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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Study Summary

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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	266
Study Location/s	Nottingham, Newcastle, Northampton, London and Oldham
Participant Inclusion Criteria	▪ Adults ≥ 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) determined by the Hamilton Depression Rating Scale (HDRS-17) over 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). Each 10 second cycle will consist of 10 bursts (consisting of 2 seconds of stimulation and 8 seconds rest) with a total of 20 cycles performed per run over a site determined from the assessment of maximal strength of connectivity between the anterior insula and the left dorsolateral prefrontal cortex (DLPFC) from fMRI using neuronavigation which computes the nearest location for TBS stimulus on the scalp from the same three fiducial points, the nasion, left preauricular and right preauricular sites. The pulses are applied 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).

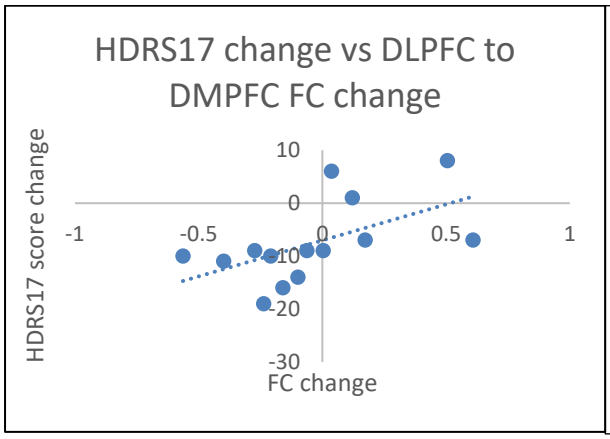


Figure 1: Correlation of HDRS17 change and functional connectivity change baseline to 3 months.

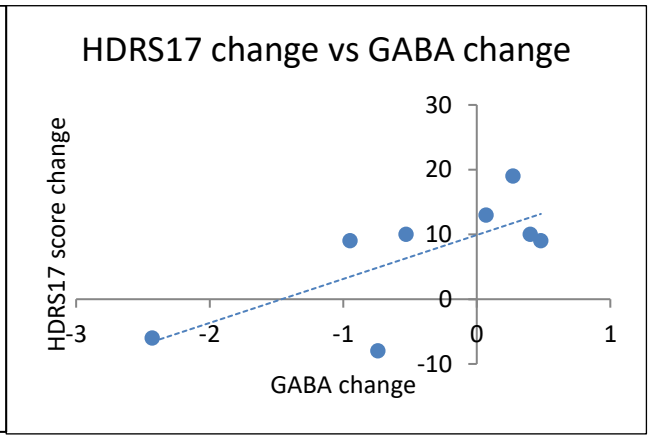


Figure 2 Correlation of HDRS17 change and GABA change baseline to 3 months.

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 compared with standard rTMS in reducing the HDRS-17 score over 26 weeks follow-up, 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 reducing the mean HDRS-17 score over 26 weeks compared to 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.
48	Complete recruitment of 266 participants
49-55	Complete follow up of all participants and scanning, database entry & checking.
49-60	Analysis of scanning
49-60	Analysis of clinical outcomes and health economics. Write up report and main publications.
61	2 weeks after completion of month 61 delivery of final report.

4.2 Participant Involvement

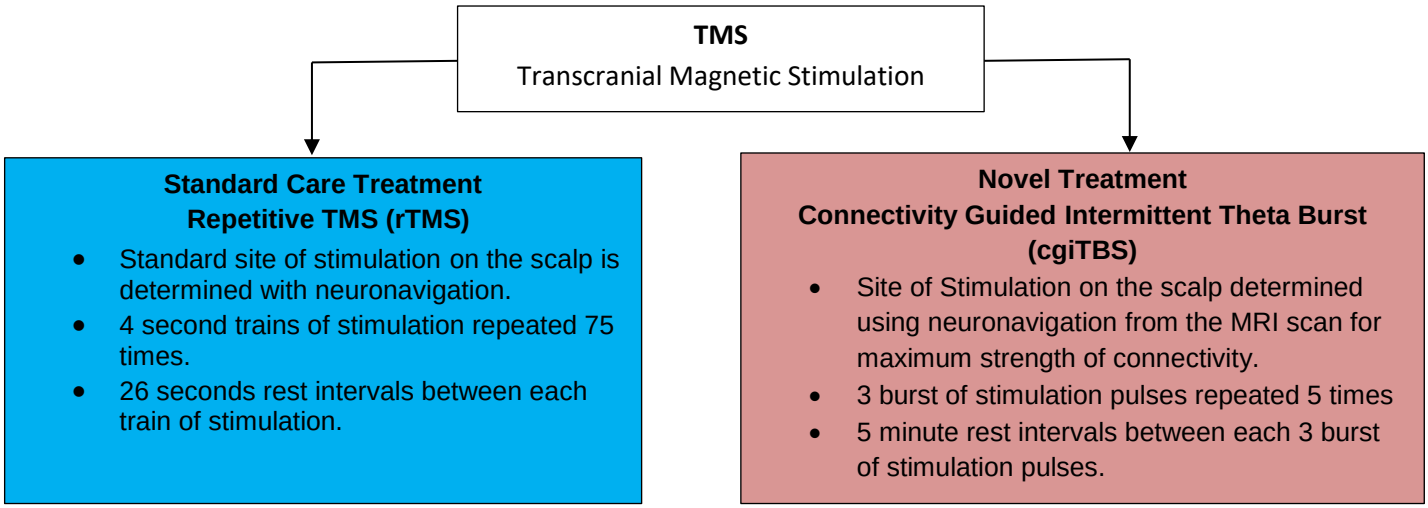
Participants in both arms will receive 20 TMS sessions delivered over 4- 6 weeks. A total of 3000 pulses will be delivered in each rTMS or cgiTBS session. At each centre, 8 participants per day could be treated.

