Study Title:

Effectiveness and Tolerability of Repetitive Transcranial Magnetic Stimulation for Preventive Treatment of Episodic Migraine: A Single Centre, Randomised, Double-Blind, Sham-Controlled Phase 2 Trial (Magnet-EM)

Development phase: 2nd

Date of protocol: 01st October 2019

1 SYNOPSIS

Title of study:

Effectiveness and Tolerability of Repetitive Transcranial Magnetic Stimulation for Preventive Treatment of Episodic Migraine: A Single Centre, Randomised, Double-Blind, Sham-Controlled Phase 2 Trial

Brief Title: Transcranial Magnetic Stimulation in Episodic Migraine (Magnet-EM)

Sponsor: Research Management Centre (RMC) Universiti Putra Malaysia

Clinical Phase: 2

Investigators:

Investigators will be medical practitioner practicing in internal medicine and neurology.

Main Principal Investigator	Institutions
A/P Dr Wan Aliaa Wan Sulaiman	Universiti Putra Malaysia
Name of Co-Investigators	Institutions
Dr. Liyana Najwa binti Inche Mat	Universiti Putra Malaysia
Prof. Dr. Hamidon Basri	Universiti Putra Malaysia
A/P Dr. Hoo Fan Kee	Universiti Putra Malaysia
Musmarlina Omar	Universiti Putra Malaysia
Nur Ain binti Amir	Universiti Putra Malaysia
Nabil Izzaatie binti Mohamad Safiai	Universiti Putra Malaysia

Study period: 3 years
Planned date of first subject enrolment: 1st December 2018
Planned date of last subject completed: 1st December 2020

Objectives:

- Primary objective:

To evaluate the efficacy an of r-TMS in the adjunctive treatment of episodic migraine subjects

- Secondary objectives:

1. To evaluate the safety of r-TMS in the treatment of migraine.
2. To identify the factors that predicts good responses to TMS treatment.
3. To determine the biochemical migraine biomarkers associated with pre and post r-TMS treatment.
4. To determine the clinical neurophysiological parameters among patients with migraine pre and post r-TMS treatment.
5. To examine the neuropsychological findings among patients with migraine pre and post r-TMS treatment.
6. To determine the health-related quality of life (HRQOL) among patients with migraine pre and post r-TMS treatment.
7. To determine the lifestyle factors associated with migraine patients.
8. To identify genetic polymorphism between migraine patients.
8. To evaluate the patient satisfaction measures to TMS treatment.

Hypothesis:
Repetitive Transcranial Magnetic Stimulation as new preventive treatment of episodic migraine.

Methodology:

This is a single-centre, randomised, double blind, placebo controlled, parallel group design clinical trial.

Number of patients:

The sample size was calculated based on the expected differences in the primary outcome variable, headache days. “Hypothesis testing of two population means” formula was used. With 80% power, 5% level of significance, 30% of attrition calculated sample rate, the sample size for the study was 29 in each arm. Accounting for a drop-out rate of 30%, the sample size will be increased to 38 in each arm. The total sample size will be 76.

Number of centres: 1

Inclusion criteria:

1. Males or females aged 18 to 60 years of age.
2. Subjects fulfilling criteria for episodic migraine as per the Third Edition of The International Headache Society (ICHD-3) for at least 1 year.
3. Frequency of migraine attacks 2-8 times per month with less than 15 headache days per month for at least 3 months prior to screening.
4. Demonstrated compliance with the headache diary during the run-in period by entry of headache data on a minimum of 24/30 days (80% compliance).
5. A signed and dated informed consent document indicating that the subject has been informed of all pertinent aspects of the study including any known and potential risks and available alternative treatments.

Exclusion criteria:

1. Patients with previous history of rTMS treatment.
2. Onset of headache more than 50 years
3. Headache with red flags symptoms that may suggest organic secondary headaches.
4. Pregnant or lactating women.
5. Patients with contraindications to TMS such as metallic implant and pacemaker based on the Screening 13-item Questionnaire for rTMS candidate.
6. Patients with medical conditions such as severe hypertension, infections, malignancy, cardiovascular and cerebrovascular diseases, epilepsy degenerative central nervous system diseases, renal failure, hepatic failure, bleeding diathesis and ***serious mental illnesses.***

Test treatment, dose and mode of administration: TMS devices treatment, high frequency 20 Hz repetitive stimulation, non-invasive, external application on the scalp

Duration of treatment with study medication: 2 weeks

Criteria for evaluation:

Primary Outcome Measure

1. Change from baseline in mean monthly migraine days. The mean monthly migraine days will be calculated using the monthly migraine days from each of the month of the double-blind treatment phase. [Time frame: 4 months after the first session of r-TMS]

Secondary Outcomes Measure

1. Change from baseline in mean monthly migraine attacks. The mean monthly migraine attacks will be calculated using the monthly migraine attack from each of the month of the double-blind treatment phase. [Time frame: 4 months after the first session of r-TMS]
2. Proportion of subjects with at least a 50% reduction from baseline in mean monthly migraine days. [Time Frame: 4 months after first session of r-TMS]. Change from baseline in mean monthly pain intensity of migraine attacks. The mean monthly pain intensity will be based on the record of the maximal pain intensity by means of a verbal scale (i.e. 0 =no headache; 1 = mild headache; 2 = moderate headache; 3 = severe headache) prior to taking symptomatic medication. [Time Frame: 4 months after first session of r-TMS]
3. Frequency and severity of adverse events in response to r-TMS. [Time Frame: 4 months after first session of r-TMS]
4. The DASS 21 score changes in migraine patients in response to r-TMS. [Time

Frame: 4 months after first session of r-TMS]. Mean score changes from baseline for depression, anxiety and stress category.

5. The MIDAS score changes in migraine patients in response to r-TMS. [Time Frame: 4 months after first session of r-TMS]. Mean score changes from baseline.
6. The MSQ score changes in migraine patients in response to r-TMS. [Time Frame: 4 months after first session of r-TMS]. Mean score changes from baseline.
7. The EQ-5D score changes in migraine patients in response to r-TMS. [Time Frame: 4 months after the first session of r-TMS. Mean score changes from baseline.
8. The ABNAS score changes in migraine in response to r-TMS. [Time Frame: 4 months after first session of r-TMS]. Mean score changes from baseline.
9. The PSQI score changes in migraine in response to r-TMS. [Time Frame: 4 months after first session of r-TMS]. Mean scores change from baseline.
10. The FFQ score changes in migraine in response to r-TMS. [Time Frame: 4 months after first session of r-TMS]. Mean score changes from baseline
11. The IPAQ score change in migraine in response to r-TMS. [Time Frame: 4 months after first session of r-TMS]. Mean score changes from baseline
12. Transcranial Doppler (TCD) pattern changes in migraine patients in response to r-TMS. [Time Frame: Baseline and after treatment sessions (month 4).] Mean flow velocity (cm/s).
13. Electroencephalography (EEG) pattern change in migraine patients in response to r-TMS. [Time Frame: Baseline and after treatment sessions (month 4).] EEG pattern differences based on report.
14. Serum serotonin level and DNA changes in migraine patients in response to r-TMS. [Time Frame: Baseline and after treatment sessions (month 4)] Serum serotonin (ng/ml).
15. Serum beta-endorphin level changes in migraine patients in response to r-TMS [Time Frame: Baseline and after treatment sessions (month 4)]. Serum beta-endorphin (ng/ml).
16. C-Reactive Protein (CRP) level changes in migraine patients in response to r-TMS [Time Frame: Baseline and after treatment sessions (month 4)] Serum CRP mg/dL
17. Serum Calcitonin gene related peptide (CGRP) level and DNA changes in migraine patients in response to r-TMS. [Time Frame: Baseline and after treatment sessions (month 4)] Serum CGRP pg/mL
18. Satisfaction measures of efficacy, tolerability, safety and expectations of r-TMS among the participants. A 5-point, Likert scale will be used to evaluate satisfaction with r-TMS in migraine prevention. [Time Frame: 4 months after first session of r-TMS]

Statistical methods:

Characteristics of the patients in each of the groups will be compared with parametric tests for normally distributed data using Paired T-test for univariate and ANCOVA within GEE for multivariate and with nonparametric tests if otherwise using Fried-Mann test for univariate and Kruskall-wallis for multivariate. For all outcome measures, treatment effects will be calculated for each subject by the differences between the baseline values before and after r-TMS stimulation using analysis of covariance (ANCOVA) test. Compliance with treatment in each group will between compared with Mann-Whitney tests. Frequencies of adverse events were compared with Fisher's exact tests. All other endpoints will be evaluated using generalized estimating equations (GEE) models. GEE will be used to analyse correlated data, particularly when analysis of variance assumptions is not met. Two-tailed p values <0.05 were considered statistically significant. Post-hoc analysis will be performed with Bonferroni corrections.

