Nottinghamshire Healthcare NHS
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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.

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Contents

Contents

Study Summary

Enter a brief description of your study

Full Study Title	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.
Short Study Title	Brain Image Guided Transcranial Magnetic In Depression (BRIGhTMIND)
IRAS Number	245025
Ethics Reference Number	18/EM/0232
Study Design	The study is a multicentre parallel group, double blind, randomised controlled trial of the efficacy of Connectivity Guided Intermittent theta-burst stimulation (cgiTBS) versus no connectivity guided standard Repetitive Transcranial Magnetic Stimulation (rTMS) in patients with a primary diagnosis of moderate to severe MDD who have not responded to 2 different antidepressant regimes, antidepressant augmentation strategies, high prolonged dosages of antidepressants and/or ECT in their current episode.
Study Participants	Participants with Treatment Resistant Depression with capacity to consent.
Study Sample Size	368
Study Location/s	Nottingham, Newcastle, Northampton and London
Participant Inclusion Criteria	- Adults $\geq$ 18 years - With diagnosis of Major Depressive Order (MDD) (defined according to DSM-5) that is treatment resistant (defined as scoring 2 or more (42) on the Massachusetts General Hospital Treatment Resistant Depression staging score (51). - HDRS-17 score of 16 or more (moderate to severe depression) (52) - Capacity to provide informed consent before any trial related activities
Primary Research Questions	To determine the efficacy of Connectivity Guided Intermittent theta-burst stimulation (cgiTBS) at 16 weeks and 26 weeks compared with standard Repetitive Transcranial Magnetic Stimulation (rTMS); in people with Treatment Resistant Depression.

Secondary Research Question/s	To explore secondary clinical outcomes of importance to patients and clinicians namely cognition, social function, quality of life and overall clinical improvement
	To examine cost effectiveness of cgiTBS versus rTMS in a UK National Health Service (NHS) population.
	To examine the patient acceptability and patient experience of cgiTBS and rTMS.
	To study the mechanisms of therapeutic efficacy using multimodal MRI, and to develop a response prediction model.
Interventions	Participants will receive 20 TMS sessions delivered over 4-6 weeks. A total of 3000 pulses will be delivered in each rTMS (standard) or cgiTBS (Novel) session.
	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 site for TMS stimulation from 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 gives a more precise and reproducible location for the TMS stimulus over 20 TMS sessions. .
	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) for 40 seconds duration 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 using neuronavigation which computes the nearest location for TBS stimulus on the scalp from the same three fiducal points, the nasion, left preauricular and right preauricular sites.. The pulses are HDRS for a total of 5 runs with 5 minutes rest intervals between runs.

1 Abbreviations

Define any terms/acronyms (in alphabetical order) that you will be using throughout your project. Add or delete acronyms are appropriate.

CI	Chief Investigator
CRF	Case Report Form
CBT	Cognitive Behavioural Therapy
cgiTBS	Connectivity Guided Intermittent Theta Burst Stimulation
CRN	Clinical research Network
CTU	Clinical Trials Unit
DLPFC	Dorsolateral prefrontal cortex
DMPFC	Dorsomedial prefrontal cortex
ECT	Electroconvulsive Therapy
EEG	Electroencephalography
eFC	Effective functional connectivity
FC	Functional Connectivity
fMRI	Functional Magnetic Resonance
GABA	Gamma-amino butyric acid
GCP	Good Clinical Practice
GP	General Practitioner
ICF	Informed Consent Form
ITBS	intermittent theta-burst stimulation
MDD	Major Depressive Disorder
MRS	Magnetic Resonance Spectroscopy
NIHR	National Institute for Health Research
NHCT	Nottinghamshire Healthcare NHS Trust
NHS	National Health Service
NRES	National Research Ethics Service
PI	Principal Investigator
PIS	Participant/ Patient Information Sheet
PPI	Patient and Public Involvement
QOL	Quality of Life
RCT	Randomised Controlled Trial
R&D	NHS Trust R&D Department
REC	Research Ethics Committee

RsfMRI	Resting state (task-free) functional MRI
rTMS	Repetitive Transcranial Magnetic Stimulation
SOP	Standard Operating Procedure
TMS	Transcranial Magnetic Stimulation
TRD	Treatment resistant depression
VNS	Vagus Nerve Stimulation

2 Rationale

Lay Abstract

Depression is the 2nd leading cause of disability worldwide and suicide from depression is the biggest killer in people aged 15-49 years. Antidepressants and talking therapies help two thirds of people with depression, but the remaining third have treatment resistant depression (TRD). Until recently, a few patients with TRD were offered Electroconvulsive Therapy (ECT), but they may not accept this treatment due to its possible side effects. An alternative treatment called transcranial magnetic stimulation (TMS) has recently been used employing magnets and not requiring an anaesthetic. In December 2015, NICE reviewed the evidence for TMS and advised that it may be used to treat depression. NICE reports that TMS is safe and effective in reducing symptoms for a short while, but has asked for further research to be carried out. In this trial we compare rTMS the standard treatment and a novel type of TMS called theta-burst stimulation (TBS). A pilot study showed that TBS guided by a brain scan (cgiTBS) can maintain the improvement longer than the rTMS treatment but this needs further research before it is used in clinical practice. Patients with depression experience changes in some parts of the brain particularly in the frontal area. If an intervention is delivered precisely to these specific parts of the brain, it may avoid unwanted effects and improve the outcome, based on a brain scan, for each patient a specific point in the brain is identified to deliver the magnetic pulses.

2.1 Existing research: Treatment resistant depression.

The lifetime prevalence of major depressive disorder (MDD) is approximately 13% of the general population (1), the second most disabling condition in all health in terms of years lived with disability (2). Suicide, mostly due to depression, is the largest cause of mortality in the 15-49 year age group (3). While antidepressants and psychotherapies are effective in treating MDD, 33% patients in specialist care fail to respond to two antidepressants (4) as do 22% in general primary care (5). Such "treatment resistant depression" (TRD) has a 12 months prevalence of 1-2% in the general population, making it as common as other serious mental illnesses such as schizophrenia (6-7). Compared with MDD that is not treatment resistant, TRD is associated with higher rates of suicide (8), hospitalisation, poor physical health and increased costs (9). In a review of 59,462 patients from 62 studies (10), TRD had an episode duration as long as 4.4±3.3 years, and patients had completed 4.7±2.7 unsuccessful drug trials involving 2.1±.3 drug classes. TRD also has a major impact on quality-of-life (QoL). Using a scale of 0-1 (0 indicating death and 1 indicating perfect health), at baseline prior to a treatment trial, patients with TRD scored just 0.41±0.8 (10). However, improvement in mood has a significant impact on QoL. If patients showed a 50% improvement in depressive symptoms (the definition of response) they improved by 0.26±0.8 points. If they reached full remission they achieved a score of 0.82±0.7 (10).

2.2   Repetitive transcranial magnetic stimulation.

Therapeutic interventions that can directly modulate the function of targeted brain regions have been shown to have a significant impact on reducing the burden of TRD symptoms (11). One of these neuromodulation approaches is TMS, which employs intense localised magnetic fields to alter activity in neural circuits in the brain implicated in the pathophysiology of depression. These do not produce seizures and therefore there is no need for anaesthesia (unlike other treatments for TRD such as ECT, VNS and DBS). TMS does not cause cognitive deficits nor any other untoward neural event, compared to ECT. It also has a lack of debilitating side-effects of antidepressants and other psychotropics used for TRD (e.g. lithium or quetiapine) such as weight gain, renal and thyroid dysfunction, metabolic syndrome or sexual dysfunction.

NICE (IPG 542, December 2015) appraised the evidence for rTMS in TRD and found it to be safe and effective in reducing depressive symptoms compared to sham TMS and requiring neither hospital admission nor anaesthesia. It was therefore recommended for the treatment of depression, including TRD. The biggest drawback to its use is that the beneficial effects of rTMS on mood tend to only last for a short period of time after a course of treatment (around one month) (12, 13). Additionally, uncertainty remains around patient selection for TMS, the best TMS treatment regime for use, its use as a maintenance treatment (given the relatively short-lived duration of response after each course of treatment), and long-term outcomes of patients undergoing the treatment. Hence NICE encourages studies addressing these issues (12). A more recent review of 16 RCTs in 510 TRD patients found TMS to be robustly effective versus sham TMS on depression symptoms, response or remission but no differences with different scalp sites of stimulation, the strength of stimulation in relation to the motor threshold, duration of treatment or treatment intensity with rTMS (13), although potentially effective alternatives have yet to be tested. NICE emphasised the importance of the identification of a more effective method of using TMS as well as predictors for responders and non-responders to TMS (12).

Despite these limitations, a recent health economics analysis found TMS to be a cost effective treatment for depression with the greatest cost benefit seen with the application of TMS at earlier treatment resistance compared to current care (14). Therefore, improving the efficacy of TMS combined with the identification of patients likely to respond to treatment would improve patient response rates, reducing the economic cost to the person and society. An alternative form of TMS, intermittent theta-burst stimulation (iTBS), may induce longer-term improvement in symptomatology (15). In our pilot randomised controlled trial (RCT), connectivity guided intermittent TBS (cgiTBS – see below), led to a longer more clinically useful duration of depression response of 3 to 6 months. This prolonged duration of response means that potentially just two courses of cgiTBS may help some patients remain symptom free from depression for a year.

2.3   Evidence base for Theta Burst Stimulation (TBS).

Up to now, there have been a small number of underpowered RCTs of TBS in MDD and TRD (and importantly these have been without connectivity guidance – see below). The existing data are complex to interpret due to the design of the published RCTs often varying greatly with both continuous and intermittent forms of TBS delivered together and sometimes short courses of treatment (10-15 sessions). Despite these issues, the evidence points to TBS leading to a longer duration of response than rTMS and efficacy over sham TBS (16-19).