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). Each 10 second cycle will consist of 10 bursts (consisting of 2 seconds of stimulation and 8 seconds rest) with a total of 20 cycles performed per run over a site determined from the assessment of maximal strength of connectivity between the anterior insula and the left dorsolateral prefrontal cortex (DLPFC) from fMRI and structural MRI using neuronavigation which computes the nearest location for TBS stimulus on the scalp from the

same three fiducial points, the nasion, left preauricular and right preauricular sites. The pulses are repeated for a total of 5 runs with 5 minute rest intervals between runs.

Comparison of TMS Treatments:



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:

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

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

- Remission rate at 8, 16 and 26 weeks measured using HDRS-17 (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 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 17 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	✓	✓(When completed at a separate visit whilst COVID-19 mitigation restrictions in place)		✓(Not completed whilst COVID-19 mitigation restrictions in place)	✓	✓(When completed at a separate visit whilst COVID-19 mitigation restrictions in place)	✓(Not completed whilst COVID-19 mitigation restrictions in place)
QIDS-	✓			✓	✓		
SCID Research Interviews	✓						
CTQ (Replaces PSTD section in SCID Questionnaire.)	✓						
Client Resource Questionnaire	✓				✓		✓
Patient Acceptability			✓	✓	✓		✓
Side Effects Checklist (Adverse Events)			✓	✓			
MRI		✓				✓(Not in London)	
rsfMRI		✓				✓ (Not in London)	
MRS (Not in London & Oldham)		✓				✓	
Diffusion weighted imaging		✓				✓(Not in London)	
Arterial Spin Labelling (Not in London & Newcastle)		✓				✓	

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 after randomisation 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. 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). Pennine Care Trust will be the 5th site to recruit to the study, there is a new TMS service in this area but the centre is only used to treat people with severe depression with other treatments such as electroconvulsive therapy. 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.

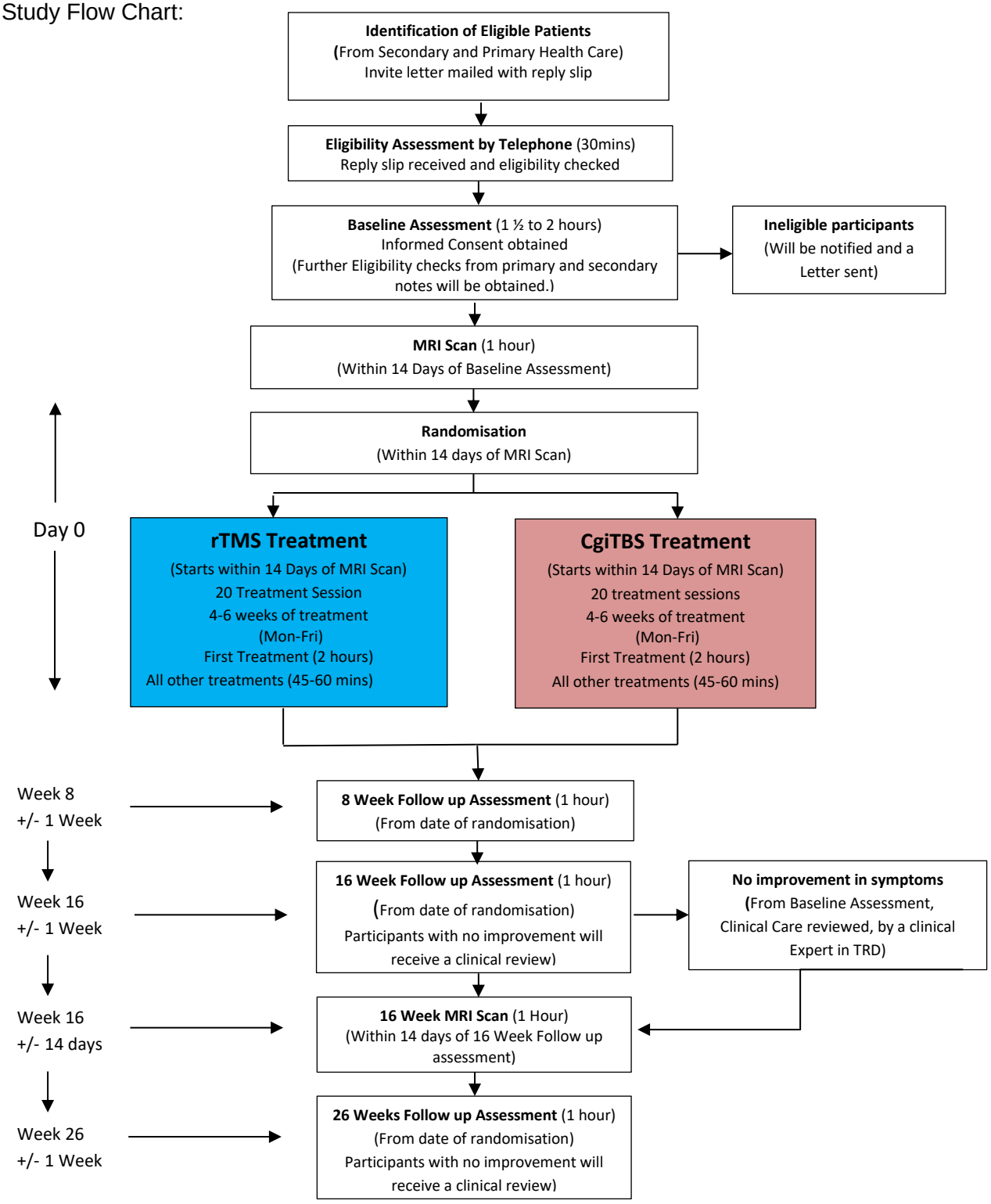
20 Treatment sessions will be delivered over a 4-6 week period (Treatment sessions must not have a discontinuity of more than 4 days), with each session lasting 45-60 minutes, with the exception of the first treatment taking 2 hours.