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3 LIST OF ABBREVIATIONS

5-HT	5-Hydroxytryptamine
ACE	Angiotensin I-Converting Enzyme (ACE)
AE	Adverse Event
BLAST	Basic Local Alignment Search Tool
BMI	Body Mass Index
BLS	Basic Life Support
CGRP	Calcitonin
CRF	Case Report Form
CV	Curriculum Vitae
DNA	Deoxyribonuclease
EDTA	Ethylenediaminetetraaacetic Acid
EEG	Electroencephalography
EQ-5D	Euroqol 5 Dimension Questionnaire
FFQ	Food Frequency Questionnaire
GCP	Good Clinical Practice
GEE	Generalized Estimating Equations.
HRQOL	Health-Related Quality of Life
ID	Identification
IPAQ	International Physical Activity Questionnaire
MA	Migraine with Aura
MeSH	Medical Subject Headings
MIDAS	Migraine Disability Assessment
mmHg	Millimetre Mercury
MO	Migraine Without Aura
MSQ v2.1	Migraine Specific Quality of Life Questionnaire Version 2.1
PSQI	Pittsburgh Sleep Quality Index
r-TMS	Repetitive Transcranial Magnetic Stimulation
SAE	Serious Adverse Event
SMI	Structure Migraine Interview
TCD	Transcranial Doppler
TMS	Transcranial Magnetic Stimulation
TNF	Tumour Necrosis Factor
VNTR	Variable Number Tandem Repeats

4 GLOSSARIES OF TERMS

(Comprehensive list of commonly used terms is found in Malaysian Guidelines for GCP)

Eligible	Qualified for enrolment into the study based on strict adherence to inclusion and exclusion criteria.
Evaluable	Meeting all eligibility criteria, complying with the procedures defined in the protocol and therefore included in analysis.
Investigator	Treating physician
Monitor	An individual assigned by JKEUPM who is responsible for assuring proper conduct of a clinical study.
Protocol amendment	Any change in a study protocol which affects the safety of subjects, the scope, design, assessments or scientific validity of the clinical investigation.
Subject(s)	Individuals enrolled in the clinical study.

5 ETHICS & REGULATORY CONSIDERATIONS

5.1 Ethical conduct of the study

The study will be conducted in compliance with the protocol and JKEUPM standard operating procedures. These are designed to ensure adherence to the ethical principles that have their origin in the "World Medical Association Declaration of Helsinki", "Malaysian Guidelines for Good Clinical Practice" and applicable regulatory Requirements. Applicable government regulations and Universiti Putra Malaysia research policies and procedures will also be followed.

This protocol and any amendments will be submitted to the JKEUPM for formal approval to conduct the study. The decision of the JKEUPM concerning the conduct of the study will be made in writing to the investigator. All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the JKEUPM. The formal consent of a subject, using the JKEUPM -approved consent form, will be obtained before that subject is submitted to any study procedure. This consent form must be signed by the subject or legally acceptable surrogate, and the investigator-designated research professional obtaining the consent.

5.2 Informed consent and subject information

Informed Consent Process

Informed consent is a process initiated prior to an individual agreeing to participate in a study and continues throughout the individual's participation. Informed consent is required for all patients participating in this study. In obtaining and documenting informed consent, the investigator should comply with applicable regulatory requirements and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. Discussion of objectives, risks and inconveniences of the study and the conditions under which it is to be conducted are to be provided to patients by staff with experience in taking consent and who are familiar with the study. All potential participants will be given a patient information sheet (PIS). Upon reviewing the PIS, the investigator will explain the research study to the patient and answer any questions that may arise. The investigator will inform every subject in detail about the nature of the study, its purpose, the treatments and the probability of random assignment to treatment groups, those aspects of the study that are experimental, the procedures involved and the discomfort they may entail, the possible risks including to an embryo, foetus or nursing infant where applicable, the reasonably expected benefits the expected duration and the approximate number of subjects involved and the subject's responsibilities.

A contact point where further information about the study may be obtained will be provided. The patient should have the opportunity to discuss the study with their surrogates and think about it prior to agreeing to participate. A copy of the informed consent document will be given to the patient and/or consultee for their records. Consent will be obtained for the participants name and address to be provided to the

co-ordinating centre and a copy of the consent form, participant detail form and enrolment form will be kept there. The patient or consultee may withdraw from the study at any time by revoking the informed consent. The rights and welfare of the patients will be protected by emphasising to them that the quality of medical care will not be adversely affected if they decline to participate in this study.

Study subjects will be informed that:

1. Participation in this study is voluntary and that he/she may withdraw from this study at any time for any reason and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.
2. They will be notified in a timely manner if information becomes available that may be relevant to their willingness to continue participation in the study.
3. Alternative procedures or treatments that may be available and the important potential benefits and risks of these available alternative procedures or treatments.
4. Any compensation for additional costs and/or injury caused to a subject attributable to participation in the study.
5. Financial expenses, if any, to the subject for participating in the study as well as prorated payment, if any, to the subject for participating in the study.
6. Any foreseeable circumstances and/or reasons under which the subject's participation in the study may be terminated.
7. The person(s) to contact for further information regarding the study and whom to contact in the event of study related injury.

Written consent will be obtained from each subject involved in the study. If written consent is not possible, oral consent can be obtained if witnessed by a signed statement from one or more persons not involved in the study, stating why the patient was unable to sign the consent form. The informed consent form used to document written or oral consent in the study must be received prior to approval from the IEC. If the subject and his/her parent/guardian are unable to read, the investigator or designee must explain to the subject the content of the Patient Information Sheet and Consent Form point by point in the presence of an impartial witness. The witness should personally sign and date the consent form. The potential study subject and/or his/her parent/guardian should be given the opportunity to ask questions and time for consideration.

A copy of the Patient Information Sheet and signed Consent Form should be given to the subject. The original must be filed by the principal investigator in the Investigator's Study File. A sample of the Patient Information Sheet and Consent Form can be found in the Appendix of this protocol.

5.3 Patient protection procedures

5.3.1 Procedures in the event of emergency

The investigator is responsible for ensuring that procedures and expertise are available to cope with medical emergencies during the study. An emergency may constitute an SAE. A medical emergency is an acute, unplanned event that has the potential for serious harm or death. This includes anaphylaxis and cardiorespiratory arrest.

Responsibilities

1. Clinical staff, including nurses, doctors and research technicians, are responsible for the identification of medical emergencies, mobilising the resuscitation team and providing initial treatment to address the emergency.
2. Research nurses and technicians are responsible for ensuring that emergency equipment is available and is in good working order.
3. Non-clinical staff are responsible for assisting in the management of emergencies, mobilising the resuscitation team when asked to do so and facilitating emergency procedures.
4. Clinical staff are responsible for ensuring that BLS (Basic Life Support) training is up-to-date, as appropriate to their role.
5. The CRF Manager/Lead Research Nurse is responsible for arranging any additional training and for arranging regular emergency simulation training.

Procedures

1. Maintenance of equipment: Resuscitation trolleys (Adult) are located in the medical lab. Trolleys are checked weekly by study staff to ensure that all drugs and equipment are in-date and functional. Contents are checked against the checklist, which is kept on the trolley.
2. Staffing: Whenever there are study participants in the headache research clinic, two members of staff should usually be present to ensure that an emergency can be managed as safely as possible. At least one member of staff should be a member of the study clinical team.
3. Procedure in the event of a life-threatening emergency: In the event of an acute deterioration or collapse of any person in the study, study clinical staff will perform an ABCDE assessment in accordance with the current Resuscitation Council guidelines. A member of staff should collect an arrest trolley. If cardiac or respiratory arrest has occurred, staff should initiate cardiopulmonary resuscitation and defibrillation in line with Resuscitation Council guidance (Figure 2). Staff caring for the patient must call activate emergency alarm. On hearing the emergency alarm all available staff must attend immediately. A member of clinical or non-clinical staff will contact the resuscitation team on 999 stating ‘adult cardiac arrest’ and give the location. A member of staff should go to the nearest entrance to facilitate access for the resuscitation team. Once the resuscitation team arrive, a member of study clinical staff will hand over to the resuscitation team using a structured handover technique, such as Situation, Background, Assessment and Recommendation (SBAR). Study staff should remain on hand to assist the resuscitation attempt. Staff should be aware that

the resuscitation team may be unfamiliar with the layout of the study site. The patient will be send to the nearby emergency department of Hospital Serdang and an emergency physician who is also sub investigator of this study will be alerted.

4. Procedure in the event of a non-life threatening emergency: In the event of mild adverse event such as headache, dizziness, nausea and vomiting, study clinical staff will perform an ABCDE assessment and will direct the person to a treatment room with a bed located at the study site. Symptomatic treatment will be provided to the person. Patient should bring their own medicines prescribed for their acute headaches and the rescue medicine will be administered. Study staff should remain on hand to assist the patient. Patient who has persisting symptoms will be referred to the emergency department in Hospital Serdang. An emergency physician who is also sub investigator of this study will be alert for further assessment.
5. Procedures in the event of seizure: During the event of seizure, patient will be put into left lateral position, immediately be given initial assessment and initial first aid for seizure as well as monitoring in the first five minutes. The onset of seizure should be noted. Intramuscular midazolam will only be given to the patient if the seizure persists more than 2 minutes. The dosage of 5mg midazolam will be given stat, and the maximum dose given will not exceed 10 mg. The time of midazolam taken by the patient and the time of seizure stop should be noted and recorded.
6. A collaboration with Pusat Pengimejan Diagnostik Nuklear (PPDN) was done to handle intramuscular midazolam for usage during emergency. During the emergency situation, one of the research staff will run to PPDN immediately and collect midazolam vials from PPDN staff according to procedures set up by PPDN.