The efficacy of TBS in TRD is supported by a RCT of 60 moderately to severely depressed patients that found there were more responders at the end of treatment between participants given iTBS,

continuous TBS (cTBS) plus iTBS and cTBS compared to sham TBS (16). It is noteworthy that 83% patients given iTBS maintained their response at 14 weeks unlike the other treatment groups (16). Interestingly a subsequent analysis of data from this RCT found that only iTBS compared to the other treatment groups was associated with improved frontal executive function at 2 weeks (17). Similarly, an RCT in 32 people with TRD compared 30 sessions of iTBS over the left DLPFC combined with cTBS over the right DLPFC versus bilateral sham TBS reported significantly more responders with TBS (18). In a RCT in 56 moderately to severely depressed TRD patients (19), 15 sessions of cTBS applied to the right DLPFC plus iTBS applied to the left DLPFC was compared to rTMS and sham TMS. There were no significant differences in outcome except a trend for an improvement with both active TMS treatments over sham (19). These positive findings are in contrast to one negative RCT of TBS but TBS was delivered continuously not intermittently (20). However, this RCT in 29 people with moderate or severe unipolar or bipolar MDD study employed just 10 sessions of cTBS (compared to 20 sessions in our pilot study) and 62% of the sample changed medication within a week of starting TMS (20). However, another non-randomised study in 185 patients comparing 20 sessions of iTBS to 20 sessions of rTMS delivered to the dorsomedial frontal cortex found no difference in depression response rates in medication resistant patients with depression at 6 weeks (21), showing that further comparisons of iTBS and rTMS are required in TRD.

Another important potential explanation for the lack of a difference in these treatment studies between TBS and rTMS is the lack of anatomical targeting of TBS (the reason for individualised localisation of TBS is discussed below). However, preliminary data from our pilot RCT (clinicaltrials, NCT02016456) conducted in Nottingham of 29 patients with TRD showed improvement in clinical response in depression symptoms (defined as >50% reduction in the 17-item Hamilton Depression Rating Scale (22) from baseline) with individualised localised iTBS of 69% at 1 month and 88% at 3 months compared to rTMS responses of 56% at 1 month and 44% at 3 months, a non-significant trend towards greater efficacy of TBS (p=0.13). In relation to the Beck Depression Inventory (23), a measure of self-rated depression symptoms, iTBS and rTMS showed similar response rates at 1 month of 31% and 33% respectively, but at 3 months a considerable difference emerged with 67% response rate with iTBS but only 22% with rTMS, further pointing to a potential longer-term benefit of iTBS over rTMS. Only 10% participants failed to complete either type of TMS (2 in rTMS – 1 in response to rTMS, 1 unrelated to TMS; 1 in cgiTBS unrelated to TMS) with 10% loss to follow up of outcome or scan at 3 months.

2.4 Connectivity guided theta burst stimulation (cgiTBS)

To maximise the efficacy of TBS, it is important to understand its mechanism of action and how this may relate to the pathology underlying depression. Neuroimaging has had a major impact on our current understanding of dysfunctional brain circuitry in MDD with consistent demonstration of altered network communication within and between affective, cognitive control and default mode networks (24-27). In depression disruption of a reciprocal loop between the dorsolateral prefrontal cortex (DLPFC) and insula extending to the sensory regions was described (27). There is increasing recognition of the potential of brain connectivity changes as detected by non-invasive resting state (task-free) functional MRI (rsfMRI) to individualise neurostimulation therapy of MDD (28). RsfMRI may advance neuromodulation therapy in three ways through (i) *individual target selection* (connectivity based optimisation of stimulation site), (ii) *mechanistic evaluation* of effects and (iii) *response prediction.* Towards these aims two complementary characteristics of brain network function can be derived from rsfMRI: metrics that quantify the degree of synchronisation of neural activity between regions or networks (functional connectivity [FC]) (26) or the influence one brain region's activity exerts on another (effective functional connectivity (eFC) (24, 27).

iTBS is a patterned form of TMS pulse delivery that employs high frequency stimulation. Unlike rTMS, iTBS is associated with cortical long-term potentiation that may induce plasticity in more distal brain areas such as the hippocampus (15), and longer-term effects on depression. iTBS may also affect brain cortical systems through altering inhibitory GABA-related and excitatory glutamate mediated activity both at the site of stimulation and more distally (28-30). GABA and glutamate mediated synaptic inhibitory and excitatory balance are associated with depression severity (31). Unlike traditional rTMS, iTBS may be seen to induce widespread and longer term network change. However, in order to effect change clinically, it is likely that precise anatomical localisation of the target circuitry is required for maximal efficacy of iTBS aiming to normalise dysfunctional fronto-limbic circuitry. To optimise the remote effect of the most common stimulation site, the dorsolateral prefrontal cortex (DLPFC), the DLPFC subregion that has the strongest eFC on limbic and paralimbic network nodes, in particular the insula need to be identified. Such localisation between networks effective connectivity in rsfMRI through Granger Causality Analysis (GCA) (24) was demonstrated in our pilot work. The connectivity of the insula predicts efficacy of rTMS in patients with depression (32) as well as response to CBT and antidepressants (33). Also a recent large (n=1188 MDD patients) study identified FC signatures linked to depressive symptoms, and showed that one particular biotype characterised by strong connectivity between the insula and other regions of the brain was related to partial treatment response of at least 25% symptomatic improvement on HDRS-17 score in 80% of participants (34). The reduced responsiveness of their other biotypes might be due to their choice of stimulation protocol (rTMS of DMPFC). In contrast, based on our pilot data we will individually optimise stimulation using cgiTBS to maximise the modulatory effect on the insula and linked affective and default mode networks which we hypothesise will improve the responsiveness to TBS.
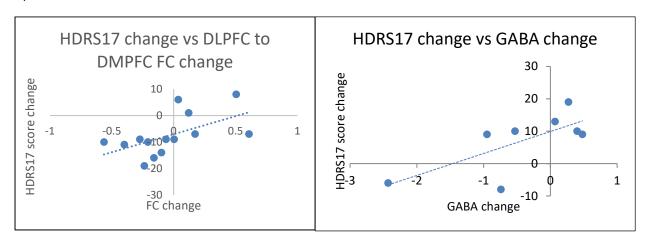
2.5   Recent and pilot work leading to the application.

2.5.1   Proposed mechanism of iTBS action

We have shown that iTBS dampened fronto-insular eFC and reduced ratio of prefrontal GABA to a composite measure of glutamate and glutamine levels (Glx) in both the DLPFC and the anterior cingulate gyrus (35).

Although eFC based localisation of TMS treatment may increase the network changes induced by both rTMS and TBS, our pilot study suggests cgiTBS may be more effective, possibly due to greater long-term potentiation at sites quite distal to the site of stimulation (15, 28-31). In our pilot study in TRD comparing connectivity-guided iTBS (cgiTBS) with guided rTMS, GABA change was directly linked to mood changes. Preliminary mechanistic evidence further suggests that DLPFC targeted TMS normalises dysfunctional fronto-limbic networks in TRD reporting TMS induced decrease of hyperconnectivity between the subgenual anterior cingulate cortex, ventromedial and dorsomedial PFC (DMPFC) and DLPFC (36). Our pilot data showed reduction of FC between DMPFC and DLPFC due to DLPFC targeted TMS or iTBS, and importantly we found a moderately strong significant interrelation between FC reduction and reduced low mood score (r = 0.57, p<.05; Figure 1).

Figure 1: Correlation of HDRS17 change and functional connectivity change baseline to 3 months.

Figure 2 Correlation of HDRS17 change and GABA change baseline to 3 months.

2.5.2   Prediction of iTBS response

Our pilot study, showed a strong significant correlation between prefrontal GABA at baseline and both HDRS-17 score (r = 0.68, p<.05) (Figure 2) and self-rated Beck Depression Inventory (BDI) score (r = 0.63, p=05) at 3 months post cgiTBS. We also found a significant relationship between the BDI score at baseline and baseline fronto-insula connectivity (r = 0.39, p<.05). A similar pattern is also emerging for levels of GABA at baseline and HDRS-17 scores. We have also found that the strength of baseline effective connectivity of anterior insula to left DLPFC (used for localising each individual's TBS target) is predictive of the degree of HDRS-17 score change 3 months after treatment.

2.5.3   Anatomical relevance of eFC based target selection

In our pilot study we demonstrated that the variation between subjects in optimal location was much greater than the extent of the region exhibiting strong eFC between insula and DLPFC observed in many subjects. Given the correlation between the strength of baseline eFC of anterior insula to left

DLPFC and the degree of HDRS-17 score change at 3 months, ideally the site of cgiTBS stimulation should be anatomically close to the site of connectivity.

Therefore, we have preliminary evidence for both greater lasting efficacy of cgiTBS over rTMS and for specific mechanisms of action for the response to TBS. Thus, the study of choice in terms of maximising clinical effectiveness and underlying neurochemical and network change would be a comparison of cgiTBS versus standard non-connectivity guided rTMS. While the current proposed cgiTBS requires structural and functional magnetic resonance imaging (fMRI) to maximise efficacy, such scans are readily available in current NHS facilities and have the additional potential of individual response prediction. Such imaging is only required once for a patient even if multiple courses of treatment are needed to maintain their health over the longer term, demonstrating the potential practical utility of the technique.

2.6   Rationale for the current study

The proposed study will help establish the efficacy of cgiTBS in people with TRD. Current NICE recommended rTMS is of limited therapeutic benefit because its treatment response tends to have worn off by 3 months. In contrast cgiTBS in our pilot study showed increasing effectiveness over time for at least 3 months after treatment was completed. Moreover, because it is accurately targeted on specific brain networks and uses lower energy, it is also likely to produce fewer side-effects. We have preliminary evidence of both the underlying mechanisms of action (increasing insula GABA activity, reducing fronto-limbic and default mode network connectivity) and potential predictors of outcome (baseline prefrontal GABA levels and measures of frontal-insula effective connectivity). If cgiTBS proves efficacious at 16 weeks after baseline compared to rTMS there is the possibility of a stratified approach to identifying those people with TRD who may benefit most from cgiTBS, and those who would benefit from non-TBS treatment approaches. We will explore moderators of response in relation to the severity of baseline depression symptoms, degree of treatment resistance and age; mediators of outcome in terms of number of treatment sessions; and predictors of outcome in relation to the underlying biological mechanism (connectivity, brain GABA). Overall, there is little evidence that medication affects iTBS outcomes but degree of treatment resistance and severity of depression might moderate depression response. It is unclear whether older age is associated with poor response given that neuroplasticity may be reduced in older people (37). The current study will enhance our understanding of the neurobiological effects of cgiTBS in MDD. For researchers, this understanding will provide a solid knowledge base for future clinical application of TBS as a routine treatment for MDD. This project will also lead to a better understanding of the disruption of the networks associated with the insula in MDD and how they relate to cognition and symptomatology, a vital aspect of the theoretical framework on which TBS efficacy is based.