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:



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.

5.6 Optional sub-study

Qualitative study to explore the reasons and meanings behind why participants request a copy of the images taken during their MRI scan.

This sub- study is, not being funded by the Efficacy and Mechanism Evaluation (EME) Programme. The Views expressed in this publication are those of the author(s) and not necessarily those of the Efficacy and Mechanism Evaluation (EME) Programme.

Further information regarding this sub-study is contained in Appendices. (See appendix 3:)

6 Research Data

6.1 Data Analysis

Efficacy. All analyses will be agreed and specified in advance of database lock in a statistical analysis plan. 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 change the mean HDRS-17 score over 26 weeks when compared to rTMS on an intention to treat population. The primary analysis of the primary outcome will be a mixed effects model with participant as random effect to account for repeated measures over time. Each participant will contribute up to 3 repeated outcome measures to the model in addition to the baseline HDRS-17 score. The model will be adjusted for the stratification and minimisation variables: baseline HDRS-17 score, baseline Massachusetts General Hospital Treatment Resistant Depression score, visit number and centre. The primary analysis of the primary outcome will fit this model on all available data. Participants with at least one follow-up measure of HDRS-17 will contribute to the model. Provision of HDRS-17 at follow-up visits is expected to be very high, where this expectation isn't met imputation methods will be utilised to account for missing data and maintain the intention to treat principle. As a secondary analysis, a mixed effects model will be repeated in completers (those with 10 or more sessions rTMS or cgiTBS, assessed at baseline and 16 weeks) and a per protocol analysis adjusting for the same variables as in the primary analysis. 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.

The Data Monitoring Ethics Committee (DMEC) will monitor the safety and conduct of the study through regular reports of accumulating data. Data on recruitment, treatment and protocol compliance, design assumptions and adverse events will be presented to the unblinded DMEC.

6.4 Analysis of baseline factors

6.4.1 Interim Analysis of Baseline MRI and Clinical data

Analysis of baseline MRI and clinical data will explore 5 key themes that will support and boost both the impact and inference of the main study outcomes. These themes are treatment resistance, co-morbid anxiety, cognitive impairment, trauma, and medication and other confounds. All baseline analyses will remain blinded to treatment allocation (cgiTBS or rTMS) and trial outcomes (responder/non-responder) until after final database lock. Analyses will follow a prespecified and agreed statistical analysis plan and occur in two steps: 1) Pre-processing the relevant imaging data and generating all required subject-level statistical maps ready for group-level analyses, 2) Input from Clinical Trials Unit, providing clinical data in order to group / carry out regression style analyses.

Established quality checks for all MRI data will be carried out. Imaging data will be analysed using established toolboxes such as FSL (FMRIB Software Library), Statistical Parametric Mapping (London, UK), Freesurfer, and REST (Resting-State fMRI Data Analysis Toolkit). MRS data will be analysed using specialised toolboxes LCModel and Gannet. In-house tools may be utilised when appropriate usage is not available via the established toolboxes.

Statistical analysis outline per theme:

1. Treatment resistance:
    a. Correlation analysis will be utilised to assess the hypothesised relationships between imaging measures (connectivity and GABA levels) and treatment resistance (MGH-S).
    b. Exploratory analyses of the interrelationships between age, depression severity (BDI-II/PHQ-9/HDRS-17), and duration will be carried out using correlation analyses assessing the relationship between these scores and how they interact with image-based correlates of treatment resistance.
2. Co-morbid anxiety
    a. Correlation analysis will be utilised to investigate insular<>vmPFC connectivity relationship with anxiety.
    b. Comparisons of imaging measures (connectivity, GABA, and cerebral blood flow) from subjects with and without co-morbid anxiety will be assessed.
3. Cognitive impairment
    a. Correlation analysis will be utilised to assess the hypothesised relationships between imaging measures (connectivity) and cognitive scores.
4. Trauma
    a. Correlation analysis will be utilised to assess the hypothesised relationships between imaging measures (connectivity and GABA levels) and trauma.
5. Medication and other confounds
    a. Where appropriate, analyses will be carried out to assess the influence of confounding variables such as medication usage, disease duration, disease severity, and age on brain imaging measures. This will be assessed using multiple regression modelling suitable to the type of dependent variables.

(See appendix 4: for further details on the rationale and background of the analysis of Baseline MRI and Clinical data).

6.5 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).

6.6 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

6.7 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.

6.8 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.

6.8.1 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.)

6.8.2 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.

6.9 Participant Sample Size

A sample size of 266 participants gives 89.3% power to detect a mean difference of 3 points in the HDRS-17 over 26 weeks between the groups at the 5% two-sided significance level assuming a standard deviation of 8 (informed from both our Pilot Study and a multicentre randomised controlled trial in chronic persistent depressive disorder led by the chief investigator (Morriss et al, 2016), a correlation between follow-up measures of 0.7 (1 baseline measure with correlation of 0.27 to the follow-up measures) and 20% data loss/drop-out. NICE defined 3 points as a clinically important difference in outcome on the HDRS-17 in its NICE Clinical Guideline for Depression in 2004 and 2009.