5.3.2 Procedures in the event of pregnancy

The subject must be instructed to inform the investigator if she becomes pregnant during the study and seek advice regarding continuation of the study treatment. The investigator should follow up the pregnancy until the outcome is known.

5.3.3 Patient data protection

1. The investigator must assure that the anonymity of the subjects will be maintained and that the confidentiality of records and documents that could identify subjects will be protected, respecting the privacy and confidentiality rules in accordance with applicable regulatory requirements.

2. Subjects must be identified only by their assigned identification number and initial on all CRFs and other records and documents submitted to JKEUPM and sponsor.

3. The investigator will keep a Patient Identification List with complete identification information (name, address, contact number, IC#) on each subject.

4. Documents not for submission to JKEUPM such as subject's written informed consent form, should be maintained by the investigator in strict confidence. Monitors and auditors from JKEUPM and sponsor, and representatives of IEC or other regulatory agencies will be granted direct access to subject medical records and other study documents for verification of study procedures and data without violating the confidentiality of the subject. The subject should be informed that by signing a written informed consent form, the subject or his/parent or guardian is authorizing such access.

   All electronic data processed at JKEUPM will be identified by patient numbers only, thereby ensuring that patients' identity remains unknown to JKEUPM and the sponsor. In the event that the study is discontinued all samples and data already received will be kept anonymised /pseudonymised and analysed where possible.

5.3.4 Insurance

With respect to any liability directly or indirectly caused by the investigational products in connection with this study, the sponsor assumes liability by law on behalf of the investigator and his/her staff for possible injury to the subject, provided the investigator and his/her staff have followed the instructions of the sponsor in accordance with this protocol and any amendments thereto, that the investigational products administered to the subject in this study have been supplied by the sponsor and that the investigator and his/her staff have in general performed this study in accordance with scientific practice and currently acceptable techniques and know how.

6 INTRODUCTION AND BACKGROUND

Migraine is a common chronic debilitating disease with an estimated global prevalence of 14.7% (Steiner 2013). Medications such as propranolol or topiramate, have an important role in abortive and prevention of attacks but are limited in effectiveness while carrying side effects. Transcranial magnetic stimulation (TMS), is a non-invasive neuromodulation procedure for people with migraine that has been proved to be safe and effective option of a non-pharmacological migraine treatment. TMS is given using a table-top or handheld device that delivers a predetermined level of magnetic pulses to the head. Based on the theory that repetitive TMS alters brain excitability and neurotransmitter activity, several studies that examined TMS as a preventive migraine treatment and some had shown positive results. However, there is still uncertainty of the extend of efficacy of TMS and we are lacking information to identify patient that will benefit from TMS (Lan 2017). Therefore, its role as an effective and safe non-pharmacological treatment for migraine need to be further determined especially among our population.

Besides all the environmental factors, studies also suggest migraine basically caused by genetic factors. First-degree relatives or family suffers from migraine with aura (MA) are prone to inherit the genetic and hold almost four-fold enhancement risk to suffers while for Migraine without aura (MO) have two-fold increased risk (Kowalska et al., 2015). There are many studies associated between genes candidates and their variation with different populations (Guler et al., 2014). The finding of epigenetic changes in migraine will assess the role of environmental risk factors that may reduce or enhance the risk of migraine. B endorphin is suggested by Misra et al, 2013 associated with migraine headache as it is found that level of B endorphin was significantly lower in migraine (4.35 2.29 ng/ml) compared to controls (6.68 2.93 ng/ml). Interestingly, the improvement in migraine after r-TMS was associated with increase in B endorphin level (Misra et al. 2013).
There are many outstanding issues and unanswered questions about r-TMS for migraine prevention treatment, mainly on identifying the responders and non-responders to this treatment.
This current study is planned to produce outcome data needed for evidence-based use of r-TMS in migraine.

6.1 Potential Risks

(i) Potential adverse reactions

Potential adverse reactions to TMS (e.g. seizures, syncope, migraines) TMS is widely considered to be a safe technique, however, has induced brief seizures in a small number (<20) of individuals worldwide. As a result of these reported incidents, guidelines were published specifying safe operating parameters for stimulation with respect to intensity, frequency and duration (Wassermann, 1998). Since 1998, seizures due to TMS have occurred, but mostly in studies operating outside the safe limits previously defined. Incidents of seizures in studies operating within the safe parameters occurred in subjects using pro-epileptogenic medication. Considering the very large number of subjects who have participated in TMS studies since 1998 and the small number of seizures, the risk of TMS inducing seizures is considered to be

very low (Rossi et al., 2009). Because of these potential risks, all researchers carrying out TMS must do so due so according to the parameters for intensity, frequency and duration described in the international guidelines (Wasserman 1998; Rossi et al., 2009). To further ensure that risks are minimised, subjects are also required to fill out a TMS safety screening form before participating to rule out other contraindications to participation. These include: family history of epilepsy, a history of neurological or psychiatric conditions or transient lowering of seizure thresholds e.g. as a result of lack of sleep, high consumption of alcohol, caffeine, or through taking anti-malarial medication. Please refer to the enclosed TMS Safety Screening Questionnaire for a complete list of contraindications (Appendix 5). The guidelines on how often a subject can participate in a TMS study are unclear. Many studies are using TMS to treat disorders (e.g. psychiatric disorders). TMS can cause syncope, or fainting in some participants. This reaction is often caused by situations of anxiety and psycho-physical discomfort and is a more common adverse reaction to TMS than a seizure. Screening prior to stimulation will not reliably rule out any predisposition to fainting, so to avoid inducing syncope it is important to ensure that participants are fully informed and comfortable with the procedure before beginning. Researchers should monitor a subject‘s ongoing reactions to TMS and will avoid stimulating if the subject appears to be uncomfortable. Researchers undergo basic life support training so they are able to ensure the participant‘s safety and comfort in the event of syncope.

(ii) Discomfort

A loud clicking sound is produced each time the stimulator discharges. Since the coil is usually held in close proximity to the ears, subjects are given earplugs during stimulation. TMS causes localised tapping sensations on the scalp at the point of stimulation. Stimulation of motor cortical regions may also cause localised motor discharges, which manifest as muscle twitches. Neither of these effects should be unpleasant but may become uncomfortable when stimulating at high intensities and for long periods. Subjects are encouraged to let the researcher know if TMS is causing undue discomfort. Sometimes, muscles on the head or peripheral facial nerves are stimulated directly causing muscle contractions, jaw movements or eye blinks. Whilst these are not dangerous, and many subjects tolerate them comfortably, some of these reactions have potential to cause discomfort. Again, subjects are encouraged to make the researcher aware if they are at all uncomfortable. Researchers minimise these reactions through monitoring the state of the participant and adjusting coil position and output intensity accordingly. Headaches have been reported as a side effect of participation in brain stimulation studies. This risk can be minimised by ensuring participants are physically comfortable and take regular breaks if necessary. Participants are made aware from the start that a headache is a potential minor risk of TMS and that these usually respond well to over-the-counter analgesics (e.g. paracetamol).

(iii) No device-related serious adverse events were reported in the RCT of 164 patients. The incidence of adverse events was similar between the sTMS group (14%, 14/102) and sham group (9%, 9/99) within 48 hours after treatment. All events (headache, migraine, sinusitis and paraesthesia) were mild or moderate with the exception of severe nausea (n=1 in each group), severe migraine (n=1, sTMS group) and severe headache (n=1, sTMS group) (Lipton 2010). Slight ‘unsustained’ dizziness (n=1) drowsiness (n=1) and tiredness (n=2) were reported in the case series of 42 patients after treatment with low- or high-intensity TMS. None of these events recurred

or needed medical attention (Clarke 2006). Sleepiness (n=1 in each group), uncomfortable or long-lasting sitting (n=1 in each group), headache (n=2 in sham group) and uncomfortable assessment of visual motor threshold (n=5 in r-TMS group; n=4 in sham group) were reported during treatment in the case series of 27 patients. Amyostasia (muscle tremor causing difficulty in standing), irritability (n=1 in each group), 'vigorous dreams' and phonophobia (n=1 each in r-TMS group) were reported after r-TMS treatment in this study (Teepker 2010). Other risk for acute adverse events including neck pain, seizure, scalp burns, hearing impairment, impaired cognition, trouble concentrating and acute mood changes.

(iv) Loss of confidentiality

Other risks include loss of confidentiality. Good Clinical Practice should ensure this does not happen. Physical risks are limited to those of the extra venepuncture including bruising. The extra blood tests will, where possible be done at the same time as routine venepuncture to minimise this risk. The clinical care is directed by the responsible physician. There may be psychological risks as participants recall the impact their illness has had on their quality of life.

6.2 Potential Benefits

An RCT of 11 patients comparing r-TMS (n=6) against sham treatment (n=5) showed a significant reduction in the outcome measures (attack frequency, headache index and medication use) during and 1 month after r-TMS treatment compared with baseline ($p<0.0005$). No significant differences in the outcome measures were observed in the sham group (Brighina 2004).