In addition to examining the clinical efficacy of cgiTBS, the study will also examine the cost effectiveness of the treatment and factors maximising this. For example, identification of predictors of treatment response will reduce the number of individuals who will undergo unnecessary treatments that they are unlikely to respond to. This is particularly important for patients with TRD who have usually gone through multiple trials of ineffective treatments, with a significant burden of side effects, and the prolonged disability and distress of unrelenting symptoms of depression. It is likely that if cgiTBS had efficacy over 3 to 6 months with high patient acceptability and tolerability, there would be widespread benefits to health services and society. These arise not only from reduced use of other types of treatment for depression, reduced self-harm, suicide and hospitalisation but also from return to work, improved physical health, and improved parental and

other family care. Given how highly recurrent MDD can be, especially for patients with TRD, long term maintenance of health is also critically important. Patients who remain well with cgiTBS over 6 months may only require two courses per year, again further decreasing costs of repeated treatment that is often necessary in practice with rTMS. Therefore, we are exploring the cost effectiveness of cgiTBS versus standard rTMS from health, social care and society perspectives.

An RCT in MDD of 20 sessions of iTBS applied to left DLPFC versus rTMS applied to the left DLPFC, with change in HDRS-17 score at week 6 as the primary outcome measure, has been registered as a clinical trial in Canada, but no protocol or results have been published (38), although it is a repetition of their non-randomised RCT showing no added benefit of iTBS versus rTMS (21). Compared to our RCT their RCT is in non-treatment resistant MDD rather than TRD, the iTBS is not connectivity guided using fMRI, the primary outcome is measured sooner and the duration of follow up is shorter. In our view the clinical importance of cgiTBS is in relation to its putatively greater response rate at 16 weeks than at 6 weeks and its greater duration of effect in people with TRD. We believe this to be the case based on the findings of our pilot study, the demonstration of long-term potentiation and plasticity at the site of stimulation and at more distal sites associated with the integration of default mode, affective and cognitive systems, and the considerable inter-individual variation in the optimal site of TBS stimulation. Current treatment options for TRD are not without problems, for example while electroconvulsive therapy (ECT) can be effective in this group of patients (39), it is associated with the risk of memory deficits (40) and risk of death from anaesthesia. In a recent study of patients with moderate to severe persistent TRD, 80% had other comorbid mental disorder and 64% had one or more long-term physical condition such as diabetes, chronic obstructive airways disease making drug treatment or physical treatments involving anaesthesia both difficult and undesirable (41). In a European study, there were more side-effects from drug treatments in patients with TRD than seen in other patients with depression (11). Medication side-effects such as weight gain, sedation and sexual dysfunction can be debilitating in themselves.

MDD is an expensive condition with direct costs of £1·7 billion per year and indirect costs of £7·5 billion per year in England alone in 2008 (8). Of these totals, around 75% is due to TRD (10). In direct NHS and social care costs, TRD costs around £4-5,000 per patient per year often for many years (41). For patients seen in a specialist depression service offering both NICE recommended psychotherapy and pharmacotherapy the costs are typically £7-8,000 (41). In addition to ECT, other invasive neuromodulation approaches such as deep brain stimulation (DBS) or vagus nerve stimulation (VNS) may be employed for TRD. These all carry high degrees of risk by their invasive nature or through serious and sometimes permanent cognitive side-effects. They require the expertise of other specialist services such as anaesthetists and neurosurgeons. A major problem is that the majority of patients with TRD are managed within secondary care mental health services that do not have expertise in high level psychotherapy or pharmacotherapy or around the use of DBS and VNS. An easy to deliver, effective, well tolerated and relatively cheap intervention for TRD, such as transcranial magnetic stimulation (TMS), is therefore required.

For a long-term condition where motivation is a characteristic issue such as TRD, the requirement with rTMS for the person with TRD to attend hospital daily for several weeks does not seem to be justified given the response rates are low (just over one quarter respond) and its short duration of effect, typically only one to two months. The current clinical and financial investment in TMS for TRD is insufficient for widespread implementation into NHS practice. However, cgiTBS may offer both a greater response rate and longer duration of depression response (88% at 3 months) with great acceptability and few side-effects potentially making cgiTBS a more attractive treatment option than conventional TMS.

Our proposed RCT will complement and build on the results of the RCTs described above by firstly determining the efficacy of cgiTBS over a 6 month period compared to rTMS. The design of the intervention is based on our proof of concept study (clinicaltrials,NCT02616835) (35). Preliminary data from the pilot RCT (clinicaltrials, NCT02016456) of cgiTBS versus rTMS has also shown promising results in regard to the TBS in patients with TRD. Since we have already conducted a pilot RCT and implemented TMS services into NHS practice, we can offer a definitive efficacy RCT that meets the EME call over 44 months. Furthermore, the proposed study is of a size to definitively establish the efficacy of cgiTBS compared to standard rTMS in people with TRD, and its duration of efficacy over 6 months using a widely used and NICE adopted measure of depression symptom response as well as examining economic outcomes and quality of life of patients. Using state of the art 3T MRI (rsfMRI analysis and GABA measurement), the study will be able to test specific underlying mechanisms of action. RsfMRI in combination with structural MRI will also afford discovery and validation of brain signatures of treatment response. With established PPI involvement and qualitative research, we will establish the relative acceptability to patients of cgiTBS compared to rTMS (effectiveness, side-effects, convenience).

3   Study Objectives

3.1   Main objective

To determine the efficacy of cgiTBS at 16 weeks (primary clinical outcome, 50% drop in HDRS-17 score from baseline to 16 weeks) and 26 weeks compared with standard rTMS; in people with TRD

The primary aim of this study is to examine the efficacy of connectivity guided, short bursts of high frequency 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 a MGH score of 2 or more, who are not responding to 2 different antidepressant regimes, antidepressant augmentation strategies, high prolonged dosages of antidepressants or ECT in their current episode.

3.2   Secondary Objectives

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

To examine cost effectiveness of cgiTBS versus rTMS in a UK National Health Service (NHS) population.

To examine the patient acceptability and patient experience of cgiTBS and rTMS.

To investigate the neural mechanism of efficacy in cgiTBS and rTMS.

To develop response prediction models from brain biotypes and clinical features

To examine the independence of changes in brain activity associated with improvements in cognition from changes associated with improvement in mood.

The exact physiological mechanisms underlying the therapeutic effect of TMS in major depression have not been well understood up to now. Connectivity-based neuroimaging methods show great promise in understanding the neural networks underlying the response to cgiTBS and rTMS. Our pilot RCT comparing cgiTBS with rTMS in TRD provided preliminary evidence that mood improvement may be related to prefrontal GABA increase and reduced DLPFC-DMPFC functional connectivity (FC). 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. In order to understand the relationship between TBS-induced fronto-insular network change, clinical response and neurochemical excitatory and inhibitory dysbalance, prefrontal GABA and Glx will be quantified using dedicated magnetic resonance spectroscopy (MRS).

There are no safety concerns with rTMS. iTBS delivers less energy to the brain than rTMS and is better localised so it may be particularly well-tolerated. However, patient qualitative experience of rTMS or iTBS has attracted little attention in the scientific literature, and is a key concern of our PPI groups. 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).

4   Study Design

4.1   Study Outline

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 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.

(TRD) (42). Our primary hypothesis is that cgiTBS is more efficacious in increasing the proportion of patients who a show a response (50% reduction in depression symptoms from baseline on the HDRS-17)(22) at 16 weeks than standard rTMS in patients with TRD.

4.1.1   Hypothesis for the mechanistic component
The specific hypotheses for the mechanistic component of the study are:

1. To determine the differential change at 16 weeks between responders and non-responders to treatment (in either treatment arm) in functional connectivity between affective, default and cognitive control networks. Our main hypotheses are that connectivity between insula and DLPFC at baseline will distinguish responders from non-responders, and that DLPFC-DMPFC connectivity decrease will be greater in responders than in non-responders.
2. To discern whether DLPFC-DMPFC FC change at 16 weeks is correlated with change in HDRS-17 score at 16 weeks. Our hypothesis is that a greater reduction in DLPFC-DMPFC FC is correlated with a greater reduction in HDRS-17.
3. To assess whether prefrontal GABA change at 16 weeks is correlated with change in HDRS-17 score at 16 weeks. Our hypothesis is that TBS-induced GABA changes are correlated with a reduction in HDRS-17.

4. To evaluate neurophysiological defined brain signatures at baseline as predictors of depression response or nonresponse to cgiTBS or rTMS. Our exploratory hypothesis is that functional connectivity based biotypes can be optimised using advanced computational analytics to individually predict treatment response in TRD patients.
5. To further study the neural mechanisms underlying therapeutic efficacy we will assess interrelations of changes in complex brain network metrics (including the use of graph analysis) with improvement of clinical symptoms. This is an exploratory aim.