Therefore a target **total of 266 participants will be recruited (133 per arm)**.

The table below outlines the power for the targeted sample size as well as power if the recruitment occurs at a lower rate than expected, at the 5% significance level.

Given the uncertainties of recruitment to the study in the current pandemic, we note that under the same assumptions, a sample size of 232 would reassuringly still yield >85% power (85.1%).

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

We will monitor drop-out rates with our trial steering committee and data monitoring and ethics committee and if they are notably greater than 20% we will consider updating the sample size calculation.

If 266 participants are randomised into the study, we would expect 127 participants to provide data for both DLPFC-DMPFC FC change at 16 weeks and HDRS-17 change at 16 weeks, based on data observed from those who are due this follow-up data to date (48% provided data for both). The remaining 52% without this data are due to a combination of participants being randomised at the London site and therefore not having the scans, loss to follow-up at 16 weeks for HDRS-17 score as well as loss to MRI scans follow-up. If we allow for 5% further loss due to poor imaging quality, although quality checks to date show 0% loss for this, this will give us a total of 120 participants for assessing the correlation of DLPFC-DMPFC FC change at 16 weeks and HDRS-17 change at 16 weeks.

A sample size of 120 achieves 96.3% power to detect a difference of -0.3 between the null hypothesis correlation of 0.2 and the alternative hypothesis correlation of 0.5 using a two-sided hypothesis test with a significance level of 0.05. The null hypothesis of 0.2 represents a very weak/weak correlation whilst the alternative of 0.5 represents a moderate correlation [ref]. The correlation between DLPFC-DMPFC FC change at 12 weeks and HDRS-17 change at 12 weeks in our pilot data was 0.58.

[ref] https://www.bmj.com/about-bmj/resources-readers/publications/statistics-square-one/11-correlation-and-regression

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

This project (16/44/22) is funded by the Efficacy and Mechanism Evaluation (EME) Programme, an MRC and NIHR partnership. The Views expressed in this publication are those of the author(s) and not necessarily those of the MRC, NIHR or the Department of Health and and Social Care.

Total research costs not including NHS Support and treatment costs is £1,987,601.26

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 (58,59). 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 (56). 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 (60, 62), 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 (62).

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 (63 62). 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.

Appendix 3:

Sub-study to explore the reasons Why MRI scans are requested.

Introduction & Rationale

25-30 participants in the main BRIGhTMIND study, have asked for a copy of the images that were taken during their MRI scan. We envisage that more participants will come forward with similar requests during the duration of the main trial. Therefore, we propose a qualitative study to explore the reasons and meanings behind such requests.

Recent surveys have indicated that 87% of research participants would like to receive a copy of their MRI reports [64], with 89.5% of participants indicating that receiving such reports were a benefit to participating in research [65]. Despite such findings, little existing research has explored why people would like copies of their MRI scans or reports. However, qualitative studies exploring subjective experience of undergoing an MRI scan, could provide some insight into the reasons behind the requests for copies of MRI scans. For example, the following themes have been identified: feelings of personal achievement by completing the scans [66], individuals wanting to share their health journey and the role that the MRI played in this [67], finding the experience positive and reassuring and thus enjoying the opportunity to view images [68], having the perception that the MRI scan could hold the power to legitimise or delegitimise their symptoms [68] and a feeling of tenacity and courage to beat diagnosis (67). Furthermore, researchers have argued that providing access to MRI scans, demonstrates respect for an individual's autonomy (69), with altruism and finding out about incidental findings identified as strong motivators for individuals wanting to complete MRI research (70).

As previously mentioned, the above literature has explored the subjective experience of undergoing an MRI and focused on individuals with physical health concerns or illness. However, there has been little research that has provided an in-depth exploration of the reasons behind why people want copies of their MRI scans or reports, particularly in individuals with mental health conditions. Given that a large proportion of individuals would like copies of their MRI scans warrants further investigation. The prior literature may suggest key areas to focus on include personal/intrinsic reasons, research/treatment reasons and other/extrinsic reasons. This qualitative study, therefore, has the potential to provide a profound insight into participants' beliefs about the nature of depression, the utility of the scan, the process of the BRIGhTMIND study and the attitudes held by others. The findings generated from this study may also be generalisable and have value beyond that of the mental health field.

Qualitative Analysis

A purposive sample of 8-12 participants from all centres, whom have contacted the research teams to request copies of their MRI scans, will be selected for the qualitative interviews. If new topics are still being added by interviewees, then additional participants will be recruited up to 20. Each interview should last 20-30 minutes, either face to face or over the telephone and can be completed upon the participants request for their MRI scans, until the end of the study. The completion of this qualitative interview should not exclude the participants from also being invited to complete the acceptability qualitative interview (section 6.7). We will ask participants about their reasons for requesting a copy of their MRI scans, using a semi-structured interview guide. This topic guide has been developed with the aid of the PPI representatives, PPI facilitator for BRIGhTMIND and based on statements made by participants within the main BRIGhTMIND trial, who have previously requested copies of their scans. The topic guide will encourage discussion of the participant's reasons for requesting their scans, including personal/intrinsic reasons, research/TMS reasons and other/extrinsic reasons. Informed consent will follow the same process as outlined in section 5.4, with the exception that written informed consent will be obtained at the qualitative interview, rather than at the baseline assessment.

Interviews will continue until 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 Trust. NVivo 11 will be used to manage the transcripts & data coding. An inductive approach to the thematic analysis will be adopted such that the themes will be generated from the data through open coding. Interpretation of themes will be aided by the PPI representatives.