A case series of 27 patients with migraine comparing low-frequency r-TMS (n=14) against sham stimulation (n=13) for prevention reported no significant differences between groups for all reported outcomes (including number and duration of migraine attacks, mean pain intensity and use of analgesics). The 'within-group' findings from this study showed a significant decrease in the number of migraine attacks during 8 weeks within the r-TMS group from 9.36±2.82 attacks to 6.79±4.28 attacks ($p=0.007$), and a non-significant decrease within the sham group (numbers not reported; $p=0.216$). There was a significant reduction in migraine days during 8 weeks in both r-TMS and sham groups (from 17.69±11.63 days to 13.15±9.27 days [$p=0.012$] and from 14.36±5.07 days to 9.50±6.80 days [$p=0.006$] respectively). The r-TMS group showed a significant reduction in migraine hours during 8 weeks from 125.93±80.31 hours to 85.36±72.27 hours, $p=0.035$; the difference was not significant in the sham group (numbers not reported; $p=0.080$) (Teepker 2010).

Mean pain intensity changed from 6.26±1.33 to 6.11±1.26 ($p=0.455$) in the r-TMS group; and from 5.52±1.72 to 5.17±2.51 ($p=0.839$) in the sham group. Differences between the r-TMS and sham groups were not significant ($p=0.942$). The intake of analgesics changed from 14.21±10.13 pills to 12.50±14.65 pills ($p=0.232$) in the r-TMS group; and from 15.15±11.24 pills to 11.81±9.89 pills ($p=0.094$) in the sham group. Differences between the r-TMS and sham groups were not significant ($p=0.577$) (Teepker 2010).Overall, there will be future benefits in gaining more knowledge on r-TMS treatment as well as important biochemical and genomics work in migraine.

7 OBJECTIVES

7.1 Primary objective:

To evaluate the efficacy an of r-TMS in the adjunctive treatment of episodic migraine subjects

7.2 Secondary objective(s):

1. To evaluate the safety of r-TMS in the treatment of migraine.
2. To identify the factors that predicts good responses to TMS treatment.
3. To determine the biochemical migraine biomarkers associated with pre and post r-TMS treatment.
4. To determine the clinical neurophysiological parameters among patients with migraine pre and post r-TMS treatment.
5. To examine the neuropsychological findings among patients with migraine pre and post r-TMS treatment.
6. To determine the health-related quality of life (HRQOL) among patients with migraine pre and post r-TMS treatment.
7. To determine the lifestyle factors associated with migraine patients.
8. To identify genetic polymorphism between migraine patients.
8. To evaluate the patient satisfaction measures to r-TMS treatment.

8 STUDY DESIGN

8.1 Overall study design

The overall study design is a randomized, sham controlled, double-blind, parallel clinical trial.

8.1.1 Schematic diagram of study design:

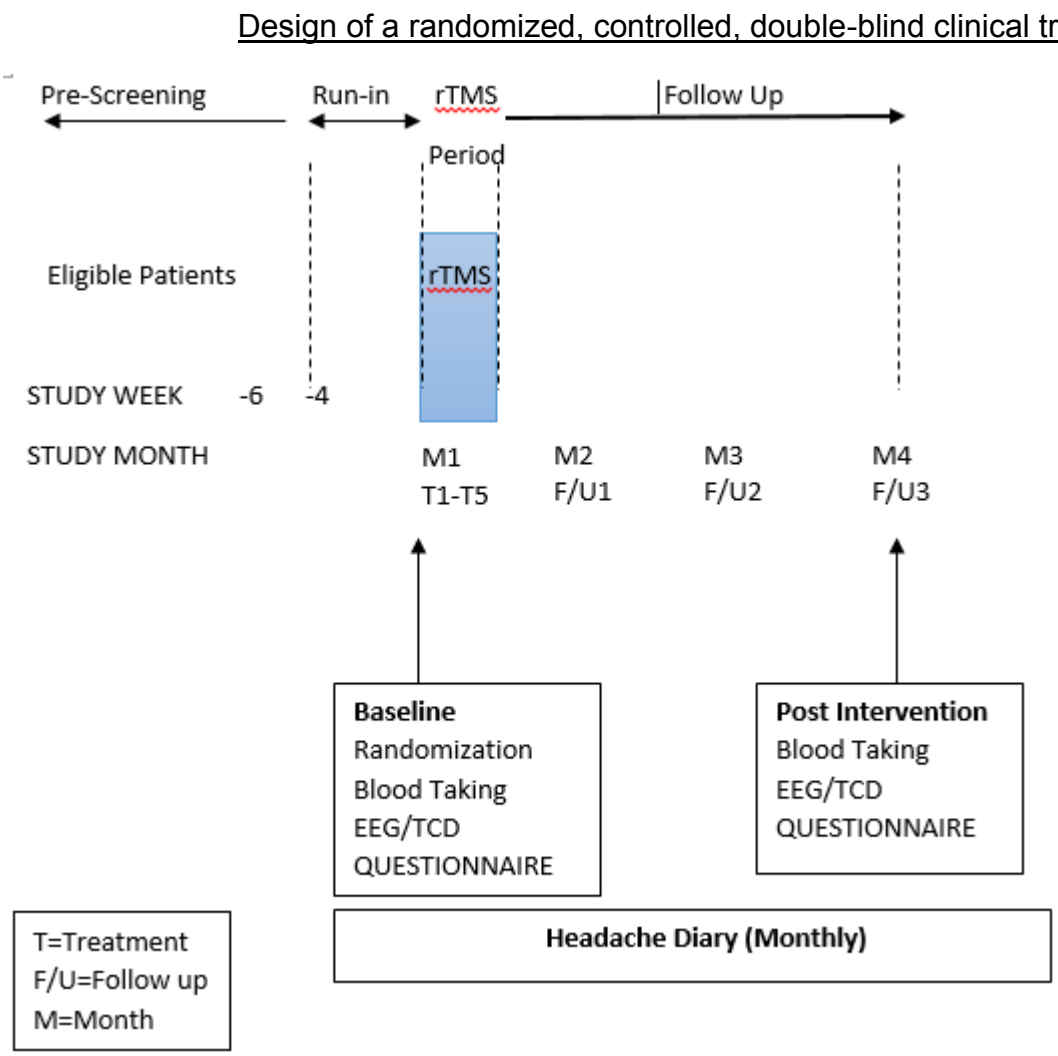
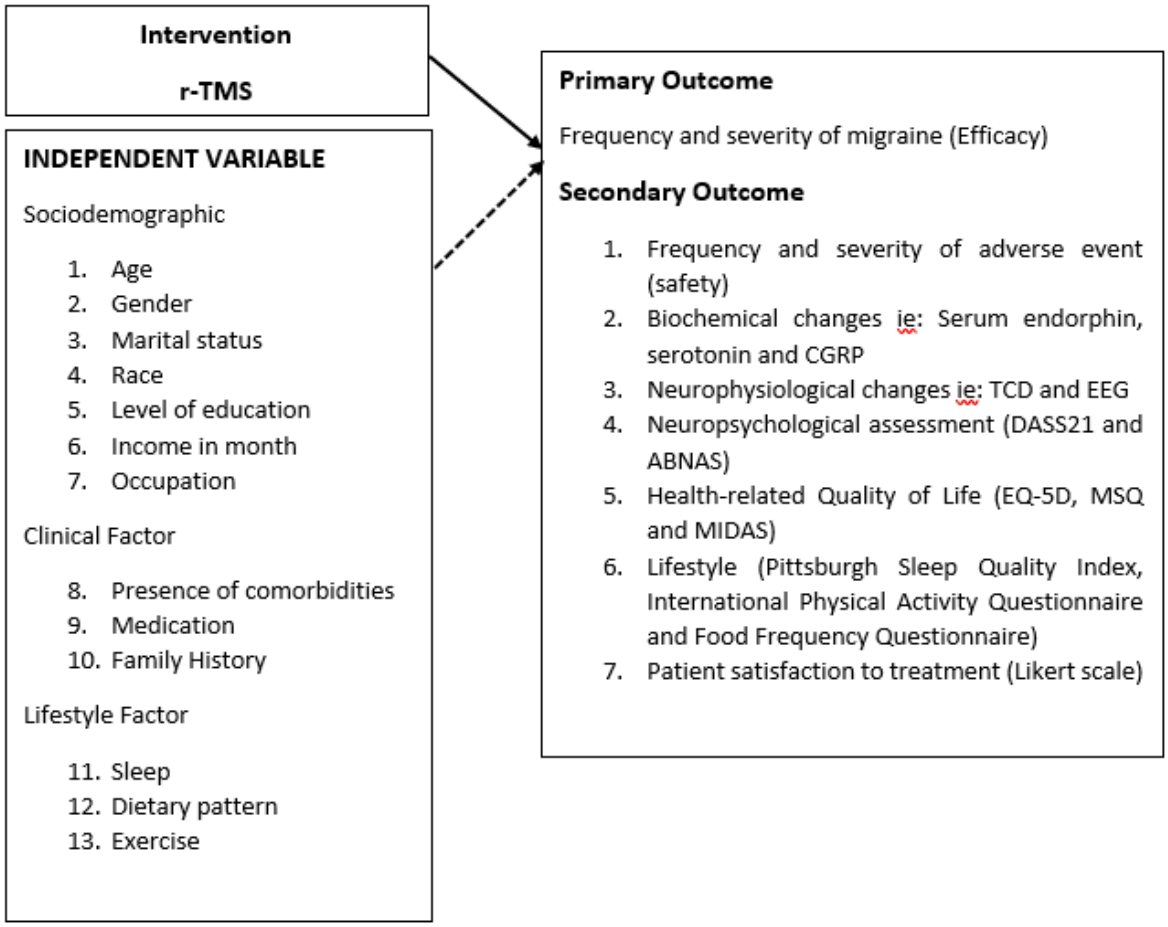


Figure 1: Study design of r-TMS clinical trial

Conceptual Framework (r-TMS in patients with episodic migraine)



8.1.2 Discussion of study design

Single-centre, randomized, sham-controlled double-blind study.