4.1.2 Anticipated Project timetable

Month of project	Action
0-10	Ethics and HRA approval. Pilot and inter-rater reliability of anatomical localisation and blinding protocol across all sites. Training of TMS staff and raters of outcome at each site.
10-13	**Site initiation and commencement of recruitment**
10-17	Internal pilot with monthly review of recruitment. Each site will reach maximum recruitment by month 18 sustained to month 32.
18	Report of internal pilot presented to trial steering committee and data monitoring and ethics committee. Decision on continuation of recruitment to RCT.
10-44	Completion and qualitative assessment of patient acceptability of TMS.
32	Complete recruitment of 368 participants
33-39	Complete follow up of all participants and scanning, database entry & checking.
33-44	Analysis of scanning
39-44	Analysis of clinical outcomes and health economics. Write up report and main publications.
45	2 weeks after completion of month 44 delivery of final report.

4.2 Participant Involvement

Participants in both arms will receive 20 TMS sessions delivered over 4- 6 weeks. A total of 3000 pulses will be delivered in each rTMS or cgiTBS session. At each centre, 8 participants per day could be treated.

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.

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) for 40 seconds duration 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 fiducal 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.

Comparison of TMS Treatments:

TMS
Transcranial Magnetic Stimulation

Standard Care Treatment
Repetitive TMS (rTMS)
- Standard site of stimulation on the scalp is determined with neuronavigation.
- 4 second trains of stimulation repeated 75 times.
- 26 seconds rest intervals between each train of stimulation.

Novel Treatment
Connectivity Guided Intermittent Theta Burst (cgiTBS)
- Site of Stimulation on the scalp determined using neuronavigation from the MRI scan for maximum strength of connectivity.
- 3 burst of stimulation pulses repeated 5 times
- 5 minute rest intervals between each 3 burst of stimulation pulses.

4.2.1   Baseline Characteristics and Outcome measures

Screening for eligibility will completed by telephone and eligible patients will be invited to attend a Baseline assessment.

Information on socio-demographics, diagnosis (checked using SCID research interview for DSM-5, Post traumatic disorder section will not be completed, a Childhood Trauma Questionnaire CTQ will be completed instead), past medical and psychiatric history including a detailed assessment of treatment resistance will be obtained from case files and primary care notes after consent has been given). The following outcome measures will be completed at baseline assessment (90 mins) and at each follow up point (60mins).

Primary Outcome Measure:

A binary variable of responder or non-responder at 16 weeks. Individuals observed to have a 50% drop or greater in HDRS-17 from baseline to 16 weeks are defined as responders. Less than a 50% reduction or a null value is classified as no response. The 17-item HDRS (22) is a widely used interview measure of depression symptoms given in GRID form to improve inter-rater reliability(If the time window between baseline assessment and the start of TMS treatment exceeds 4 weeks then a HDRS–17 interview measure should be re-assessed. (If the HDRS measure shows <16 treatment can still be administered with intention to treat analysis).

Secondary outcome measures:

- Response at 8 and 26 weeks measured using HDRS-17
- Beck Depression Inventory 1 (BDI), self-rated measure of depression symptoms (23); THINC Integrated Tool (THINCIT), Assessment of cognitive functioning

- Patient Health Questionnaire (PHQ-9) Self rated measure of symptoms of depression (45)
- Generalised Anxiety Disorder Assessment (GAD-7), Self rated measure of Anxiety and depression.(46)
- Work and Social Adjustment Scale (WSAS), Self rated measure of impairment in functioning (47)
- EuroQol-5D-5L, self-rated health utility and quality of life (48) that also measures pain;
- Quick Inventory of Depressive Symptomology (QIDS-SR16) self-rated measure of mood.
- Patient acceptability (0-5 scale) and patient experience of overall improvement using the Patient Global Impression of Change (1-5 scale very much improved to very much worse) (49)
- Adverse Event (checklist will be asked after each TMS session.)
- FC,eFC, GABA

A purposely designed patient proforma will be used to collect patient resource level information. This will cover relevant items outlined in the CSRI (50) and add the tailor the resources items measured following good practice approaches used by the health economics DiRUM (database of instruments for resource use measurement) group to estimate costs.

Patient acceptability (0-5 scale) after each TMS session, and at 8,16 and 26 weeks post randomisation, follow up, along with side effect checklist after each TMS session and 8 week follow up assessment. It is good practice to rate overall change, side effects and overall acceptability to understand adequately the participant experience of receiving both treatments. The acceptability of them might because they feel worse overall or because of additional side-effects but even if these are experienced, the participant may still consider the treatments acceptable. The quantitative analysis will be supplemented by a qualitative analysis of participant experience (outlined in section 7.1).

4.2.2 Assessment and Follow up
Assessment of efficacy and mechanism of action.

Following consent interviews and assessments of participants will take place at baseline assessment and then at the follow up assessments at 8, 16 and 26 weeks from randomisation.

Participants undergo baseline MRI assessment of structural, functional (task-free, eyes open rsfMRI, diffusion weighted imaging to assess structural connections between relevant brain regions), and MRS scans (not in London where only fMRI and structural MRI scans will be performed). Target identification will be analysed centrally in Nottingham (blind to treatment group allocation) on pseudoanonymized scans (at source) with triple identifier (study number, scan date and initials). Transfer of pseudoanonymized scans will be using an adapted web-based database using XNAT technology that is being adapted for the trial needs and to meet the data protection and governance regulation in the last 3 months of set-up with training and support of the scanning site responsible scan operators during the initial phase of the trial. From experience, there is a need for a back-up of web-based data transfer and individual check of full removal of identifiers that may be hidden in the scan header. This will be addressed in two ways: for technical transfer issues we will use the standard default of shipping anonymized CDs with first class mail for XNAT upload by the Nottingham team. All data uploaded onto XNAT will be checked for anonymization, availability of the triple code, completeness and quality before being entered in securely controlled research XNAT.

Using GCA of fMRI scans in each subject, coordinates for the stimulation target within the left DLPFC that shows maximal connectivity with the right anterior insula will be identified.

For the MRS scans, voxels will be placed in the DLPFC and ACC, using a method similar to the pilot work and proof of concept study (35), which is highly reproducible with acquisition training. The sequence used will be the MEGA-PRESS sequence for GABA-edited MRS, which is the most widely used sequence for quantifying GABA at 3T.

The scans are repeated at 16 weeks as part of the mechanistic element of the study. Highly trained radiographers will support the MRI acquisition.

In our pilot study, we employed technically complex neuro-navigation equipment to identify the optimum location of the TMS wand in order to deliver the pulse of magnetic energy at the intended target site within the brain. However this neuro-navigation equipment is technically demanding and expensive, and therefore unsuitable for use in routine clinical practice in an NHS setting.   We have therefore developed a computational procedure to identify the target location on the scalp surface overlying the brain target site, based on measurements on a computed surface mesh fitted to the scalp surface visible in the structural MRI image. The procedure computes the distance of the scalp target site from three visible anatomical landmarks: two pre-auricular points adjacent to left and right ears and the nasion, a visible feature at the top of the bridge of the nose. This allows us to use a simpler neuronavigation system devised specifically for the Horizon TMS machine that are we are using in the study. The site of stimulation on the scalp is identified as distances from the two pre-auricular sites and the nasion using a neueonavigation sytem which utilises a camera in the TMS coil and a wand with a green light which is shone onto the two pre-auricular sites and the nasion. A stimulus can only be given if the camera in the TMS coil detects it is at the correct site at the correct angle to the scalp. The same approach will be used to identify the F3 site for standard rTMS stimulation. These sites are then stored for the remaining 19 sessions so that the TMS stimulus is delivered at the same location at each session.   In the first TMS session, an e-mail will be opened to reveal whether that participant has been randomised to receive either cgiTBS (individual sweetspot site) or standard rTMS (F3 site). The advantages of the neuronavigation guided approach compared to the cap and measurement approach we proposed before is that it is simple to use for nursing staff, more acceptable and comfortable to patients who do not need to wear a cap or have a pen mark on their skin, and it is more precise and more reproducible, Although the equipment is more expensive, it is likely to be only an additional one-off capital cost of £12,000 per machine so it would be an affordable option for the NHS.

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. Baseline depression will be measured by HDRS-17 score (classified as moderate (16-23) or severe (≥24)) and treatment resistance will be measured by Massachusetts General Hospital Treatment Resistant Depression staging score (classified as low resistance (2-3.5), medium resistance (4-6) and high resistance (≥6.5 or more based on distributions in the ADD study (42). 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 in to 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.

If the time window between baseline assessment and the start of TMS treatment exceed 4 weeks then a HDRS–17 interview measure should be re-assessed. (If the HDRS measure shows < 16 treatment can still be administered with intention to treat analysis).

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. We will provide each participant with a £10 shopping voucher as a thank you for completing outcome measures at 16 and 26 weeks because a high follow up rate is essential to the study outcomes. We recognise that completion of follow up so long after the course of treatment requires effort and time on the part of the participants with a condition where there is inherently poor motivation to complete such tasks. The voucher is a mark of respect and gratitude for the time and input of the participants beyond the point that they are receiving the active treatments in the trial. Such a voucher will not adversely affect benefits in those people who receive them and is low value so that it does not influence the decision to take part in the study.

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.

To ensure high inter-rater reliability on the primary outcome and key interview based secondary outcomes, all researchers will use the GRID version of the HDRS-17 (22) and specific training at all sites from the same trainers. Inter-rater reliability assessments will be made by pairs of raters on 10 cases each at the beginning of the RCT and towards the end of recruitment to assess both inter-rater reliability overall and inter-rater drift between the beginning and the end of the study to demonstrate the reliability of assessment throughout the duration of the study and across sites.

