variables: baseline HDRS-17 score, baseline Massachusetts General Hospital Treatment Resistant Depression score, visit number and centre. The primary analysis of the primary outcome will fit this model on all available data. Participants with at least one follow-up measure of HDRS-17 will contribute to the model. Provision of HDRS-17 at follow-up visits is expected to be very high, where this expectation isn’t met imputation methods will be utilised to account for missing data and maintain the intention to treat principle. |

In addition to the minimisation, stratification and visit number variables, the categorical variable for treatment arm (rTMS arm as reference) will also be included in the Primary Analysis of the Primary Outcome.

Participant IDs will be included in the model as a random effect to model participant heterogeneity within sites.

As mentioned in section 3.2, the multiple imputation technique will be implemented in order to ensure the population remains truly ITT. In order to achieve this, missing data corresponding to all variables included in the primary analysis of the primary outcome model will be imputed using a multiple imputation procedure which will substitute the missing data with predicted values from an equation. The following variables will be used as predictors of the primary outcome at each time point in the regression equation: gender, ethnicity, age, center, baseline HDRS-17 score and degree of treatment resistant depression at baseline as well as the primary outcome at the other two time points. Missing values for these predictor variables will also be imputed if needed using similar methodology.

MI replaces missing values with multiple sets of simulated values to complete the data, performs standard analysis on each completed dataset and adjusts the obtained parameter estimates for missing-data uncertainty using Rubin’s rules to combine estimates (Rubin). The imputation technique will be carried out by the MI command in Stata. A total of twenty imputations will be estimated and a seed will be set in order to ensure the results are reproducible.

The variance-covariance matrix for the random effect (participant ID) will be assumed to be unstructured and the models will be estimated using restricted maximum likelihood. Model residuals are assumed to follow a normal distribution and to have constant variance. These assumptions will be ascertained by producing residual diagnostic plots. Variable transformations will be considered and performed in the event the assumptions are not met.

A treatment comparison estimate will be presented as an adjusted mean difference between the treatment arms along with a two-sided 95% confidence interval. Statistical significance is considered at less than or equal to 5%.

The estimand of the mean difference in HDRS-17 score over 26 weeks is presented in the table below in accordance with the ICH E9(R1) addendum on estimands and sensitivity analyses in clinical trials:

| **Estimand attribute** | **Definition** |
| --- | --- |
| *Population* | Adult patients aged 18 or above with a primary diagnosis of moderate to severe MDD who have a MGH score of 2 or more. This includes individuals who have not responded to 2 different antidepressant regimes, antidepressant augmentation strategies, high prolonged dosages of antidepressants and/or ECT in their current episode |
| *Treatment condition* | Connectivity guided intermittent Theta Burst Stimulation (cgiTBS) vs. standard repetitive Transcranial Magnetic Stimulation (rTMS) treatment to be delivered in 20 sessions over 4-6 weeks |
| *End point* | Hamilton Depression Rating Scale (HDRS-17) measured over 26 weeks at 8, 16 and 26 week assessments |
| *Population-level summary* | Mean difference in the HDRS-17 score over 26 weeks between the treatment arms |
| *Intercurrent Event* |  |
| Delivery of TMS treatment to the incorrect coordinates (i.e. not as per MRI data or changes allowed in the TMS SOP) | Treatment policy strategy (i.e. ITT) |
| TMS discontinuation due to AES | Treatment policy strategy (i.e. ITT) |
| TMS discontinuation due to participant not being able to tolerate treatment | Treatment policy strategy (i.e. ITT) |
| Death | Treatment policy strategy (i.e ITT) |
| Challenges due to the COVID-19 pandemic  | Treatment policy strategy (i.e. ITT) |

### Secondary Analyses of Primary Outcomes

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| --- |
| As a secondary analysis, a mixed effects model will be repeated in completers (those with 10 or more sessions rTMS or cgiTBS, assessed at baseline and 16 weeks) and a per protocol analysis adjusting for the same variables as in the primary analysis. |

#### Completers population

A secondary analysis of the primary outcome will be performed using the Completers population. As mentioned in section 3.4, participants with 10 or more sessions delivered to the correct coordinates as per MRI data as well as participants whose TMS sessions were delivered as per changes allowed in the TMS SOP will be included in the Completers population.