The centre for this study is the clinical neurophysiology medical laboratory which is currently providing TMS treatment for migraine patients mainly from Hospital Serdang. A headache research clinic will be set up in this laboratory to cater the logistic for this clinical study. Investigators involved are UPM medical lecturers. Every PI and sub investigator involved have current GCP status. The RCT design will follow the CONSORT 2010 protocol.

CONSORT 2010 FLOW DIAGRAM

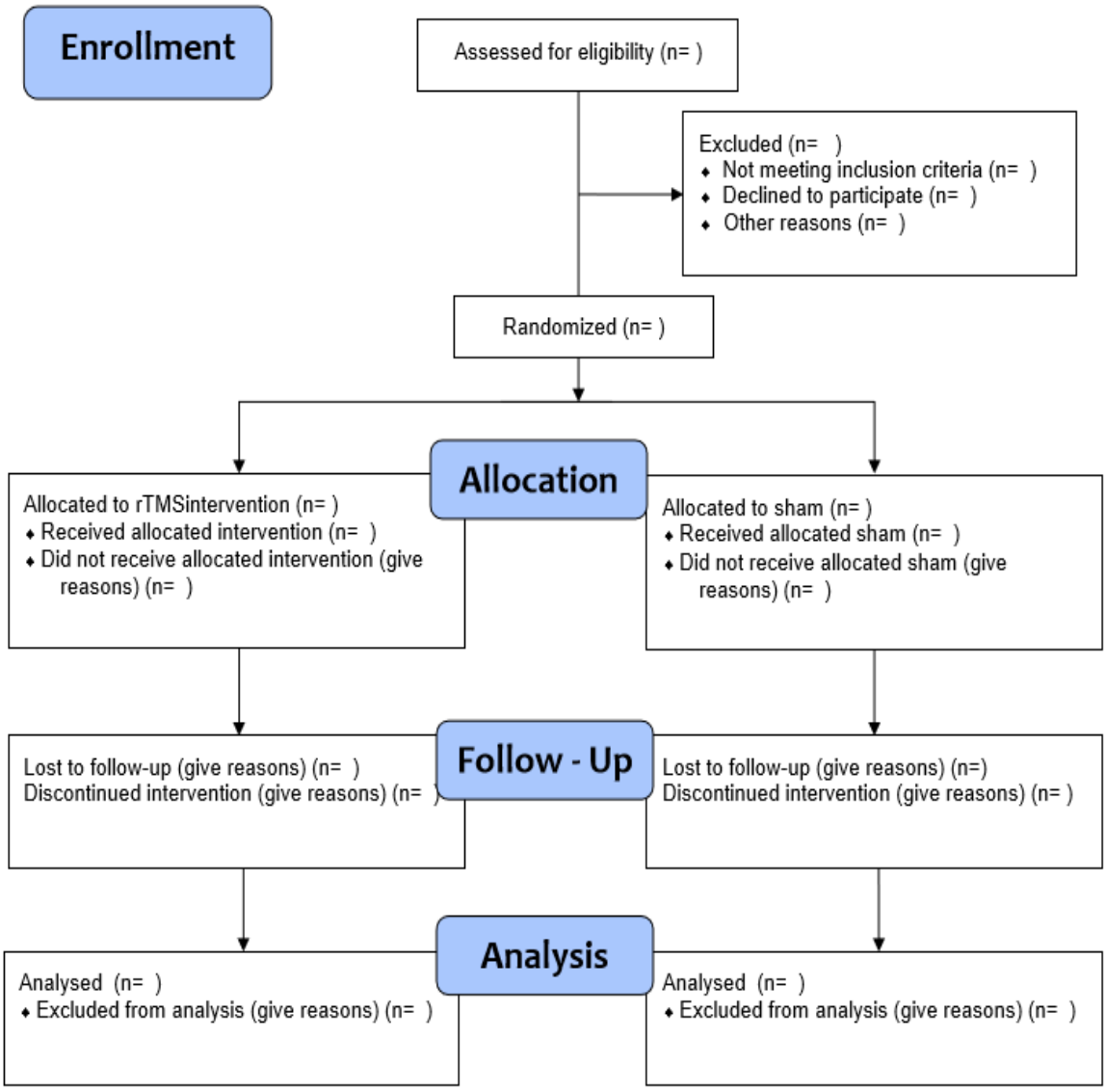


Figure 2: Consort diagram for r-TMS clinical trial

8.1.3 Study population

Patients with migraine in the community as well as staff and students of UPM attending community screening programme.

Patients with migraine attending UPM primary care facilities (PKU) and private general practitioner (GP) clinics are also eligible for enrolment.

In addition, this study will be advertised to the general public via formal and informal media. Interested subjects will be directed to the headache research clinic and will be recruited if they meet trial study criteria for clinical trial participants.

The subjects will undergo pre-screening to identify whether or not they meet the inclusion and exclusion criteria before enrolment to the clinical trial. Consent forms will be prior to the screening result. If the subjects not meet the inclusion criteria, the subjects will be considered screening failures.

8.1.3.1 Inclusion criteria

1. Males or females aged 18 to 60 years of age.
2. Subjects fulfilling criteria for migraine as per the Third Edition of The International Headache Society (ICHD-3) for at least 1 year.
3. Frequency of migraine attacks 2-8 times per month with less than 15 headache days per month for at least 3 months prior to screening.
4. Demonstrated compliance with the headache diary during the run-in period by entry of headache data on a minimum of 24/30 days (80% compliance).
5. A signed and dated informed consent document indicating that the subject has been informed of all pertinent aspects of the study including any known and potential risks and available alternative treatments.

8.1.3.2 Exclusion criteria

1. Patients with previous history of rTMS treatment.
2. Onset of headache more than 50 years
3. Headache with red flags symptoms that may suggest organic secondary headaches.
4. Pregnant or lactating women
5. Patients with contraindications to TMS such as metallic implant and pacemaker based on the Screening 13-item Questionnaire for rTMS candidate.
6. Patients with medical conditions such as severe hypertension, infections, malignancy, cardiovascular and cerebrovascular diseases, epilepsy degenerative central nervous system diseases, renal failure, hepatic failure, bleeding diathesis and ***serious mental illnesses.***

8.1.3.3 Subject withdrawal & drop-out

Subjects are free to withdraw from the study at any time for any reason. In consenting to the study, patients are consented to study follow-up and data collection. If voluntary withdrawal occurs, the patient should be asked to allow continuation of scheduled

evaluations and complete an end-of-study evaluation. Subjects may withdraw from the study or follow up at any time. Data already collected will still be used in the final analysis unless otherwise requested by the participant/consultee. Two written attempts and one phone call will be made to follow up patients before a patient is defined as lost to follow up. Methods to motivate compliance (check-ups, pamphlets, education) and monitor compliance will be used.

Subjects may also be withdrawn from the study at any time at the discretion of the investigator based on these possible reasons:

1. Adverse event(s)
2. Protocol violation (e.g., incorrectly enrolled or randomised)
3. Subject requires use of unacceptable concomitant medication
4. Subject not compliant with protocol procedures
5. Subject develops a condition during the study that violates the inclusion/exclusion criteria
6. Lost to follow-up
7. Death

8.1.3.4 Procedures for handling withdrawal

Patients who withdraw from the study for other reasons have previously consented to follow-up in the study. Data up to this time can be included in the study if anonymised. Subjects who withdraw or are withdrawn from the study should:

1. Have the reason(s) for their withdrawal recorded
2. Be asked about the presence of any AEs and if so should be followed up by regular scheduled visits, telephone contact, correspondence or home visits until satisfactory clinical resolution of AEs is achieved.
3. Be seen by an investigator and all final assessments will be performed and recorded in the Termination page of CRF.
4. Be encouraged to continue coming for regular visits and assessments
5. Have at least one follow-up contact (scheduled visit, telephone contact, correspondence or home visit) for safety evaluation during the 30 days following the last administration of study treatment
6. In the event of pregnancy, the subject should be monitored until conclusion of the pregnancy and the outcome of pregnancy reported.

8.1.3.5 Dealing with drop-outs:

Dealing with dropouts will be considered from the start during the calculation of sample size in addition to dealing with missing values using GEE.

8.1.4 Enrolment

Screening criteria

a) Males or females 18 to 60 years of age suspected of migraine
Patients will be screened from community screening programme when they have suspected migraine (see definitions). They will be allocated a screening number. They can be considered for inclusion in the study by the research study teams (on

clinical suspicion of migraine), or by self-diagnosis (based on the SMI criteria). Only episodic migraine with or without aura will be included. Chronic migraine will be excluded from this study.