4.2.3 Outcome Measures Table

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 week from 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	✓			✓	✓		✓
QIDS-	✓			✓	✓		
SCID Research Interviews	✓						
CTQ (Replaces PSTD section in SCID Questionnaire.)	✓						
Client Resource Questionnaire	✓				✓		✓
Patient Acceptability			✓	✓	✓		✓
Side Effects Checklist (Adverse Events)			✓	✓			
fMRI		✓				✓ (Not in London)	
MRI		✓				✓ (Not in London)	
rsfMRI (Not in London)		✓				✓	
MRS (Not in London)		✓				✓	
Diffusion weighted imaging		✓				✓ (Not in London)	

4.3 Participant Recruitment

Recruitment will be from both primary and secondary care settings using the expertise of 4 NHS sites with established TMS and/or TRD NHS services: Nottingham, Newcastle, Northampton and London. Patients with TRD with capacity to consent will be invited to participate in the study. Existing psychotropic medications or psychological interventions will be kept stable for 16 weeks for the duration of the trial except for those at risk to themselves or others. Benzodiazepine, diazepam, zopiclone, zolpidem and zaleplon should only be used consistently at a low dose but not intermittently at a low dose or any other dose from baseline assessment to the end of TMS treatment, if inconsistent use of any of these occur then participants' study treatment will be stopped

(for 24 hours) but all randomised participants follow-up data will be collected including participants whose treatment is stopped for any reason.

Prescription of lamotrigine, gabapentin, pregabalin should be not be taken at time during the trial, if any use of these occur then participants' study treatment will be stopped (for 24 hours) but all randomised participants follow-up data will be collected including participants whose treatment is stopped for any reason.

Participants at 16 weeks who have not improved will receive further clinical review. We will note any changes in medication or other forms of treatment from 16 to 26 weeks. Recruitment will be from TRD services and all parts of secondary mental health services at the lead NHS Trust at each site and also from at least one neighbouring mental health Trust (e.g. Derbyshire and Lincolnshire with Nottingham, Leicestershire and Warwickshire with Northampton, Tees, Esk and North Yorkshire and Cumbria with Newcastle, Camden and Islington with Central and North West London, and Barnet, Enfield and Haringey). With the help of the Clinical Research Network we will recruit from Improving Access to Psychological Treatment and primary care services as well. We will put posters advertising the study in other community settings such as GP practices (who agree), library notices boards. We will also use digital and social media to help promote the study, whilst interest and patient feedback regarding the study will be generated via other media outlets (e.g. press releases, radio) where possible. If necessary we will recruit from a neighbouring third Trust at each centre and open up a 5th centre in Birmingham using CRN and research assistant support from Nottingham or Northampton plus the TMS service supervised by Dr Alex O'Neill Kerr, one of the current applicants with scanning in Nottingham. TMS services in Nottingham, Northampton and London have 200 TRD patients each and the specialist services for TRD in Nottingham and Newcastle see 160 participants per year. Recent RCTs in TRD with Clinical Research Network support recruited 4 eligible participants per month from 2 adjoining Trusts so we can recruit 45-50 participants per year per site (13, 42). 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). If 68 patients are recruited during the internal pilot and each site recruits 5 participants per month between months 18 and 32 the study will achieve recruitment of 368. Qualitative interviews of barriers to recruitment will be completed until the end of the study and will help to optimise strategies to improve recruitment.

5 Participation Eligibility Requirements

5.1 Inclusion Criteria

- Adults $\geq$ 18 years
- Diagnosis of MDD (defined according to DSM-5) that is treatment resistant (defined as scoring 2 or more (42) on the Massachusetts General Hospital Treatment Resistant Depression staging score (51) See appendix on more detailed scoring of treatment resistance.
- HDRS-17 score of 16 or more (moderate to severe depression) (52)
- Capacity to provide informed consent before any trial related activities.

5.2 Exclusion Criteria

- History of bipolar disorder (due to risk of mania) or depression secondary to other mental disorder
- Neurological conditions e.g. brain neoplasm, cerebrovascular events, epilepsy, neurodegenerative disorders, and prior brain surgery
- Standard contraindications to MRI i.e. irremovable metal objects in and around body e.g. cardiac pacemaker, implanted medication pump and pregnancy (any doubt resolved by pregnancy test, women of childbearing age taking precautions against pregnancy) This will include other potential complicated factors such as red tattoo's which consist of iron on the head, neck and back and claustrophobia (we offer mock scanner testing and training in some sites)
- Major unstable medical illness requiring further investigation or treatment.
- Change in prescribed medication 2 weeks before baseline assessment.
- Prescription of lamotrigine, gabapentin, pregabalin in the 2 weeks prior to baseline assessment.
- Daily prescription of benzodiazepine above 5 mg diazepam equivalents, zopiclone above 7.5mg, zolpidem above 10mg or zaleplon above 10mg. These drugs should not be used intermittently in the 2 weeks before baseline assessment.
- Current substance abuse or dependence defined by DSM-5 criteria)
- Prior TMS treatment.
- At risk of suicidality.
- Potential complicated factors relating to the TMS treatment i.e Hairstyles which would impair magnetic transmission and piercings. (Participants would only be excluded if they chose to not make the changes required to ensure effective treatment.)
- Involved with any other clinical trial at the time of consent or 6 months prior.
- Unable to read or understand English.

5.3 Expected Participant Duration

A pre-screening questionnaire will be used to screen interested participants over the telephone in the first instance which will take 30 minutes. Potentially eligible participants will attend a Baseline Assessment Interview.

Informed Consent will be explained and obtained during the baseline assessment.

Baseline Assessment this is where assessments lasting 90 minutes will take place. Assessment of the participant's eligibility will be made and further checks on medical history may be required. Eligible participants will be asked to attend a Baseline MRI Scan.

Baseline MRI Scan of the brain within 14 days of their baseline assessment, this procedure will take 60 minutes.

Randomisation will take place, prior to Session 1 of treatment. the participant will be randomly assigned in a 1:1 ratio to the rTMS (Standard) and cgiTBS (Novel) arms by the nurse leading the TMS or a doctor whose only role is to deliver TMS treatment. Participant and other members of the research team will not be informed of the arm they have been randomised to, as this is a blinded randomisation process.

20 Treatment sessions will be delivered over a 4-6 week period (Treatment sessions must not have a discontinuity of more than 4 days), with each session lasting 45-60 minutes, with the exception of the first treatment taking 2 hours.

Follow Up assessments at 8, 16 weeks post randomisation will take place, with each assessment taking 60 minutes. If at week 16 there is no improvements in symptoms from baseline assessment, clinical care will be reviewed by a clinical expert in treatment resistant depression.

MRI scan within 14 days of the 16 week follow up assessment will be performed to observe any changes, taking 60 minutes.

26 week Follow Up assessment will mark the end of participation in the study and the participant will be informed as to which treatment arm they had been randomised too. Along with a clinical care review by a clinical expert in treatment resistant depression if their symptoms have become worse or if the patient and clinical team (GP or psychiatrist) requests such advise. Final appointment will take 60 minutes.

Study Flow Chart:

Identification of Eligible Patients
(From Secondary and Primary Health Care)
Invite letter mailed with reply slip

↓

Eligibility Assessment by Telephone (30mins)
Reply slip received and eligibility checked

↓

Baseline Assessment (1 ½ to 2 hours)
Informed Consent obtained
(Further Eligibility checks from primary and secondary notes will be obtained.)

→

Ineligible participants
(Will be notified and a Letter sent)

↓

MRI Scan (1 hour)
(Within 14 Days of Baseline Assessment)

↓

Randomisation
(Within 14 days of MRI Scan)

Day 0

rTMS Treatment

(Starts within 14 Days of MRI Scan)

20 Treatment Session

4-6 weeks of treatment
(Mon-Fri)

First Treatment (2 hours)

All other treatments (45-60 mins)

CgiTBS Treatment

(Starts within 14 Days of MRI Scan)

20 treatment sessions

4-6 weeks of treatment
(Mon-Fri)

First Treatment (2 hours)

All other treatments (45-60 mins)

Week 8
+/- 1 Week

→ **8 Week Follow up Assessment** (1 hour)
(From date of randomisation)

Week 16
+/- 1 Week

→ **16 Week Follow up Assessment** (1 hour)
(From date of randomisation)
Participants with no improvement will receive a clinical review)

→ **No improvement in symptoms**
(From Baseline Assessment, Clinical Care reviewed, by a clinical Expert in TRD)

Week 16
+/- 14 days

→ **16 Week MRI Scan** (1 Hour)
(Within 14 days of 16 Week Follow up assessment)

Week 26
+/- 1 Week

→ **26 Weeks Follow up Assessment** (1 hour)
(From date of randomisation)
Participants with no improvement will receive a clinical review)

5.4 Informed Consent

- The participant must personally sign and date the latest approved version of the informed consent form before any trial specific procedures are performed.
- A written version of the participant information sheet and informed consent form will be given to the participants, detailing no less than: the exact nature of the trial; the implications and constraints of the protocol; the known side effects and any risks involved in taking part. It will be clearly stated that the participant is free to withdraw from the trial at any time for any reason without prejudice to future care, and with no obligation to give the reason for withdrawal. The participant will be allowed a minimum of 48 hours and as much time as wished to consider the information, and the opportunity to question the Investigator, their GP or other independent parties to decide whether they will participate in the trial.
- At the baseline assessment, the research team member will check the person's eligibility to participate, give an unbiased explanation in detail as to what the trial involves (including benefits and risks) and answer any questions they may have. Written Informed Consent will then be obtained by means of participant dated signature and dated signature of the person who explained the trial and obtained the informed consent. The person who obtained the consent will be suitably qualified and experienced, and have been authorised to do so by the Chief/Principal Investigator as detailed on the Delegation of Authority and Signature log for the trial. The original signed form will be retained at each site within the Investigator site file. A copy of the signed Informed Consent Form will be given to participants and a copy sent to their GP.

5.5 Participant Withdrawal

Participants are free to withdraw from the trial at any time, without giving any reason, and without their legal rights being affected. In all cases the anonymised data will be included in the analysis up until the point that withdrawal took place. If participants request to discontinue treatment, they will be encouraged to attend all follow up assessments. Otherwise they will be withdrawn from any further participation on the study. Routine clinical care provided will not be affected if they chose to withdraw. This information is provided to the participant in the patient information leaflet.

6 Research Data

A full statistical analysis plan will be agreed before data lock for the interim analysis.