Dissemination of this study will follow the same processes as outlined in section 11. It is expected that our PPI group will co-author any publications that arise from this study.

Funding

This sub-study will be funded from a Senior Investigator award.

Appendix 4:

Interim Analysis of Baseline MRI and Clinical Data

The in-depth baseline phenotyping collected as part of the BRIGhTMIND study allows for the interrogation of a range of important characteristics and mechanisms of treatment-resistant depression. We aim to capitalise on this rich information to test a limited number of predefined pathophysiological hypotheses of treatment-resistant depression, and to develop a composite treatment-resistant 'signature' that can serve as an optimised biomarker for assessing and predicting the mechanistic treatment outcomes at the completion of the trial. We will use advanced computational approaches for multimodal MRI analysis, and cognitive testing, to test key neurobiological hypotheses of depression complemented by data-driven discovery. The availability of the first subset of MRI data (N=146 participants) that we acquired ahead of the COVID-19 lockdown provides us the power for hypothesis-testing as well as the additional advantage that the data-driven models can be validated on the future recruits. None of these proposals require or will use treatment randomisation or outcome data.

Background

Major depressive disorder (MDD) is a highly heterogenous condition, with subtypes defined on characteristics, treatment response and underlying neurobiology that provide complexity for clinicians and likely hinder treatment (71,72). Additionally, it is common for it to present with other concomitant psychiatric disorders, particularly anxiety disorders (73) with several transdiagnostic models based on shared risk factors or shared underlying mechanisms.
Treatment outcomes are disappointing in depression with only about 1 in 3 responding well to treatment: 1 in 3 are considered to be treatment resistant (TRD) with major management challenges for the latter group that are associated with increased rates of suicide, hospitalisation, poor physical health and increased healthcare costs (9). Contrary to the prevalence of TRD, little is known about what distinguishes these individuals from those that respond to treatment.

Neurobiological models of depression such as the chronic stress (74), dysfunctional emotion and emotion-regulatory networks (75) and neurotransmitter deficits including GABAergic pathways (76) have been proposed to pull together the wide ranging brain dysfunctions observed in animal and human studies. Whilst these theories highlight the importance and prevalence of mechanisms such as the increased activity of the HPA axis in depression (77), regions of treatment sensitive hyper/hypo-metabolism (25) and the reduction in GABA in depressed individuals, it is clear that there is no single factor, brain region, or neurotransmitter that is the key mechanism of (treatment resistant) depression. It is the interaction of these factors within the pathways and networks of the brain that are consider to underlie TRD (78, 79, 75), but it remains unclear whether TRD is a severity characteristic that can occur in various subtypes of depression, or constitutes a defined subgroup with as yet unknown complex pathomechanisms.

Brain signature of treatment resistant depression

(80) suggest that brain signatures are a particularly useful class of multivariable brain models that utilise distributed information across the brain in order to facilitate population-level, and between-subject predictions about the engagement of a mental process (or dysfunction). Ideally, these signatures show sensitivity to the strength of engagement of the process, and thus can be used to track the efficacy of treatments such as TMS. In order to build such a model, there needs to be quantifiable data findings such as those from MRI, thus allowing the use of specific and quantitative predictions that can be tested and falsified. This pattern of work aims to build towards a model that could thus be tested in TRD subjects and beyond.

To date, the specific neural correlates of TRD largely remain unexplored, with the majority of studies in depression investigating subjects with MDD or with investigations into TRD either being of low power (N<30) and only comparing against healthy controls (81,82,83,84); or focused upon treatment response and the prediction thereof (85). There are, however, some consistent findings that warrant further investigation. For instance, reduced FC to the DMN and within the DMN has been found repeatedly to differ between subjects with treatment resistant depression, non-treatment resistant depression and healthy controls (81, 86, 87, 88, 89). More specifically, whilst this DMN FC was reduced when compared to both non-treatment resistant and healthy subjects (81.,86, 87), one study further reported differential networks of regions to be altered compared to healthy controls (89). Lui et al (2011) specified that treatment resistant subjects displayed alterations mainly within a thalamo-cortical network whilst non-treatment resistant subjects displayed wider limbic-striatal-pallidal-thalamic connectivity compared to controls, thus suggesting that whilst there is likely to be

an overlap in the affected regions, the interplay between regions in treatment resistant depression may be the key area of investigation moving forward.
It is likely that persisting alterations in brain function are associated with alterations in grey matter structure reflecting plastic changes in the brain. Diverse changes in grey matter and surface morphology have been reported to be associated with treatment resistance (90) and also therapeutic changes induced by ECT in cases of severe illness (91). In particular, van Eijndhoven et al (91) reported that the increase in thickness of the bilateral insular cortex was greater in treatment responders than in non-responders. The BRIGhTMIND protocol targets a DLPFC site that is effectively connected to insula. Therefore, investigating the effect of TMS on insula thickness in the BRIGhTMIND longitudinal data has the potential to elucidate the mechanism of relatively enduring therapeutic effects of TMS. As a preliminary step in the baseline data, it is potentially informative to investigate the relationship between grey matter structure and treatment resistance, and to establish if insula thickness is related to the degree of treatment resistance. Furthermore in light of the evidence that the cerebral effects of ECT include linked changes in insula grey matter structure and prefrontal cortex function (92) it is potentially relevant to the mechanism of TMS to establish the relationship between insula grey matter structure and the effective connectivity between insula and DLPFC at baseline.