E.g.
Screening point 1:
A clinician identifies a patient that meets the inclusion criteria and refer patient to the headache research clinic.

Screening point 2:
A patient self-identified as probably having the diagnosis for migraine from the public adverts and self-referred to the headache research clinic.
Enrolment should occur within the first screening visit if they fulfil the requirements.
A screening register or log will be required at the site and reasons for non-inclusion will be listed in the screening log. Screening log will be kept at site.

Screening failures

Patients who fail to meet the inclusion and exclusion criteria are defined as screening failures. The investigator will maintain a Screening Log which includes screen failures. The log will document the subject number, subject initials, demographics and the reason(s) for excluding the patient from the study. This log will be kept in the Investigator's Study File.

8.2 Future Plan Study

This genetic and biochemical study can be further explored by analysing candidate genes related to different metabolism, conducting exome sequencing, DNA methylation study and possible other genome-wide association study (GWAS) associated with loci region and traits.

9 TREATMENT AND STUDY PROCEDURES

9.1 Description of study intervention

At baseline, all participants will have blood tested for CGRP, serotonin, and endorphin. Questionnaires will be administered to assess patient's medical history, lifestyle, neuropsychological assessment and HRQOL. Patients will also undergo the EEG test. Patients then will be given headache diary to prospectively collect baseline information of the headache attacks and days during the 1-month run-in phase.

After baseline (run-in) period, patients will be randomised into the active intervention r-TMS group and sham r-TMS group. For the active intervention, Repetitive TMS (r-TMS) using Magstim Rapid-2 (Whiteland, Walsh, UK) with an air-cooled figure- eight coil of 7 cm diameter will be administered to the scalp of the patients from visit 1 to 8. A total of 5 sessions will be done in every day for three consecutive days per week in the first week and 2 consecutive days in 2nd week. Then patients will be followed up

at month 2, 3 and 4. The r-TMS treatment will be administered by a trained technician under the responsibility of the PI.

TCD and EEG will be done on patient at month 1 and 4. The blood tests will be repeated at month 4 during follow-up phase. The neuropsychological and HRQOL assessment will be repeated at month 4. Patients are required to fill the headache diary monthly for 4 months. Patient satisfaction measures will be assessed at the completion of the study.

9.2 Comparator intervention

The sham stimulation will be given in the same manner using a sham coil. The sham coil is a Magstim Rapid-2 (Whiteland, Walsh, UK), 70mm Double Air Film Sham Coil. Motor threshold measurement was not done in the sham stimulation group. The Magstim Air Film sham coil is identical in all but stimulation output. Patient assigned to sham coil will undergo similar procedures with the r-TMS coil. The sham treatment will be administered by a trained technician under the responsibility of the PI.

9.3 Dosage and administration

The stimulator will be placed antero-posteriorly parallel to midline on the left dorsolateral prefrontal cortex (Brighina et al,2004) corresponding to the hot spot of the right abductor digiti minimi (7 cm lateral and 5 cm anterior to the inter- aural line). For stimulation, 80 % of the motor threshold was used. The motor threshold was determined at the hot spot of the right abductor digiti minimi as the minimum stimulus intensity able to elicit 5 or more motor-evoked potentials of 50 IV out of 10 consecutive stimuli. Each session of r-TMS consisted of 2000 pulses. The impulses will be given in 40 trains, each train duration is 5s consisting of 50 pulses at 20 Hz with intertrain interval of 25s. Adverse events during stimulation and follow-up will be monitored.

9.4 Investigational product supply and handling

9.4.1 Supply, packaging and labelling

Each study coil will be labelled with the following information:

1. Sponsor identification
2. Manufacturer's identification
3. Protocol number
4. Caution statement
5. 'For Clinical Trial Use Only' statement
6. Investigational product identification (name/treatment no.) and batch number
7. Storage conditions

9.4.2 Storage

The investigational product must be stored in accordance with the manufacturers' instructions. Required conditions for storage will be printed on the label.

Investigational product should be kept under adequate security by the investigator and only accessible to authorised study personnel.

9.4.3 Accountability

The investigator or designee must maintain current and accurate record of the receipt, inventory and dispensing, including shipping invoices, of all study supplies. The Investigational Product Accountability Log must include:

1. Date received
2. Delivery order (D.O.#) reference number and amount received and placed in storage
3. Name of study coil
4. Amount currently in storage area
5. Label ID number or batch number/Lot number
6. Name and initial of person responsible for each investigational treatment
7. Amount transferred to another area for storage
8. Non-study disposition (e.g. Lost, wasted, broken)
9. Amount returned to sponsor or JKEUPM
10. Amount destroyed at study site

9.5 Concomitant treatment

No concomitant treatment will be provided. Patient is allowed to take their acute abortive medicine for their acute migraine attacks.

9.6 Treatment allocation and randomization

Patients' randomisation is done by an independent statistician using a random number generating programme www.randomizer.org. into two groups (intervention and sham controlled group) using mixed block randomization technique at the ratio of 1:1 i.e.

group A and group B. The independent statistician will then code the active TMS coil and the sham coil into group A and group B.

The written allocation of assignment for each participant with an identification number (code) was sealed in a brown opaque envelope. This envelope will be opened by the researcher on recruitment of a participant. The key coding to the allocation will be revealed by the independent statistician at the completion of the study. The r-TMS and sham treatment will be administered by a trained technician under the responsibility of the PI. The sham r-TMS are an exact replication of the active r-TMS but with a different serial number. An independent statistician will label the active r-TMS and sham r-TMS as either treatment 'A' or treatment 'B'.

The participants are assigned to either an r-TMS intervention or a sham control arm in a parallel intervention mode. The principle of random allocation is employed to assign the participants to an intervention and a control arm. To achieve an unbiased comparison group and to have a balanced randomization, permuted block randomization with a varying block size is used for the study. The sample size estimated for the study is 76. Hence, there are ten blocks with a block size of four participants each and ten blocks with a block size of two participants each. One-to-one allocation ratio is used.

Random sequence generation is done with the help of a Research Randomizer, an online random number generator (Urbaniak & Plous, 2014). An external member, who is not directly involved in the study, generates the sequence. To have a strict implementation of the generated random sequence, the concealed allocation is achieved using sequentially numbered, opaque and sealed envelopes (SNOSEs). An aluminium foil is kept inside the envelope to prevent from possible chances of deciphering. An external member, who is not directly involved in the study, would prepare the SNOSEs.

The final code is only known to the statistician and the document will be stored in a secure locked safe. The following information will be recorded during the randomization; study ID (assigned during the study initiation), investigator password (assigned during the initiation), subjects screening status, date of informed consent signed by subject, subject's ID no (e.g. Last 4 digits of IC), upon successful randomization, the subjects will be assigned randomization number and treatment. Documents the subject's ID no. and randomization no. on the Patient Enrolment Log and Patient Identification List.

9.7 Blinding & emergency unblinding procedures

The participants and outcome assessor of the study is blinded about the allocation status of the participants. In the event that an AE or pregnancy occurs for which knowledge of the identity of the test drug is necessary to manage the subject's condition, the sealed emergency code key for that subject may be broken and the test drug identified by the medical monitor. The medical monitor will have a set of sealed emergency code keys (one for each subject) kept in a secured location and he/she will be accessible at all times by telephone. Should emergency unblinding be required, the investigator will call the medical monitor who will break the emergency code key for that subject, identify the test coil and inform the investigator. A detailed report with the date and reason for identifying the study drug will be prepared by the medical monitor and attached to the CRF. This report must be signed by the medical monitor

and the investigator. All unused sealed code keys will be accounted for at the end of the study.

Except in the case of emergency, the treatment blind will be maintained until all subjects have completed the treatment and the database has been cleaned and locked. Any broken code will be clearly justified and explained by a comment on the case report form, along with the date on which the code was broken.

9.8 Baseline assessment and laboratory tests

1. Social demographics
2. Medical history and clinical examination
3. Laboratory blood test (CGRP, Serotonin, CRP, B-Endorphins, Gene studies)
4. Headache diary
5. Lifestyle questionnaire (PSQI, IPAQ, FFQ)
6. Neuropsychological assessment (ABNAS, DASS-21,)
7. HRQOL assessment (MIDAS, MSQ, EQ-5D)
8. Clinical neurophysiology assessment (EEG, TCD)

9.9 Primary Outcome Measure (Assessment of efficacy)

1. Change from baseline in mean monthly migraine days. The mean monthly migraine days will be calculated using the monthly migraine days from each month of the double-blind treatment phase. [Time frame: 4 months after the first session of r-TMS].