6.1 Data Analysis

The primary outcome is:

- Response at 16 weeks (defined as by a 50% or greater reduction in HDRS-17 score from baseline)

Secondary outcomes include the following:

- Response (as defined above) at 8 weeks and at 26 weeks
- Remitters at 8, 16 and 26 weeks (defined as a score of 8 or less on the HDRS-17)
- Sustained response at 16 and 26 weeks (defined as a continuing response as defined above following a response at the previous time point)
- Beck Depression Inventory (BDI) at 8, 16 and 26 weeks

- THINC Integrated Tool (THINCIT), at 8, 16 and 26 weeks
- Quick Inventory of Depressive Symptomology (QIDS), at 8 and 16 weeks.
- EuroQol-5D-5L at 8, 16 and 26 weeks
- Patient Health Questionnaire (PHQ-9) at 8, 16 and 26 weeks
- Generalised Anxiety Disorder Assessment (GAD-7) at 8, 16 and 26 weeks
- Work and Social Adjustment Scale (WSAS) 8, 16 and 26 weeks
- Patient acceptability (0-5 scale). After each TMS session and at 8, 16 and 26 weeks
- Adverse Event checklist after each TMS session
- FC,eFC at baseline and 16 weeks (Not in London.)
- GABA at baseline and 16 weeks

Efficacy. A consort flow diagram of participant's involvement through the study will be produced Descriptive characteristics and outcome data will be summarised overall and by treatment group, as mean (standard deviation) for symmetrically (e.g. normal) distributed continuous variables, median (interquartile range) for skewed continuous variables, and number (percentage) for categorical variables. The primary analysis will test the null hypothesis that treatment with cgiTBS does not increase response rate as measured by HDRS-17 compared to rTMS at 16 weeks on an intent to treat population with any missing response data at 16 weeks being imputed as no response having been achieved. The proportion of patients achieving a response at 16 weeks as defined by a 50% or greater reduction in HDRS-17 score from baseline will be shown along with 95% confidence intervals for each group. A logistic regression will be fitted for the outcome of response with treatment arm, centre, baseline HDRS-17 score and Massachusetts General Hospital Treatment Resistant Depression score. The primary analysis of the primary outcome will fit this model using the intention-to-treat population with missing outcomes being imputed as non-response. As a secondary analysis a logistic regression 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. 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.

6.2 Subgroup analyses

We will explore moderators of depression response at 3 months such as severity of depression by baseline HDRS-17 score, degree of treatment resistance and age and number of TMS sessions attended as a mediator of outcome in exploratory sub-group analyses of the primary outcome.

6.3 Interim analyses

Recruitment in the pilot study will be assessed using the following stopping rule: On average between month 12 and 14 (inclusive) 3 participants per site per month should be recruited as a minimum. In addition if recruitment is lower than expected 4 patients per month at a particular site(s), barriers to recruitment identified and mitigation plan at each site. If a site is not recruiting at

minimum, consideration will be given to stopping recruitment at that site and replacing it with another, or more likely share study resources (and additional Clinical Research Network resources) with additional sites (Birmingham, South London) to ensure the trial is meeting its overall target.

All other interim data analyses will be descriptive to enable the Data Monitoring Ethics Committee (DMEC) to monitor safety and conduct of the study.

6.4 Mechanism of action.

Established quality checks, MRS, functional connectivity and network analysis will be blindly undertaken on all fMRI and MRS scans. Functional connectivity analysis and GCA (24) will be employed for analysis of the imaging data.

To test our main mechanism of action hypothesis that the reduction in DLPFC-DMPFC functional connectivity is greater in responders than non-responders a t-test will be used. Correlation analyses of GABA change (baseline to 16 weeks, relative or absolute) and DLPFC-DMPFC connectivity change (baseline to 16 weeks) with change in depression symptoms (HDRS-17 symptoms and response baseline to 16 weeks) will be carried out. Relationships between baseline imaging variables that predict response, and relationships between symptom improvement and cgiTBS induced changes in brain network properties will be further explored using advanced in-house and established network analysis toolboxes (e.g. Neuroimage toolbox software).

6.5 **Economic analysis.**

The economics analysis will take an NHS & personal social services cost perspective in accordance with NICE guidance, and a wider societal perspective to capture the broader effects of rTMS and cgiTBS on depression, as such it will collect data on paid employment and the effects on other friends and family and any caring responsibilities they undertake. Data from a purposively designed patient resource proforma will collect patient r level resource information using interviewer completion. This measure will collect data on all aspects of patient treatment and follow up: including medication, inpatient and outpatient hospital visits and primary and community care use. The measure will be designed with input from the PPI group. The proforma will be used to collect data at baseline, 16 and 26 weeks from all participants. This resource data will then form the units on which cost data, using source such as the Unit Cost of Health and Social Care \PSSRU (52) the BNF, and national reference costs can be attached. The nurse & health care assistant at each centre will complete a diary of time spent managing each participant in the RCT to derive treatment costs for rTMS and cgiTBS. The number of treatment sessions for the alternative therapies will be carefully recorded and a separate intervention cost assigned to each of the therapies. Much of the treatment cost will be common across both groups and as such does not require detailed measurement, as the commonality cancels out in each group. They will differ by frequency and image guidance and it is therefore the additional cost of the image guidance that will be assigned to the cgiTBS group along with session numbers for each intervention. We will delineate the time spent delivering cgiTBS or rTMS from time spent on research only procedures, that would not be used in the real clinical world. The outcome measure for the economic evaluation will be the number of QALYs based on a six month time horizon with no discounting for costs or outcomes as they accrue within a 12 month period. An incremental analysis will be used between the two groups and where appropriate an incremental cost effectiveness ratio (ICER) will be reported between

rTMS and cgiTBS. We will use the net monetary benefit framework & implement a net benefit regression (54) to estimate the extent to which, & the probability that, the cgiTBS intervention is cost-effective compared to standard rTMS at a range of threshold values for the willingness to pay per QALY, generating cost effectiveness acceptability curves (CEACs). Data will be analysed for baseline and centre effects. Key cost drivers will be examined using probalistic sensitivity analysis

6.6   Qualitative analysis.

A purposive sample of 25-30 participants from both arms & all centres, reflecting a mix of demographic characteristics, consent or non-consent to participate, adherence & non-adherence to treatment & follow up will be selected for qualitative interviews, each lasting for an hour, after the 16 week assessment (the primary outcome) until the end of the study. We will ask about their general views of TMS, benefits from, disadvantages from or dislikes about receiving TMS. Interviews will continue under saturation is achieved, i.e. no more themes emerge in subsequent interviews. All interviews will be recorded & transcribed verbatim. Anonymised transcripts of patient interviews will be obtained from digital recordings made with the interviewee's consent. Dict8 are a professional transcription service who will be used to transcribe all anonymised data (audio tape and study number only) provided. They are an approved transcribing service for the Nottinghamshire Healthcare Foundation TrustNVivo 11 will be used to manage the transcripts & data coding. Inductive thematic analysis using a grounded approach will be adopted. Interpretation of themes will be aided by the PPI representatives

Paper Case Report Forms (CRF) and study questionnaires are the primary data collection instruments and treated as source data. All data requested in the CRF will be recorded. All missing data will be explained. If the item is not applicable to the individual case, N/A will be written. All entries will be printed legibly in black ink. If any entry error has been made, to correct the error, a single line will be drawn through the incorrect entry and the correct data entered above it. All such changes will be initialled and dated. For clarification of illegible or uncertain entries, the clarification will be printed above the item and this will be initialled and dated.

Data captured in the paper CRFs will then be entered into a validated database under the management of the LCTU. A copy of the patient consent form and information sheet will be placed in the hospital notes of all participants and in the Investigator Site File. A sticker will be placed on the cover of the notes (or inside cover) detailing the study title, contact details of the PI and the fact that the notes should not be destroyed. All study visits and AEs will be recorded in the hospital notes.

6.7   Cognitive function Analysis.

We will explore research aims relating changes in cognitive function (THINC-it) to changes in self-reported mood and resting-state brain connectivity.

6.7.1   Cognitive Scanning Changes

We will explore the correlations between executive function and intraindividual variability (IIV) on the THINC-it battery of cognitive tests (measured with the method of ref. 56) and resting-state functional connectivity between the "frontoparietal network" (FPN) and the "default mode network" (DMN). We will also look at the mediating effects of low mood (measured with the QIDS) on these relationships. This will help address the extent to which cognitive and affective symptoms are separable elements of the pathophysiology of depression (57).

We will perform separate correlations using baseline measures of each variable, and using change in each variable from baseline to 16 weeks. Analyses will be performed without unblinding TMS treatment allocation group by the Imaging department at the University of Nottingham. We predict a positive correlation between IIV and FPN-DMN functional connectivity at baseline, and a positive correlation between change in IIV and change in FPN-DMN connectivity. (See Appendix 2 for more details.)

6.7.2   Cognition (Thinc-it) Changes

We will examine the relationship between IIV in attentional task response times and mood. Mood disorders are associated with cognitive dysfunction across a range of domains including memory, executive function and attention. Studies looking at individual responses from an attentional reaction time task suggests that some patients have greater IIV in response times compared to controls. They are seen to have 'lapses' on some response – that is they have some response times that are much longer than the majority of their responses. When responses times are plotted in a frequency distribution, what is seen is a skewed distribution, with these slow response/lapses showing as a skew to the right. This can be analysed by decomposing the distribution into a Gaussian and an exponential component. We have previously shown that the time constant of this exponential component is a more sensitive measure differentiating patients from controls than simple mean reaction times (56). This work simply analysed cross sectional data from patients. What is not known is whether the increased IIV is a state or trait difference compared with healthy subjects. As a result, will examine the relationship between mood and IIV using QIDS and THINC-it data. Analyses would be performed without unblinding TMS treatment allocation group by identified staff at the Newcastle University.