#### Per Protocol population

A secondary analysis of the primary outcome will also be performed using the Per Protocol population, which will include all participants who do not have any major protocol deviations recorded.

The completers and per protocol analyses will be conducted using same model as the primary analysis of the primary outcome (section 5.3.1). No imputation will be carried out for this analysis, instead an available data approach will be used.

Treatment comparison estimates will be presented in both models as adjusted mean differences between the treatment arms and two-sided 95% confidence interval for each estimate. Statistical significance is considered at less than or equal to 5%.

### Sensitivity Analyses

#### Primary Analysis under Missing Not At Random (MNAR) assumption

The primary analysis imputation methods assume the missing data mechanism is missing at random (MAR). We will evaluate this assumption by implementing a Control-based Multiple imputation approach (Cro et al, 2020). All participants with missing outcome data will have their primary outcome value imputed with the mean value of the rTMS treatment arm. The model for this analysis will be adjusted for the same variables as in the model for the final analysis.

#### Pre and Post COVID-19 period

Sensitivity analyses will be conducted using similar methodology as the primary analysis of the primary outcome, noting that they will be performed using data corresponding to participants whose HDRS-17 assessment at 26 weeks was due before and up to 18th March 2020 (pre-COVID-19) and also after this cut-off date (post-COVID-19). A variable for pre/post COVID-19 period as well as an interaction term for pre/post COVID-19 period and treatment group will be included in the model.

Baseline characteristics of participants in each group defined above will be presented by treatment arm and overall.

The imputed datasets from the primary analysis of the primary outcome will be used for this analysis.

#### Centre as random effect

A sensitivity analysis will be conducted using similar methodology as the primary analysis of the primary outcome fitting a mixed effects model with centre as random effect.

The imputed datasets from the primary analysis of the primary outcome will be used for this analysis.

## Secondary Outcome Analyses

### Primary Analysis of Secondary Outcomes

|  |
| --- |
| Secondary outcomes proportion of responders and remitters at 8, 16 and 26 weeks and sustained responders at both 16 and 26 weeks will be compared between groups using logistic regression adjusted for treatment centre, baseline HDRS-17 score and balance Massachusetts General Hospital Treatment Resistant Depression (5% significance). Repeated measure linear models will be used for continuous outcome (BDI, EQ-5D). Patient acceptability (5-point scale and qualitative interviews – see below) and safety of both TBS and rTMS (side-effect checklist) will be reported descriptively. |

**Binary Outcomes**

1. ***Proportion of responders at 8, 16 and 26 weeks***
2. ***Proportion of remitters at 8, 16 and 26 weeks***
3. ***Proportion of sustained responders at 16 and 26 weeks***

The proportion of responders and remitters as well as the proportion of sustained responders will be analysed by implementing a parametric approach on the Intention-To-Treat population. These binary outcomes will be compared between treatment arms using Multilevel Logistic Regression models. An available data approach will be implemented when carrying out these analyses.

Treatment comparison estimates will be presented as adjusted Odds Ratios (OR) and two-sided 95% confidence intervals. Statistical significance is considered at less than or equal to 5%.

In the event that the assumptions of the Multilevel Logistic Regression are not met, a non-parametric approach will be implemented instead.

**Continuous Longitudinal Outcomes**

1. ***Patient Health Questionnaire (PHQ-9) score at 8, 16 and 26 weeks***
2. ***Generalised Anxiety Disorder Assessment (GAD-7) at 8, 16 and 26 weeks***
3. ***Work and Social Adjustment Scale (WSAS) at 8, 16 and 26 weeks***
4. ***Beck Depression Inventory (BDI) at 8, 16 and 26 weeks***
5. ***EuroQol-5D-5L at 8, 16 and 26 weeks***
6. ***Quick Inventory of Depressive Symptomology (QIDS-SR16) at 8 and 16 weeks***

The secondary outcomes listed above will be analysed by implementing a parametric approach on the Intention-To-Treat population. Prior to the implementation of this approach, an assessment of normality will be carried out as to investigate whether the assumptions are met. In case these are not satisfied, an alternative approach will be considered and implemented. An available data approach will be implemented when carrying out these analyses.