Neurotransmitter abnormalities have long been considered key biological features characterising depressive states that may drive the altered neuronal circuitry in MDD and TRD. Monoaminergic transmitters are undetectable by MR spectroscopy, but an increasing body of evidence highlights GABA depletion as a consistent marker of the depressed state in unipolar and bipolar depression with confirmatory reports of GABA increases after clinical response to pharmacological and non-pharmacological therapies (93). It has been hypothesised that GABA depletion may explain increased functional connectivity and activity in the pregenual ACC in depression (disinhibition), impaired DMN/SAL anticorrelation and low DLPFC FC and activity, but experimental evidence is lacking and there are no studies on DLPFC GABA associations with TRD (94). A combined approach studying the links between DLPFC GABA with rAI, pgACC and DLPFC FC and regional CBF (indexing baseline brain activity) will provide important insight into the neural abnormalities of MDD/TRD and its potential use as biomarker.

Building upon this evidence, we seek to interrogate the link between the levels of treatment resistance (controlling for confounds such as depression severity and medication usage where possible), with imaging markers including brain connectivity (structural and functional) and neurochemical levels such as GABA that have been shown to change in response to TMS in controls (95), and treatment resistant subjects (96,97). These markers may provide further treatment prediction targets/markers, for instance, the study by Levitt et al (2019) observed that those subjects taking GABA agonistic medication during TMS were less likely to respond to treatment than those not.

Co-morbid anxiety

Anxiety is a commonly observed co-morbidity with depression (73) and is thought to contribute to a large number of observed treatment failures in depression (98). It is thus imperative that the neural mechanisms underlying this co-morbidity is further interrogated and whether different neural targets could be elucidated for treatments like TMS.

In their review, Kim and Yoon (99), found that patients with social anxiety disorder and patients with panic disorder showed similar changes in DMN network connectivity compared to controls, but whilst social anxiety disorder was also characterised by increased connectivity within the salience network, panic disorder was characterised by changes in the sensorimotor network. Studies on generalised anxiety disorder have tended to focus on the connectivity of the amygdala. In their review, Hilbert et al (100) identified decreased functional connectivity between the amygdala and the FPN as a consistent finding in anxiety, suggesting decreased top-down regulation of threat detection. The review does not take into account the functional lateralisation of the amygdala which may impact strongly on the underlying findings and their interpretation. For instance, a review by Baas et al (101) observed that the left amygdala was more commonly active than the right amygdala during functional neuroimaging studies of emotional processing tasks, indicating at least some divergence in the functional laterality. More recent studies such as that by Jung et al (102) in social anxiety disorder, and the meta-analysis by McTeague et al (103) looking across pathological cohorts (including depression, anxiety) have observed the left and right amygdalae to be differentially affected. Jung et al (102) observed increased left amygdala connectivity and reduced right amygdala connectivity within their anxious cohort compared to controls whilst McTeague et al (103) observed consistent left amygdala hyperactivity in anxiety and right hyperactivity in bipolar disorders. It is unclear whether these findings translate from subjects with isolated anxiety disorders to those with depression and co-morbid anxiety. Recent studies point support this idea however, observing shared mechanisms such as the observations of insula hyperreactivity in both depression and anxiety that correlate with disease severity (104, 105), insula to anterior DMN hyperconnectivity present in both disorders (106,107), and amygdala functional connectivity that was found to mediate the relationship between reported depression and anxiety scores (108).

Further interrogation of this co-morbidity, especially insular connectivity (that potentially presents as a transdiagnostic target) alongside measures of severity of depression and anxiety is warranted to better understand its neural underpinnings. Especially considering the suggested impact that it has on rates of treatment failure. As prior studies suggest that there may be shared networks of interest in presentations of depression and anxiety, it is feasible that we could thus identify potential intervention targets for TMS that may or may not overlap with those already utilised within the trial.

Cognitive impairment

Depression is associated with marked impairments in attention and executive function (58, 59), and these impairments may be the primary mediators of psychosocial and occupational dysfunction (109). The attentional impairment is best characterised by assessing intra-individual variability (IIV) in response times during a sustained attention task – patients with depression show a greater skew in the distribution of response times due to an increased frequency of slow responses consistent with attentional lapses (56).

It may be that attentional lapses reflect interference from brain areas involved in internally directed mental activity and rumination (DMN) on areas involved in executive function (e.g. ECN). Previous work has found that executive function in non-clinical populations is related to the degree of anticorrelation (i.e., negative connectivity) between the activities of the ECN and DMN (61,60) 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 increasingly positive connectivity between the ECN and the DMN, suggesting a breakdown of this functional segregation (62). In addition to the role of functional connectivity in cognition, structural connectivity also plays an important role. For instance, IIV has

been shown to be affected by white matter tissue integrity in healthy ageing (110), whilst tissue integrity can also be affected by the presence of depression and childhood trauma (111).

Despite the importance of attentional and executive impairment in determining outcomes in depression, the extent to which these impairments are an independent component of the pathophysiology of depression or a secondary consequence of impairments in mood and active mind wandering/rumination remains uncertain (63,57). This is of key importance, as the former would suggest a novel target for intervention. Of note, depression, particularly in older adults, has been associated with reductions in the volume of brain areas including the dorsolateral prefrontal cortex (DLPFC; 112) – a key component of the ECN – and the hippocampus (113) – a key component of the DMN (along with other structures of the medial temporal lobe). In line with this, multiple studies have observed increased hippocampal volume in TRD after courses of electro-convulsive therapy and vagus nerve stimulation suggesting that these changes are also present in TRD, and are sensitive to treatment (114)

Trauma

Childhood trauma, stress, and adversity are all strong risk factors for the development of depression in adulthood and subsequent increased likelihood of treatment resistance (115, 116,117). Beyond physiological measures such as an increased neuroendocrine stress response or immune activation, brain imaging has also identified the presence of a reduced hippocampal volume alongside reduced fractional anisotropy within the rostral/dorsal and parahippocampal cingulum (118), and functional network connectivity alterations that are driven by experiences of childhood trauma (119). It is therefore of key interest to interrogate how these measurements relate to reported trauma and whether they overlap with the proposed mechanisms of TMS that the BRIGhTMIND trial is targeting for treatment.