6.8   Participant Sample Size

Sample size is calculated on the minimum clinically important difference in responder rates from baseline to 16 weeks of 15% (equivalent to a number needed to treat or NNT of 7) between two active treatments (cgiTBS versus rTMS) in favour of the experimental condition cgiTBS. This is an effect size regarded in the literature as a clinically important difference in studies using invasive approaches to managing TRD such as vagal nerve stimulation (55). An effect size such as this was regarded as important by our PPI group as well. However, this is a much smaller effect than our pilot study found, with a difference in absolute response rate of 44% (NNT of 2 to 3) in favour of cgiTBS versus rTMS. Given that the proposed RCT is a large multicentre sample of TRD patients where participants may be less adherent to both TMS conditions, a lower response rate in the cgiTBS group at 16 weeks is expected. The most recent meta-analysis of 16 RCTs in 510 participants with TRD reports a response rate on the HDRS-17 and MADRS of 26.5% for rTMS at the end of treatment versus 13.1% for sham TMS (15). We will use the response rate for standard rTMS from this meta-analysis rather than the higher estimate of response in our pilot because we will use rTMS with sham connectivity localisation rather than connectivity guided rTMS that we used in our pilot study. Assuming a response rate on the HDRS-17 of 26.5% with rTMS and 41.5% with TBS with 80% power and 5% significance level (two-tailed), and to allow for 15% loss to follow-up at 16 weeks as indicated by the meta-analysis (higher than in our pilot study), **368 patients in total will be recruited (184 per arm)**. If as expected, the estimate is conservative, given the big effect size in our pilot, the RCT would have the following power outlined in the Table below depending on follow up rates to detect the stated differences at the 5% significance level.

	Effect size (response rates at 16 weeks, rTMS versus cgiTBS)		
Drop-out	15% (26.5% vs 41.5%)	20% (26.5% vs 46.5%)	25% (26.5% vs 51.5%)
15%	80.2%	96.0%	99.6%
20%	77.8%	94.9%	99.4%
25%	68.0%	89.3%	97.9%

We will monitor drop-out rates with our trial steering committee and data monitoring and ethics committee and if they are notably greater than 15% we will consider updating the sample size calculation. In relation to our mechanism of action study, recruiting a minimum of 253 participants would give 80% power of detecting a mechanistically important significance difference of 0.15 in the mean change of DLPFC-DMPFC in the responders compared to the non-responders at the 5% level (based on responders change being -0.15, non-responders 0, standard deviation being 0.33 in both groups, one third of individuals being responders). We also assume 15% loss to follow-up of individuals as well as 10% loss of scans due to poor quality at both baseline and 16 weeks as observed in our pilot study. Existing data indicate changes of -0.22 using rTMS (36) and -0.12 for TBS (Nottingham pilot) indicating that -0.15 is a plausible effect size, bearing in mind that effect sizes in small samples have limited reliability. The standard deviation of 0.33 was observed in the Nottingham pilot. Recruiting this many individuals is feasible and give sufficient power if MRS scans are carried out at 3 sites (Nottingham, Northampton and Newcastle).

7 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.

7.1 Common Adverse effects

Common adverse effects (all of which subside within 1-2 hours of TMS usually) include:
Headaches
Neck pain
Scalp Discomfort
Tinnitus
Dizziness
Jaw Ache
Nausea
Watering eyes

7.2 Uncommon Adverse Effects

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.

8 Regulatory Aspects

8.1 Ethical and other NHS Approvals

No changes to the protocol will be initiated without prior written approval of the relevant Competent Authority and independent ethics committee of an appropriate amendment. The only exception to this is when the change is necessary to eliminate immediate hazards to the subjects (Urgent Safety Measures) or when the change involves only logistical or administrative aspects of the trial. For any Urgent Safety Measures, these will be reported to the Competent Authority and independent ethics committee immediately in line with the Sponsor and LCTU processes.

The study will be conducted in accordance with the ethical principles based on the UK Policy Framework for Health and Social Care, Good Clinical Practice and the Declaration of Helsinki 1996 (last amended October 2000, with additional footnotes added 2002 and 2004).

8.2 Deception

The study will follow standard NHS HRA ethics approval. Participants will be informed by a research assistant of potential benefits and risks of TMS as outlined by NICE (12) and experienced by our pilot study participants, they will receive either rTMS or cgiTBS treatment and scans in both groups so that they will be blinded to treatment and the time taken. Expenses will covered for participation in the study along with a £10.00 shopping voucher at 16 and 26 Week follow up assessments. They will also be told of the need not to change any other treatment for depression for 16 weeks (unless they experience a serious adverse event). They will stay with their existing care team but their clinical care will be reviewed at 26 weeks by a clinical expert in TRD and at 16 weeks if they had made no improvement in their symptoms.

8.3 Consent

The participant must personally sign and date the latest approved version of the informed consent form before any trial specific procedures are performed.

A written version of the participant information sheet and informed consent form will be given to the participants, detailing no less than: the exact nature of the trial; the implications and constraints of the protocol; the known side effects and any risks involved in taking part. It will be clearly stated that the participant is free to withdraw from the trial at any time for any reason without prejudice to future care, and with no obligation to give the reason for withdrawal. The participant will be allowed a minimum of

48 hours and as much time as wished to consider the information, and the opportunity to question the Investigator, their GP or other independent parties to decide whether they will participate in the trial. At the screening visit, research assistant will check the person's eligibility to participate, give an unbiased explanation in detail as to what the trial involves (including benefits and risks) and answer any questions they may have. Written Informed Consent will then be obtained by means of participant dated signature and dated signature of the person who explained the trial and obtained the informed consent. The person who obtained the consent will be suitably qualified and experienced, and have been authorised to do so by the Chief/Principal Investigator as detailed on the Delegation of Authority and Signature log for the trial. The original signed form will be retained at the trial site within the Trial Master File (TMF). A copy of the signed Informed Consent Form will be given to participants and a copy sent to their GP.

8.4   Right to Withdraw

Participants are informed that participation is voluntary and they are free to withdraw from the trial at any time, without giving any reason, and without their legal rights being affected. If they withdraw then the information collected so far cannot be erased and this information will still be used in the data analysis. Routine clinical care provided will not be affected if they chose to withdraw. This information is provided to the participant in the patient information leaflet and informed of this prior to consenting.

8.5   Confidentiality and Data Protection

Ethical and legal practice and all information about participants will be handled in confidence. Participants will be informed in the Patient Information Leaflet that some parts of their medical records and the data collected for the study will be looked at by authorised persons from the Nottinghamshire Healthcare NHS Foundation Trust who are sponsoring this research and the University of Nottingham who are supporting this research and Leicester Clinical Trials Unit.

Other authorised people may also check this data to ensure that the study is being carried out correctly. All will have a duty of confidentiality to the research participant and will do our best to meet this duty.

All information that is collected about participants during the course of the research will be kept strictly confidential, stored in a secure and locked office, and on a password protected secure database. Any information about the participants which leaves the hospital will be anonymised be and a unique code will be used and logged and will be only accessible to the research team. Personal data will be kept for 12 months after the end of the study so that participants can be contacted about the findings of the study and possible follow-up studies. All other research data will be kept securely for 5 years. If the study is highly cited or seen as a landmark study then we are obliged by the Medical Research Council and NIHR to keep for 30 years.

 After this time the data will be disposed of securely. During this time all precautions will be taken by all those involved to maintain confidentiality, only members of the research team will have access to personal data.

The routinely collected clinical data will be treated in the same way as other clinical case-records are treated in the NHS. Although any disclosures during the study which is felt puts the participant or anyone else at any risk, may be deemed necessary to report to the mental health crisis team. Details of this will be with the study guidelines at each site.

Following completion of the trial data analysis, data and essential trial records, including the final study report, will be archived in a secure location, for 5 years after the completion of the trial, in accordance with EU regulations. No trial-related records, including hospital medical notes, will be destroyed unless or until the Sponsor gives authorisation to do so.

8.6 Vulnerable Groups

- Participants will be asked to provide informed consent, however, they will be given a minimum of 48 hours after receipt of the Patient information leaflet to decide if they would like to take part.
- Safeguarding training for vulnerable adults will be provided to all research team members.
- Consent Sessions will be randomly assessed by an independent person to ensure participant's rights are upheld.

8.7 Confidentiality

All investigators and trial site staff will comply with the requirements of relevant legislation with regards to the collection, storage, processing and disclosure of personal information for the Nottingham Healthcare Foundation trust, Universities of Nottingham, the Leicester Clinical Trials Unit and the local NHS Trusts.

 The personal information that is collected will be kept secure and maintained by:

- A unique participant screening ID number will generated once a patient has expressed an interest in the study. Once the patient has been entered into the randomisation process, they will then be allocated a participant study ID number (randomisation number).
- Secure maintenance of the data, in both electronic and paper forms and the linking code in separate locations
- Limiting access to the minimum number of individuals necessary for quality control, audit, and analysis
- Paper based anonymised trial records will be stored in locked filing cabinets within a locked office. Electronic records will be stored on secure University of Leicester IM&T server systems.
- The database will be password protected and only researchers collecting data will have access. All data collected during the study will be stored anonymously.
- Participant's contact details will be held separate to the study visit data and used to arrange data collection visits by the research team or direct care team.
- Any data transmitted will be done securely in approved Nottingham Healthcare NHS Foundation Trust methods (i.e. encrypted file transfer, internal email system) in accordance with LCTU SOPs.

Regular monitoring will be performed according to ICH GCP. Data will be evaluated for compliance with the protocol and accuracy in relation to source documents. Following written standard operating procedures, the monitors will verify that the clinical trial is conducted and data are generated, documented and reported in compliance with the protocol, GCP and the applicable regulatory requirements.

The trial manager will also undertake quality checks and assurance audits to ensure compliance with protocol, GCP and regulatory requirements.

All source data, study documents, and participant notes will be made available for monitoring, audits and inspections by the Ethics Committee, the Sponsor (or their delegate) and the Competent Regulatory Authority.

9.8 Indemnity

Sponsorship and insurance for the study will be provided by the Nottinghamshire Healthcare NHS Foundation Trust. If a participant is harmed due to negligence, this would be covered by the local NHS Trust(s) indemnity arrangements for all participants in clinical trials. If a study participant wishes to make a complaint about any aspects of the way they have been treated or approached during the research project, the standard National Health Service complaint system will be available to them, the contact details for which are in the participant information sheet.