9.10 Secondary Outcomes Measure

1. Change from baseline in mean monthly migraine attacks. The mean monthly migraine attacks will be calculated using the monthly migraine attack from each of the month of the double-blind treatment phase. [Time frame: 4 months after the first session of r-TMS]
2. Proportion of subjects with at least a 50% reduction from baseline in mean monthly migraine days. [Time Frame: 4 months after first session of r-TMS]. Change from baseline in mean monthly pain intensity of migraine attacks. The mean monthly pain intensity will be based on the record of the maximal pain intensity by means of a verbal scale (i.e. 0 =no headache; 1 = mild headache; 2 = moderate headache; 3 = severe headache) prior to taking symptomatic medication. [Time Frame: 4 months after first session of r-TMS]
3. Frequency and severity of adverse events in response to r-TMS. [Time Frame: 4 months after first session of r-TMS]
4. The DASS 21 score changes in migraine patients in response to r-TMS. [Time Frame: 4 months after first session of r-TMS]. Mean score changes from baseline for depression, anxiety and stress category.
5. The MIDAS score changes in migraine patients in response to r-TMS. [Time Frame: 4 months after first session of r-TMS]. Mean score changes from baseline.

6. The MSQ score changes in migraine patients in response to r-TMS. [Time Frame: 4 months after first session of r-TMS]. Mean score changes from baseline.
7. The EQ-5D score changes in migraine patients in response to r-TMS. [Time Frame: 4 months after the first session of r-TMS. Mean score changes from baseline.
8. The ABNAS score changes in migraine in response to r-TMS. [Time Frame: 4 months after first session of r-TMS]. Mean score changes from baseline.
9. The PSQI score changes in migraine in response to r-TMS. [Time Frame: 4 months after first session of r-TMS]. Mean scores change from baseline.
10. The FFQ score changes in migraine in response to r-TMS. [Time Frame: 4 months after first session of r-TMS]. Mean score changes from baseline
11. The IPAQ score change in migraine in response to r-TMS. [Time Frame: 4 months after first session of r-TMS]. Mean score changes from baseline
12. Transcranial Doppler (TCD) pattern changes in migraine patients in response to r-TMS. [Time Frame: Baseline and after treatment sessions (month 4).] Mean flow velocity (cm/s).
13. Electroencephalography (EEG) pattern change in migraine patients in response to r-TMS. [Time Frame: Baseline and after treatment sessions (month 4).] EEG pattern differences based on report.
14. Serum serotonin level and DNA changes in migraine patients in response to r-TMS. [Time Frame: Baseline and after treatment sessions (month 4)] Serum serotonin (ng/ml).
15. Serum beta-endorphin level changes in migraine patients in response to r-TMS [Time Frame: Baseline and after treatment sessions (month 4)]. Serum beta-endorphin (ng/ml).
16. C-Reactive Protein (CRP) level changes in migraine patients in response to r-TMS [Time Frame: Baseline and after treatment sessions (month 4)] Serum CRP mg/dL
17. Serum Calcitonin gene related peptide (CGRP) level and DNA changes in migraine patients in response to r-TMS. [Time Frame: Baseline and after treatment sessions (month 4)] Serum CGRP pg/mL
18. Satisfaction measures of efficacy, tolerability, safety and expectations of r-TMS among the participants. A 5-point, Likert scale will be used to evaluate satisfaction with r-TMS in migraine prevention. [Time Frame: 4 months after first session of r-TMS]

10 ADVERSE EVENTS

10.1 Reporting SAE

Information about all SAE will be recorded on the Serious Adverse Event Page of the CRF. All events documented in the SAE Form must be reported within 24 hours to the (JKEUPM)/sponsor by fax (see below for contact person and fax no.). The investigator should not wait to receive additional information to fully document the SAE before notifying (JKEUPM). A fax SAE form detailing relevant aspects of the SAE in question should follow telephone report of SAE. The investigator should also comply with the applicable regulatory requirements related to the reporting of unexpected serious drug reactions to the regulatory authorities. Where applicable, information from relevant medical records and autopsy reports should be obtained.

Any death or congenital abnormality, if brought to the attention of the investigator within 6 months after cessation of study treatment, whether considered treatment related or not, should be reported to (JKEUPM).

Study contact for reporting SAE:

Name: Prof Madya Dr Wan Aliaa Wan Sulaiman
Department: Medicine, Faculty of Medicine and Health Science, UPM
Tel: 03-8946 6000
Fax: 03-8609 2980
E-mail: wanaliaa@upm.edu.my
Mobile phone: +60134888405

24-hour contact information for patients and their attending medical practitioners will be provided prior to study initiation.

11 STUDY CONDUCT

11.1 Study visits and procedures

Any deviation from the study procedures described below will be noted in the CRFs and the sponsor and (JKEUPM) will be notified.

11.1.1 Screening visit

1. A pre-screening information sheet will be given to all potential subjects.
2. A written informed consent for pre-screening will be obtained from subject.
3. The following screening tests are one: pre-screening questionnaires to assess subject for eligibility to enter study according to the inclusion and exclusion criteria. In addition, a headache diary will be given to the patients to be completed during the run-in period.
4. Women of child-bearing potential must declare that they are not pregnant and should be on reliable contraception methods.
5. For subjects enrolled into the study, another informed consent will be obtained and relevant section/page of CRF will be completed.

6. Record all screened subjects in the Screening Log regardless of whether or not the subject has been enrolled in the study.

If a patient is keen to participate, a pre-screening information sheet will be given and informed consent form will be obtained to assess eligibility. Once eligible, the subject will be given a patient information sheet (PIS). Informed consent will be taken after the patient has had time to read the PIS and ask any questions. Written consent will be taken by a member of the research team.

The participant contact detail form, consent form and enrolment form will be filled in at site. The patient's screening number will be used on all these forms. Once the enrolment form is received, a subject ID number will be allocated. Once the subject ID has been allocated the CRF can be completed.

The clinical care of the patient will be under the direction of the responsible clinician and involvement in the study will not alter that.

Two written attempts and one phone call will be made to follow up patients before a patient is defined as lost to follow up.

11.1.1.1 Definitions

Migraine without aura diagnostic criteria:

A. At least five attacks fulfilling criteria B-D
B. Headache attacks lasting 4-72 hr (untreated or unsuccessfully treated)
C. Headache has at least two of the following four characteristics:
    1. unilateral location
    2. pulsating quality
    3. moderate or severe pain intensity
    4. aggravation by or causing avoidance of routine physical activity (e.g., walking or climbing stairs)
D. During headache at least one of the following:
    1. nausea and/or vomiting
    2. photophobia and phonophobia
E. Not better accounted for by another ICHD-3 diagnosis.

Migraine with aura diagnostic criteria:

A. At least two attacks fulfilling criteria B and C

B. One or more of the following fully reversible aura symptoms:

1. visual
2. sensory
3. speech and/or language
4. motor
5. brainstem
6. retinal

C. At least three of the following six characteristics:

1. at least one aura symptom spreads gradually over ≥5 minutes
2. two or more aura symptoms occur in succession
3. each individual aura symptom lasts 5-60 minutes
4. at least one aura symptom is unilateral
5. at least one aura symptom is positive
6. the aura is accompanied, or followed within 60 minutes, by headache

D. Not better accounted for by another ICHD-3 diagnosis.

11.1.2 Baseline visit

At baseline, all participants will have blood tested for CGRP, serotonin, endorphin, CRP. Questionnaires will be administered to assess patient's medical history, lifestyle, neuropsychological assessment and HRQOL. Patients will also undergo EEG test. Patients then will be given headache diary to prospectively collect baseline information of the headache attacks and days during the 1-month run-in phase.

After baseline (run-in) period, patients will be randomised into the active intervention r-TMS group and sham r-TMS group. For the active intervention, Repetitive TMS (r-TMS) using Magstim Rapid-2 (Whiteland, Walsh, UK) with an air-cooled figure- eight coil of 7 cm diameter will be administered to the scalp of the patients. A total of 5 sessions will be done in every day for 3 consecutive days in 1st week and 2 consecutive days in 2nd week. Then will be continued for follow-up at month 2, 3 and 4.

TCD and EEG will be done on patient at baseline and repeated at ***visit 10***. The blood tests will be repeated at ***visit 10***, after 4 months of the intervention. The neuropsychological and HRQOL assessment will be repeated at ***visit 10***. Patients are required to fill the headache diary monthly for 5 months, from run-in period until completion of the study. Patient satisfaction to treatment will be assessed at the end of the study.

The following data will be collected at baseline:

1. Subject's demography: date of birth/age, gender, race, marital status, level of education and occupation.

2. Background and medical history which includes the cause and trigger points of migraine, any diagnosed medical conditions within the previous 12 months, history of medication and medical procedures within the previous 30 days of entry into the study.