The continuous outcomes will be compared between treatment arms using Mixed Effects Linear Regression models, with each model adjusting for their respective baseline measure. Treatment arm, treatment centre (stratification variable), baseline HDRS-17 score and degree of treatment resistance (minimisation variables) will be fitted as fixed effects in the models while the participant ID will be fitted as a random effect.

For untransformed outcome data, treatment comparison estimates will be presented as adjusted means with two-sided 95% confidence intervals. However, for transformed data, treatment comparisons will be presented as adjusted geometric means with two-sided 95% confidence intervals. Statistical significance is considered at less than or equal to 5%.

The residuals of the model that will be fitted for each of the outcomes will be assessed for normality by performing the Shapiro-Wilk test.

In the event that the assumptions of the Mixed Effects Linear Regression are not met, a non-parametric model will be fitted instead.

**The Secondary Outcomes listed below will be reported descriptively by treatment arm:**

1. THINC Integrated Tool (THINC-IT). This outcome will be summarised as follows:
* Baseline and 16 weeks only (all time)
* Baseline and 16 weeks only (during COVID-19)
* at 8, 16 and 26 weeks (pre-COVID-19)
1. Patient Acceptability (5 point scale and qualitative interviews).
2. Safety of both TBS and rTMS after each session (side effects checklist).

It is important to note that hypothesis testing will not be conducted for any of these secondary outcomes.

### Secondary Analyses of Secondary Outcomes

No outcomes have a planned secondary analysis.

### Sensitivity Analyses

None.

## Subgroup Analyses

We will explore moderators of the continuous HDRS-17 score measured over 26 weeks at 8, 16 and 26 weeks such as:

|  |
| --- |
| […] severity of depression by baseline HDRS-17 score, degree of treatment resistance and age and number of TMS sessions attended as a (moderator\*) of outcome in exploratory sub-group analyses of the primary outcome. |

\* Protocol v6.0 states mediator of outcome, however, moderator is more appropriate as baseline variables will not be caused by treatment arm.

**NB:** the number of TMS sessions that were attended, completed and delivered to the correct coordinates as per MRI data or as per changes allowed in the TMS SOP (10 or more, as per definition of Completers population) will be explored as a moderator of the primary outcome at each of the follow-up time points.

Additionally, the degree of childhood trauma measured at baseline as defined by the total score obtained on the Childhood Trauma Questionnaire (for participants with an overall score of 56 or more) and the level of anxiety measured at baseline as defined by the total score obtained on the GAD-7 questionnaire (for participants with an overall score of 10 or more) will also be explored as moderators of the continuous HDRS-17 score measured over 26 weeks.

The model used for the primary analysis of the primary outcome will be fitted for each moderator. Moderators such as the overall GAD-7 score, number of TMS sessions and the overall CTQ score will be included in a model as categorical variables, whereas age, the overall HDRS-17 score and the Degree of Treatment Resistant Depression will be included in another model as continuous variables. An available data approach will be implemented when carrying out these analyses.

In the second model with moderators regarded as continuous variables, an interaction term between the potential moderator and treatment arm will also be included in the model. Similarly, an interaction term between each of the follow-up time points and the treatment arm, in addition to the variables included in the primary analysis, will also be fitted for each of the subgroups. An available data approach will be implemented when carrying out these analyses.

The treatment effect estimate will be presented along with a 95% confidence interval for each subgroup in a Forest plot (with and without a test of heterogeneity). Each of the subgroup analyses will be adjusted for the moderator as well as a moderator-treatment interaction.

## Exploratory Analyses

An exploratory analysis of the HDRS-6 score as the outcome of interest will be conducted using similar methodology as the primary analysis of the primary outcome in the event that a statistically significant difference is found between treatment arms on the primary outcome measure. This analysis will help determine whether the core symptoms of depression have improved rather than the symptoms of anxiety or sleep. An available data approach will be implemented when carrying out this analysis.