A recent systematic review has demonstrated that there are widespread and differential functional and structural brain abnormalities associated with childhood trauma subtypes (120). The review identified that sexual abuse is related to abnormalities in the reward circuit and genitosensory cortex, whereas, emotional maltreatment (i.e. emotional abuse and emotional neglect) is related to abnormalities in the fronto-limbic socioemotional networks (120).

In MDD, childhood trauma has been related to decreased connectivity within salience and emotion networks, increased connectivity in cognitive control networks (121) and reduced connectivity within brain regions in the prefrontal-limbic-thalamic-cerebellar circuitry (122). Trauma exposed individuals with MDD have also shown decreased connectivity between the salience network and DMN (123) rand reduced causal connectivity between the mPFC and amygdala (124). Furthermore, childhood trauma in MDD has been associated with increased rsFC between the dorsal attention network and the sensorimotor network, ECN and the ventral attention network (119). Considering the common observation of hypervigilance in subjects with prior trauma, observed imbalances between cognitive and attention-based networks (such as the ECN, the dorsal attention network and the sensorimotor networks) being hyperconnected and more internally directed networks such as the DMN and SN showing hypoconnectivity likely underlie such outward behaviours (119). Such altered connectivity could be an important point of interest within the BRIGhTMIND study, as the treatment targets the DLFPC (a key hub in the cognitive networks) and aims to impact its connectivity with the anterior insula, a key hub within the salience network. To better understand how the presence of trauma might impact the interrelation between these treatment targets is of key importance to the study.

Noteworthy to this study, childhood trauma has also been inversely associated with FC of the left DLPFC in MDD (125, 122) and decreased gray matter volume in the left DLPFC has been found in those with a history of childhood trauma, irrespective of MDD diagnosis (126). Thus, it has been suggested that the DLPFC is particularly vulnerable to childhood trauma, which may have important implications for the effects of left DLPFC targeted TMS treatment (126).

A further consequence of the adverse effects of childhood trauma in MDD could potentially be alterations in gamma-amino-butyric acid (GABA). However, there are only limited studies that have explored how childhood trauma maybe related to cortical glutamate and/or GABA concentrations. One study has shown increased childhood trauma was inversely associated with mPFC Glu/NAA concentrations, in non-psychiatric controls (127) in line with animal models of juvenile stress that also observe reduced GABA in corticolimbic structures such as the amygdala, mPFC and hippocampus (128). Furthermore, whilst not specific to childhood trauma, research has also identified lower GABA/H_20 and glutamine/H_20 in the dorsal ACC in trauma exposed veterans (129). Additionally, decreased GABA/Creatine has been identified in the insula (130) and lower GABA identified in the parieto-occipital cortex in individuals with PTSD (131). Collectively, these studies suggest that GABAergic imbalance is associated with trauma. Therefore, further work is required to explore the GABAergic system and its implication in childhood trauma within TRD.

Most of the prior investigations have utilized small sample sizes and often focused on specific childhood trauma subtypes. However, given that childhood trauma subtypes may display differential underlying mechanisms, future research is warranted in a larger sample of individuals with TRD such as the one collected here to explore within and between connectivity of brain networks and brain regions and how they are related to several childhood trauma subtypes and treatment resistance.

Medication and other confounds

Confounds such as medication usage, age, disease severity and duration are a common problem to be accounted for in scientific studies but in TRD they pose a particularly interesting challenge. For instance, the effects of age, illness severity, and duration are difficult to parse cleanly as they all interact. It is more likely that older participants will be scored as more treatment resistant as they might have simply had longer to try (and fail) more medications whilst simultaneously also accruing a longer illness duration. Medication usage is also interesting as whilst there is a small evidence that some medications (such as GABA agonists) may boost the effects of TMS (97), the general impact of this usage on brain structure and function has not been elucidated.

Meta-analyses have shown some differences in brain regions when taking into consideration medication status. For example, decreases in amygdala volume for unmedicated MDD and increases in amygdala volume in medicated MDD have been identified, when compared to controls (132). However, no correlations (at least linearly) have been observed between amygdala FC changes and the percentage of medicated MDD patients (133). Antidepressant-free MDD patients also have significantly smaller volumes in the OFC, ACC and subgenual ACC compared to MDD patients taking antidepressants (134). Furthermore, larger effect sizes in the orbitofrontal cortex, amygdala and subgenual prefrontal cortex volume has been associated with antidepressants, antipsychotics and mood stabilisers (135). Decreases in hippocampal volumes (136) and mPFC Glx levels have been found in both medicated and unmedicated MDD patients when compared to controls (137). In respect to brain networks, several studies have observed significantly reduced DMN functional connectivity after antidepressant (via both SSRI & SNRI) treatment (138, 139,140)

or in medicated MDD patients vs. non-medicated (62,141). The findings overall, suggest that medication status could be an important confounding variable within this proposal.
Depression severity and illness duration may also be important confounding variables when considering brain functioning in MDD. For example, meta-analyses have shown inverse associations between depression severity and fractional anisotropy (FA) reduction in the genu of the corpus callosum (142). Smaller grey-matter volumes in the left hippocampus have also been observed in lower depression severity samples, when compared to controls (143). Larger effect sizes, with increasing severity of illness have also been identified in the left anterior cingulate cortex and subgenual prefrontal cortex volume (135). Furthermore, increased regional homogeneity (ReHo) in visual regions and decreased ReHo in frontal regions has been associated with greater depression severity, whereas, greater ReHo changes in the fronto-insular region is associated with longer depression duration (144). No correlations have been observed between depression severity and DMN functional connectivity (62; 141) nor does depression severity exert an effect on hypoconnectivity within the frontoparietal network (62). Finally, no significant relationships have been found between depression severity and Glx levels in the mPFC (137).