8.9 Sponsor

The sponsor will be Nottinghamshire Healthcare NHS Trust. We will set up an independent trial steering committee and data monitoring and ethics committee (DMEC- chair psychiatrist, independent statistician and patient and public representative). The TSC and DMEC will be held in the first 6 months of study, at 12 months and every 12 months thereafter.

8.9.1 Trial Management Group

Initial study meetings with research team will occur monthly for 12 months, then three monthly attended by chief investigator, trial statistician, trial manager, qualitative lead, PPI representative from each centre, PPI lead, principal investigator from each centre. Twice yearly meetings of all members of the research team will held throughout the study.

8.9.2 Data Monitoring Ethics Committee

The DMEC will review un-blinded accumulating data on trial conduct and participant safety and report their recommendations with regards to the trial continuing to the TSC. The DMEC has entirely independent membership, the trial statistician will present the study data un-blinded in a closed session, the blinded progress and demographic data will be reviewed in an open session attended by the chief investigator, trail manager and imaging lead.

8.9.3 Trial Steering Committee

The TSC will meet following the production of the DMEC report. Although majority independent membership the TSC will be attended by the chief investigator, trial statistician, PPI lead, trial manager, imaging lead and principal investigator from each centre. The TSC and DMEC reserve the right to meet independently to draw conclusions about the progress of the trial and deliberate their recommendations.

9 Funding

The trial has been funded by the EME Programme National Institute for Health Research with total research costs not including NHS Support and treatment costs is £1,890,115.71.

NHS support and treatment cost are £219,231.85

Participants will be paid a £10.00 thankyou shopping voucher for attending the 16 week follow up assessment. With an additional £10.00 shopping voucher if they complete the 26 follow up assessment, this is to encourage participant retention. Travel expenses for use of a private car at

standard National Health Service rates or public transport (but not taxis) will be offered to the participant and a carer (if required) for all the treatment and assessment sessions.

10 Patient and Public Involvement

We worked with the Involvement Centre at Nottinghamshire Healthcare Trust to create a Magnetic Stimulation Advisory Group who co-produced the treatment pathway for both the pilot study and this proposal and also the treatment pathway in our NHS TMS service. They presented the proposal to service users and management. They told us TMS should be delivered intensively over 4 weeks because commitment is maintained better than less frequently over 6 weeks. Carers should accompany service users because of initial fear of the treatment that soon abates. With regard to this study a co-production approach has been taken. They told us that TBS is more effective and acceptable than other treatments even with the inconvenience of brain scanning so evidence is needed for its implementation. However patient acceptability is as important as effectiveness so it should be examined in this research.

During the study, each centre will contribute 2PPI representatives who will contribute to all study meetings and a representative will be invited to attend all research meetings. At each site PPI representatives will seek opinions, test ideas and gain support for the study helping with recruitment as well as attend study meetings. The local principal investigator will meet with the PPI representatives on a quarterly basis. Participant information sheets and other study materials have been co-designed. We will offer PPI representatives training in research methods and critical thinking, and consider them as full members of equal status in the research team. They will see oversee the interpretation of our findings, particularly the emerging qualitative analysis on barriers to recruitment and patient acceptability of TMS. The PPI process will be overseen by an experienced PPI lead who has trained supported and mentored many PPI groups over recent years. We will ensure that the voice of experts by experience is heard in all dissemination activities, including presentations or publications. We will build our links with other service user organisations e.g. Depression Alliance, Depression UK, Rethink, PPI group of NIHR MindTech HTC to recruit to the PPI group, test ideas with a wider audience and disseminate findings.

11 Dissemination

All participants will be sent a report summary of the results. Publication plans will be approved by the Trial Steering Committee will be written by the TMG during the study with the sponsor and funder approvals. It is envisaged that the results of the study will be published in the relevant peer-reviewed journals. Acknowledgement of any supporting organisations, including funders, and the Nottinghamshire Healthcare NHS Foundation Trust and the LCTU, will be included.

12 Relevant Signatures

Chief Investigator:

Name: _____

Signature: _____

Date: _____

Principal Investigator:

Name: _____

Signature: _____

Date: _____

Sponsor Representative:

Name: _____

Signature: _____

Date: _____

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14 Appendices

Appendix 1:

Definition of Treatment resistance.

Treatment resistance. On further clarification with the clinical adviser to EME Board, we understand that the concerns raised by the Board are in relation to the operationalisation of the Massachusetts General Hospital staging method (MGH-S) of treatment resistance (Fava et al, 2003).

This is a method of establishing the effectiveness number of previous biological treatments for depression, given as an adequate treatment trial, in the current episode of depression, not any other episodes of depression in the past. We have not include consideration of treatment resistance in relation to psychological treatments because resistance to such treatment has not been investigated in relation to moderation of treatment effectiveness with TMS in TRD. In contrast there is some evidence that treatment resistance to biological treatments may moderate treatment outcome although the evidence base is not robust. We will however record psychological treatment and the patient's response to it and explore whether inclusion of treatment resistance to psychological treatment might be of added value in determining response to cgiTBS or TMS. This would be an exploratory analysis conducted after the rest of the analysis in the protocol.

We will establish the degree of treatment resistance in the current episode of depression by a combination of interview with the patient and examination of primary or secondary case notes. First of all the participant will receive a standardised psychiatric interview to establish the diagnosis of a unipolar major depression episode and its current severity as a score on the Hamilton Depression

Rating Scale. The participant will then be asked using timeline follow back techniques to identify when the current episode of depression started.

We will update the MGH-S form published by Fava et al. in 2003 with medications not available at the time and remove ones that are no longer available. The staging score is based on one point being given on the MGH-S for every different antidepressant prescribed at the minimum effective dose for 4 weeks or more without response. An extra 0.5 points are scored if the dose has been increased to a maximum level (again defined in the Fava et al. 2003 paper describing the scale, which we will update), or the antidepressant has been augmented by a second drug. These are poorly defined in the Fava paper and there has been considerable research conducted since its publication. We will include any augmentation regime outlined as having at least Category B evidence as first or second line options (all supported by at least one RCT) in the British Association of Psychopharmacology Guidelines (Cleare et al, 2015). To count, the augmentation medication must have been given at a minimally effective dose (which we will define on the basis of the published research evidence supporting the agent) for a minimum of 4 weeks. As outlined by Fava et al (2003), any course of electroconvulsive therapy lasting a minimum of 4 treatment sessions is given a score of 3 points.

Each patient is scored on the MGH-S scale and a minimum inclusion criteria for the RCT is a score of 2 points or more. A score of 2 might be achieved by patients who have not responded to 2 different antidepressant regimes, antidepressant augmentation strategies, high prolonged dosages of antidepressants and/or ECT in their current episode.

 Based on data used in the ADD randomised controlled trial, we will categorise low resistance as any participant scoring 2 or 3 on the MGH-S scale, moderate resistance as scoring 4, 5 or 6, high resistance as scoring 6.5 or more. There are a small number of participants with very long duration of unipolar major depression who have received 6 or more antidepressants or antidepressant treatments but the participant does not recall all the details of treatment and case notes may not be available for the whole period of time. We will allocate all such patients to the high resistance category. We have removed the maximum score for treatment resistance.

Unlike other measures of treatment resistance we will not consider duration or number of previous episodes of depression or comorbidities in the definition of treatment resistance which we wish to restrict to failed attempts at minimum effective treatment. Therefore, treatment resistance is defined in health services research terms rather than conflated by other factors that might influence the outcome of depression treatment, each of which can be explored in relation to response to TMS as an exploratory analysis. Planned moderator analysis will test severity of depression, degree of treatment resistance and age as justified in the existing protocol; other moderator analysis will be considered exploratory and conducted after the main analysis.

Appendix 2:

Cognitive Scanning Changes
Depression is associated with marked impairments in attention and executive function (Austin et al., 2001; McDermott & Ebmeier, 2009). Part of these impairments could be explained by increased intra-individual task variability (IIV) – patients with depression show a skewed distribution of response times on sustained attention tasks, with an increased frequency of slow responses consistent with attentional lapses (Gallagher et al., 2015). It may be that these attentional lapses reflect interference from brain areas involved in internally-directed mental activity and rumination –

the so-called "default mode network" (DMN) – on areas involved in executive function – the "frontoparietal network" (FPN).

Previous work has found that executive function in non-clinical populations is related to the degree of anticorrelation between the activities of the FPN and DMN (Kelly et al., 2008; Keller et al., 2015), suggesting that the ability to separate the activities of these networks may be critical to task performance. One of the key findings of a meta-analysis of resting-state fMRI studies in patients with depression was an increase in connectivity between the FPN and the DMN, suggesting a breakdown of this separability (Kaiser et al., 2015).

We will explore correlations between IIV on the THINC-it battery of cognitive tests and resting-state functional connectivity between the FPN and the DMN, both using baseline values of each measure and using changes in each measure from baseline to 16 weeks. We will also explore the mediating effects of low mood (measured with the QIDS), on these relationships. It remains unclear the extent to which attentional and executive impairments are secondary consequences of impairments in mood or independent components of the pathophysiology of depression (Bora et al., 2013; Rock et al., 2014). Evidence of independence would imply a novel target for intervention to improve functioning in patients with depression.

Relationship to study protocol and pilot work

This sub-study partially addresses hypothesis 1 from section 5.1.1 of the study protocol ("Hypothesis for the mechanistic component") in testing for abnormal connectivity between default and cognitive control networks, as well as looking at the effects of depressive symptomatology on these relationships.

The pilot study (section 3.5) showed that greater improvement in depressive symptomatology following TMS or iTBS was associated with a greater reduction in the functional connectivity between dorsolateral prefrontal cortex (DLPFC) and dorsomedial prefrontal cortex (DMPFC). To the extent to which DLPFC and DMPFC are nodes of the FPN, and DMN, respectively, and to the extent that changes in IIV will mirror changes in depressive symptomatology, these results are consistent with the above predictions.