A treatment comparison estimate will be presented in the model as an adjusted mean difference between the treatment arms and two-sided 95% confidence interval. Statistical significance is considered at less than or equal to 5%.

## Changes to the Planned Analysis

None.

# Safety and Adverse events

|  |
| --- |
| We will use internationally agreed definitions of adverse events (any untoward medical occurrence in a clinical trial subject administered TMS whether or not it has a causal relationship with TMS) and serious adverse events (any adverse event or adverse reaction that results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect). All participants will be asked about adverse events after every treatment (immediately and maximum of 72 hours later) and at every follow up point using a side effect checklist. These two treatments are expected to have a similar profile of side effects.  |

|  |
| --- |
| Common adverse effects (all of which subside within 1-2 hours of TMS usually) include:HeadachesNeck painScalp DiscomfortTinnitusDizzinessJaw AcheNauseaWatering eyes |
| Uncommon Adverse effects include:Seizures (in the event of a seizure, treatment will be stopped and no further treatment will be administered.)We will ask each participant and clinical team to report any potential adverse or serious adverse event to the research team. Any participant found to be at risk to themselves (suicide, neglect) or others or developing a serious adverse event will be referred to the local mental health crisis team. Details will be in the study handbook for each site. Emergency un-blinding will not be clinically needed, due to every participant receives TMS treatment with equal amount of power administered overall. We will follow GCP guidance on reporting and determining causality of adverse and serious adverse events in clinical trials. |

In addition to the uncommon adverse effects outlined in the Protocol, it is important to note that serious adverse events such as Syncope can also occur after a TMS session.

All safety data will be presented according to the Safety population.

All adverse events will be listed by treatment arm and overall based on the following characteristics: seriousness, duration (measured in days), relatedness, severity, action taken, outcome and expectedness.

Adverse events frequencies by outcome, severity, treatment, action taken, seriousness, relatedness and expectedness will be summarised by treatment arm and overall.

The number and proportion of adverse events by type as well as the number and proportion of participants affected per adverse event type will be reported by treatment arm and overall.

# Internal Pilot

|  |
| --- |
| An internal pilot for 8 months (months 10 – 17) with review according to independent trial steering committee based on rates of recruitment in months 15-17 (with a hard stopping rule of 3 participants per site per month should be recruited as a minimum during these 3 months, in addition, if recruitment is lower than expected 5 patients per month at a particular site(s) barriers to recruitment will be identified and mitigation plan at each site). |

Based on what the hard stopping rule states, each site is expected to recruit 3 patients between months 15-17 (inclusive). Furthermore, considering there are 4 sites recruiting, it is expected that a total of 36 patients will be recruited during the last 3 months of the Internal Pilot.

At the end of the internal pilot a report containing a progress summary of the trial to date will be prepared and presented to the Data Monitoring and Ethics Committee (DMEC), TSC and the Funder. The following primary outcomes of the internal pilot phase will be reported:

* The number of patients recruited into the Trial per month per site in the last 3 months of the Internal Pilot.
* The number of patients recruited into the Trial per month in the last 3 months of the Internal Pilot for each site individually.

Additionally, the report will include:

* Summaries of overall recruitment progression, per site, over time and overall
* Patient disposition of randomised patients
* Treatment compliance
* Protocol deviations
* Adverse events

## Study Objectives

### Main Objective

To assess whether it is feasible, with continued recruitment, to recruit the number of participants required to sufficiently power this trial to achieve the primary objective.

### Secondary Objective

To assess the safety of continuing the Trial.

## Outcomes

### Primary Outcome

Recruitment rate (per month per site) between months 15-17 (1st April 2019 – 30th June 2019, inclusive) of the Trial Grant. Defined as the number of randomisations performed during this period, divided by 3 (months), divided by 4 (participating sites).