Ageing effects may also be implicated in brain abnormalities in MDD. For example, smaller left insula volumes have been reported for older patients with MDD (143) and decreased cerebral blood flow in the left insula inversely correlated with age (145). Smaller effect sizes in left amygdala volume have also been associated with increasing age (135), and decreased connectivity between the amygdala and right insula has been inversely correlated with age (133). Furthermore, age appears to have a significant effect on ReHo changes in fusiform, cerebellum and parahippocampal clusters (144). Age has not been associated with DMN hyperconnectivity, frontoparietal network hypoconnectivity (62), or Glx levels in the mPFC (137XU).

Overarching exploratory hypotheses

1. Treatment resistance

We seek to explore the hypothesis that functional connectivity both within DMN and DMN-SN/ECN will correlate negatively with measures of treatment resistance. Furthermore, we seek to interrogate the connectivity between the rAI and lDLPFC (the key BRIGhTMIND stimulation target mechanism), and brain structure (specifically of the insula), and levels of reported treatment resistance. We hypothesise that rAI connectivity to the DLPFC will correlate positively with greater volume/thickness of the insula. A finding that may be predictive of TMS response as suggested by earlier pilot work (Iwabuchi et al., 2019). We also hypothesise that lDLPFC GABA levels are negatively correlated with lDLPFC-pgACC FC. The interlink between age, severity and duration of depression will also be investigated to better disentangle their effects from TRD status and its neural underpinnings.

2. Co-morbid anxiety

We seek to test the interrelation of co-morbid anxiety on treatment resistance and the degree to which it drives it. We hypothesise that increased anxiety (measured by GAD7 score) will be negatively correlated with connectivity between the insula<>vmPFC. We will test for differences in these connectivity profiles between patients with and without anxiety disorder comorbidity to identify the impact that the presence of anxiety has on the neural mechanisms of TRD.

3. Cognitive impairment

We seek to test the interrelation of cognitive impairment and treatment resistance and the degree to which it may drive it. We seek to test the hypothesis that connectivity between the ECN and the

DMN will be positively correlated with intra-individual variability on attentional tasks, and negatively correlated with executive function performance (as measured with the THINC-IT battery of cognitive tests). We will then extend this analysis to interrogate how these connections relate to treatment resistance. Further investigations will be carried out linking these findings with wider clinical features.

4. Trauma
We seek to examine the interrelation of trauma with treatment resistance and the degree to which it drives it. We seek to test the key hypothesis that connectivity in the cognitive and attentional networks (focussed on the DLPFC) correlates positively with trauma scores whilst internally directed networks (such as the SN and DMN) will correlated negatively with the same scores. Additionally, we hypothesise that GABA levels in the DLPFC would correlate negatively with reported levels of trauma and the altered EC/DMN FC. Subsequent tests would assess the interrelation between these findings and levels of treatment resistance.

5. Medication and other confounds
Medication status and/or medication type has been observed to effect measures of brain connectivity (with medication reducing DMN connectivity) and brain structure (specifically the amygdalo-hippocampal complex). Additionally, due to the interrelation between age, disease severity, and disease duration and their (previously) noted impact on imaging measures, these variables will be investigated throughout the proposed themes and hypotheses for their effect on findings.

Interlinking analyses
As there is notable interrelation between these themes, their neural underpinnings as measured by MRI, and associated measures, further exploratory analyses will be carried out to assess their relationship with other imaging modalities (where not already specified) in order to give results the highest level of possible context. Given the small literature specifically published on treatment resistant depression, it is highly relevant to the outcomes of the BRIGhTMIND trial (see section 5.1.1 of the BRIGhTMIND study protocol “Hypothesis for the mechanistic component”) to better understand and evidence how these themes effect the proposed mechanisms of TMS-stimulation.

Model building
In aiming towards building a brain signature of treatment resistant depression, the proposed analyses are aimed at determining relationships between baseline factors and treatment resistance and will be thus utilised together in order to produce and refine a signature of treatment resistant depression.

Conclusion

This trial gives a unique opportunity to study the most thoroughly phenotyped cohort of TRD subjects to be found. The proposed analysis of baseline data seeks to complement the ongoing study and presents no risk to the ongoing trial. The proposed exploratory analyses would both boost the inference and impact of the main study outcomes, whilst also providing supporting data for subsequent funding applications. Another benefit would be the improvement of biomarkers/brain

signatures arising from this body of work, as biomarkers are increasingly based on multivariable models, a broader understanding of the neural mechanisms underlying TRD will then feed into, and refine, any biomarkers that are produced. Most novel of all, is that the study has been paused (due to covid-19) almost exactly halfway and thus, all analyses and models worked up at this point can be viewed as an inductive exercise with the advantage of knowing that a standardised set of data is yet to come that can be used deductively to assess the reliability of any early findings and also to test any newly generated hypotheses that may come out of this initial analysis.