### Secondary Outcomes

* Recruitment rate (per month) between months 15-17 (1st April 2019 – 30th June 2019, inclusive) of the Trial Grant for each site individually. Defined as the number of randomisations performed during this period, divided by 3 (months) for each site separately.
* Adverse Events
* Serious Adverse Events
* Protocol Deviations

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# Appendices

##  Appendix 1: Mitigation strategies to reduce risk of COVID-19

Data source: DMEC Report Recruitment presented to the Data Monitoring Committee by the Trial Manager on 23rd June 2020.

| **Study flow** | **Process** | **Reason and Change in Process** |
| --- | --- | --- |
| Eligibility Screening Telephone | * Telephone screening for eligibility completed.
* If eligible Appointment letter with following enclosed:-
	+ Patient information Sheet
	+ COVID- 19 Change of process information sheet
	+ (This will include all the changes made to minimise contact and to ensure safe for participants and staff along with Pictures of research staff and contact numbers)
	+ Participant consent form.
	+ Date of Remote appointment with instructions.
 | * COVID 19 Process Information sent to patient to clearly explain the process and reassure patients.
* Consent form sent to patient to sign at Remote Consent /Baseline Assessment.
 |
| Consent Process(Remote-Video Call Teams or Telephone participant preference) | * Consent process discussed with patient each section of the consent.
* Patient to sign their consent form whilst on the phone with the Research Assistant (RA).
* Script provided to reassure patient of measures taken for COVID-19.
* RA will sign the Researcher consent to confirm patient has agreed to each section (see attached).
 | * To minimise face to face contact with patient.
* If participant is ineligible or withdraws then researcher has signed to say patient agreed to consent.
* Participant to bring completed consent to next appointment
 |
| Baseline Assessment same remote contact /time as Consent Process.(Remote-Video Call Teams or Telephone participant preference) | * RA complete all Baseline assessments except thinc-it tool outcome measure.
* RA Arrange Face to Face appointment to complete Thinc-it outcome measure.
* Send email /letter re appointment
 | * Thinc-it measure cannot be completed remotely.
* No impact on assessments being completed remotely.
* (If patient not willing to complete Thinc- it tool, the patient must bring the copy of the consent to TMS appointment, as no treatment can be delivered until a copy of the consent has been provided. RA to notify TMS team consent required before treatment. Consent to be retained and with TMS file until participant completes study and confirmed receipt by TMS to RA.)
* (Thinc-it outcome Appointment will need to be arranged to allow MRI scan to be completed within 14 days of baseline appointment.) This will reduce face to face contact by 90 mins.
 |
| Day prior to Face to face appointment(Telephone) | * RA contacts participant to remind re appointment and bring completed consent.
* Complete COVID-19 symptoms screening questionnaire
 | * Reminder bring completed consent form. To ensure receipt of consent prior to any delivery of treatment.
* Completion of COVID-19 symptom checker to ensure does not attend appointment if any symptoms or contact with others with symptoms.
* Rearrange appointment after isolation period ends. Complete deviation if outside protocol time scales.
 |
| Thinc It Tool AssessmentSame day as MRI Scan(Face to Face) | * Confirm no changes since COVID-19 symptoms screening questionnaire
* Collect participant signed consent form
* Researcher to sign Participants copy.
* RA provides copy of Consent to Participant
* Thinc- Tool Outcome measure completed 2m distancing using 2 IPADs.
 | * Participant cannot be accompanied by a friend or relative during the assessment. They can be escorted to and from the clinic, but not stay.
* Face to face contact reduced to 30mins.
* 2M distancing guidelines apply.
* Site to obtain additional IPAD 1 for participant, I for researcher use to be able to provide instructions how to complete measure.
* Notts HC and NHFT to be completed same time as MRI.
 |
| MRI ScanSame day as Thinc-it assessment.(Face to Face) | * All sites follow own guidelines
* Distancing where possible/ PPE equipment.
 | * All sites follow own guidelines
* Distancing / PPE equipment.
* Cleaning of all equipment after each patient
* Limit to number seen at the centre.
 |
| Day Prior to TMS (Telephone) | * RA contacts participant to remind re appointment and bring consent if did not attend Thinc-it outcome measure.
* Complete COVID-19 symptoms screening questionnaire
 | * Any symptoms participant advised to follow government guidelines on social distancing.
* Rearrange appointment after isolation period ends. Complete deviation if outside protocol time scales.
 |
| TMS treatment day x 20 Sessions(Face to Face Contact) | * All sites to ensure TMS areas
* COVID screening and Participant Temperature taken prior to treatment.
* PPE worn as per trust guidelines
* Cleaning of Equipment after each participant.
 | * Participant cannot be accompanied by a friend or relative during TMS treatment. They can be escorted to and from the clinic, but not stay.
* All sites to ensure TMS areas signposted for ease of finding TMS waiting room.
* Social distancing Waiting Rooms available for completion of COVID- 19 screening.
* Any symptoms participant advised to follow government guidelines on social distancing.
* Rearrange appointment after isolation period ends. Complete deviation as outside protocol time scales.
 |
| 8 Week Follow Up Assessment(Remote-Video Call Teams or Telephone participant preference) | * Complete Follow Up outcome measures at week 8.
* Thinc-it Outcome measure not completed.
 | * Thinc-it tool cannot be completed remotely so therefore to minimise contact with participant no Thinc-it data to be collected at week 8.
 |
| 16 Week Follow Up Assessment(Remote-Video Call Teams or Telephone participant preference) | * Complete Follow up Outcome measures at Week 16.
* Thinc-it Outcome measure not completed.
 | * Thinc-it tool cannot be completed remotely so therefore to minimise contact with participant Thinc-it data to only be completed in face to face appointment.
 |
| Day prior to Face to face appointment(Telephone) | * RA contacts participant to remind re appointment.
* Complete COVID-19 symptoms screening questionnaire
 | * Completion of COVID-19 symptom checker to ensure does not attend appointment if any symptoms or contact with others with symptoms.
* Rearrange appointment after isolation period ends. Complete deviation if outside protocol time scales
 |
| 16 Week Thinc-it ToolSame day as MRI Scan(Face to Face Contact) | * Confirm no changes since COVID-19 symptoms screening questionnaire
* Thinc- Tool Outcome measure completed 2m distancing using 2 IPADs.
 | * Face to face contact reduced to 30mins.
* 2M distancing guidelines apply.
* Site to obtain additional IPAD 1 for participant, I for researcher use to be able to provide instructions how to complete measure.
* Notts HC and NHFT to be completed same time as MRI.
 |
| MRI Scan Same day as Thinc-it assessment.(Face to Face) | * All sites follow own guidelines
* Distancing where possible/ PPE equipment.
 | * All sites follow own guidelines
* Distancing / PPE equipment.
* Cleaning of all equipment after each patient
* Limit to number seen at the centre.
 |
| 26 Week Follow Up Assessment(Remote-Video Call Teams or Telephone participant preference) | Complete Follow Up outcome measures at week 8.Thinc-it Outcome measure not completed. | * Thinc-it tool cannot be completed remotely so therefore to minimise contact with participant no Thinc-it data not collected at week 26.
 |
|  |
| **Documents**  | **Addition/Change** | **Reason and Change in Process**  |
| COVID-19 Information sheet | Additionally document to be sent participant with patient information.Study Flow diagram. TMS Information sheet | Provide clear information what actions we have taken to minimise the risk to COVID-19 for the study.To reassure participants |
| Contact Sheet | Separate contact sheet for Research Assistants and TMS Delivery staff.To include telephone contact numbers and emails. | Pictures will help to build rapport with researchers.Contact number to help participant identify that researcher calling for assessments. |
| COVID-19 Symptoms Questionnaire | Additionally document to check participants day before and before any face to face contact with Study research staff1x Symptoms Questionnaire1x On the day of TMS Treatment Delivery. | Ensure eliminate participant attending any face to face appointment if show signs of any symptoms. |
| Consent Form | Additional consent form for Researcher to complete whilst consenting participant remotely. | So researcher to evidence consent was taken and signed by participant, prior to receipt to consent. |
| Thinc-it/Delivery of Consent Form Visit | Email/Text participant with details of appointment details and what should be brought to the visit. | Generate Standard wording for the Email/Text. |
| COVID 19 TMS SOP | Update with additional processes  |  |

## Appendix 2: Protocol Amendment History

Data source: DMEC Report Recruitment presented to the Data Monitoring Committee by the Trial Manager on 19th January 2021.