3. Physical examination:
    a. Complete physical examination, performed by a licensed physician, will include examination of general appearance, skin, and neurological examination.
    b. Body weight (kg) and height (cm), no shoes in light clothing
    c. Body mass index (BMI)
    d. Waist circumference (cm)
    e. Neck circumference (cm)

4. Vital signs
    a. The following vital signs assessments will be performed:
       Blood pressure and pulse rate.

5. Questionnaires assessment

The following self-administered questionnaires will be done:

a. Monthly headache diary whereby the migraine attacks and days need to be recorded in the baseline rune in period.
b. Lifestyle questionnaire will be adapted from a previously validated questionnaire on migraine patients (Nazari et. al. 2010) which consisted of 9 questions about current disease history and 59 questions about lifestyle factors including diet and eating habits, physical activities and exercise, rest and sleep, medication, smoking and stress which was rated using the Holmes and Rahe Stress Scale. The measurement scale used in the section on lifestyle for most of the questions was designed based on a Likert scale (always, sometimes, never). The scoring method varied according to the type of questions (dichotomous positive/negative questions) so that in positive questions, “always” or “yes” had the highest score while in negative questions “never” or “no” were the lowest. In the end, total scores were divided into 3 groups: not good, average, and good.
c. ABNAS- Neuropsychological function will be assessed with the ABNAS (Aldenkamp and Baker Neuropsychological Assessment Schedule). This is a patient completed assessment of cognitive impairment and function based on everyday activities, that takes approximately 5 minutes to complete (26). This has been used in epilepsy, meningitis and a range of other conditions with neuropsychological impairment, and has normative data available, but has not been used previously in migraine.
d. DASS-21- The DASS-21 is a set of three self-report scales designed to measure the negative emotional states of depression, anxiety, and stress. The 21-item instrument asks respondents to rate the relevancy of each of the three negative affective states over the past week on a four-point scale ranging from: (0) not at all, (1) some of the time, (2) a good part of the time, and (3) most of the time. Scores range from 0 to 21 in each of the three domains, and are then multiplied by two to produce a possible score of 0 to 42 in each of the three domains. Validated cut-offs were used to categorize DASS scores: minimal (score 0–9), mild (score 10–13), moderate (score 14–20), and severe (score ≥21) depressive symptoms on the DASS Depression subscale. The corresponding cut-offs for the DASS Anxiety subscale were minimal (score 0–7), mild (score 8–9), moderate (score 10–14), and severe (score ≥15). The corresponding cut-offs for the DASS Stress subscale

were minimal (score 0–14), mild (score 15–18), moderate (score 19–25), and severe (score ≥26).

e. MIDAS- Disability induced by migraine can be measured with MIDAS questionnaires developed and validated in headache/ migraine patients with good psychometric properties.
f. MSQ v.21- Among the migraine specific questionnaires, the most used were Migraine-Specific Quality-of-Life Questionnaire (MSQ). This disease-specific questionnaires are specifically designed to assess HRQOL associated with a single disease or treatment, and are more likely to be sensitive to changes after specific treatment interventions.
g. EQ-5D- The EQ-5D will be used for expressing the health outcomes as cost per Quality Adjusted Life Years (QALY). Patients and carers will be asked to answer a socio-economic questionnaire to assess the costs incurred by them (non-medical direct costs, indirect costs, and accompany person costs).
h. FFQ- Food Frequency Questionnaire will be used to measure dietary intake among the participants. Patients will be asked to complete a validated food frequency questionnaire to determine dietary pattern. There are 13 food type included in the questionnaire.
i. PSQI- Pittsburgh Sleep Quality Index will be used to measure quality of sleep among migraine patient
j. Patient satisfaction measures of efficacy, tolerability, safety and expectations of r-TMS among the participants. A 5-point, Likert scale (1= very dissatisfied, 2 = somewhat dissatisfied; 3 = neither satisfied nor dissatisfied, 4 = somewhat satisfied, 5 =very satisfied) will be used to evaluate satisfaction with r-TMS in migraine prevention.

6. Laboratory evaluations
    i. The following laboratory evaluations will be done:
        1. Biochemical analysis
        2. Clinical neurophysiology test
    ii. Biochemical analysis will be done by the respective laboratory services such as PATHLAB for biochemical parameters. While genetic analysis will be done in Nutrition Lab and Molecular Lab, Faculty of Medicine and Health Sciences, UPM
    iii. Refer to Section 11.3 for instructions regarding collection and transport of samples.
    iv. Clinical neurophysiology test will be done by the member of the research team at the study site. The EEG and TCD machines are available at the study site which is the neurology lab of UPM.

7. Complete relevant section/page of the CRF.

11.1.3 Randomisation

1. Complete the Randomization Sheet

100 subjects randomized into blocks of

4 6 6 6 6 6 4 4 4 4 4 4 6 6 6 4 4 6 6 4
www.randomization.com To reproduce this plan, use the seed 8180 along with the number of subjects per block/number of blocks and (case-sensitive) treatment labels as entered originally. Randomization plan created on 24/07/2018, 07:17:38

2. Description for randomization process

Patients' randomisation is by an independent statistician using a random number generating programme www.randomizer.org. into two groups (intervention and sham controlled group) using block randomization technique at the ratio of 1:1 i.e. group A and group B. The independent statistician will then code the active TMS coil and the sham coil into group A and group B. The sequence was concealed until interventions were assigned.

The written allocation of assignment for each participant with an identification number (code) was sealed in a numbered brown opaque envelope. This envelope will be opened by the researcher on recruitment of a participant. The key coding to the allocation will be revealed by the independent statistician at the completion of the study. The r-TMS and sham treatment will be administered by a trained technician under the responsibility of the PI. The sham r-TMS are an exact replication of the active r-TMS but with a different serial number. An independent statistician will label the active r-TMS and sham r-TMS as either treatment 'A' or treatment 'B'.

The participants are assigned to either an r-TMS intervention or a sham control arm in a parallel intervention mode. The principle of random allocation is employed to assign the participants to an intervention and a control arm. To achieve an unbiased comparison group and to have a balanced randomization, permuted block randomization with a varying block size is used for the study. The sample size estimated for the study is 76. Hence, there are ten blocks with a block size of four participants each and ten blocks with a block size of two participants each. One-to-one allocation ratio is used.

Random sequence generation is done with the help of a Research Randomizer, an online random number generator (Urbaniak & Plous, 2014). An external member, who is not directly involved in the study, generates the sequence. To have a strict implementation of the generated random sequence, the concealed allocation is achieved using sequentially numbered, opaque and sealed envelopes (SNOSEs). An aluminium foil is kept inside the envelope to prevent from possible chances of deciphering. An external member, who is not directly involved in the study, would prepare the SNOSEs.

The final code is only known to the statistician and the document will be stored in a secure locked safe. The following information will be recorded during the randomization; study ID (assigned during the study initiation), investigator password (assigned during the initiation), subjects screening status, date of informed consent signed by subject, subject's ID no (e.g. Last 4 digits of IC), upon successful randomization, the subjects will be assigned randomization number and treatment. Documents the subject's ID no. and randomization no. on the Patient Enrolment Log and Patient Identification List.

3. The following information will be recorded during randomization:

    1) Study ID (assigned during study initiation)
    2) Investigator password (assigned during study initiation)
    3) Subject's screening status
    4) Date of informed consent signed by subject
    5) Subject's ID no. (e.g. Last 4 digits of IC)
    6) Upon successful randomization, the subject will be assigned a randomization number and treatment. Document the subject's ID no. and randomization no. on the Patient Enrolment Log and Patient Identification List.

11.1.4 Study treatment and visits

Study visits will occur from the first to the final month for efficacy and safety assessments for the total 4 months duration of the study. The r-TMS will be administered on the first month. There will be a total of 8 visits.

The investigator will perform the following procedures at each visit where applicable:

1) Medical history taking
2) Record any concomitant medication
3) Record any change of dose administration of study treatment
4) Perform physical examination including vital signs
5) Administer questionnaires
6) Obtain blood sample for lab evaluations
7) Perform EEG or TCD test
8) Record monthly headache diary
9) Record any AE or SAE
10) Complete relevant section/page of CRF
11) Dispense study treatment

11.1.5 Study visits schedule and procedures are summarised in the table below:

	Screening& Run in period 1 month (VISIT 1)	***VISIT 2***	***VISIT 3***	***VISIT 4***	***VISIT 5***	***VISIT 6***	***VISIT 7***	***VISIT 8***	***VISIT 9***	***VISIT 10***
	M0	**M1**	**M1 T1**	**M1 T2**	**M1 T3**	**M1 T4**	**M1 T5**	**M2**	**M3**	**M4**
Check eligibility	**X**	**X**								
Informed consent	**X**	**X**								
Patient demographics Medical history Clinical examination	**X**	**X**	**X**							
Questionnaires	**X**	**X**								**X**
Randomisation			**X**							
Lab. Test (Biochemical Analysis)			**X**							**X**
Lab. Test (Genetic)	**X**									
Efficacy assessment								**X**	**X**	**X**
Report AE and SAE			**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
EEG		**X**								**X**
TCD		**X**								**X**
Study treatment (rTMS)			**X**	**X**	**X**	**X**	**X**			

Table 1 : Study visits and schedule. M= month, W=week and D=Day

11.1.6 Assessment of efficacy

Assessment of efficacy will be assessed repeatedly from month 1 to month 4 of the study. Patient will complete their monthly headache diary and will submit it during their ***visit 10*** to be assessed.

Table below shows the summary of the assessment of efficacy.

Month	1	2	3	4
Frequency of migraine attack				
Migraine Days				

Table 2: Effecticness of r-TMS treatment was assessed and summarised in the table.

11.2 Criteria for stopping subject treatment

1. Severe and serious adverse event(s)
2. Protocol violation (e.g. incorrectly enrolled or randomised)
3. Subject requires use of unacceptable concomitant medication
4. Subject not compliant with protocol procedures
5. Subject develops a condition during the study that violates the inclusion/exclusion criteria
6. Lost to follow-up
7. Death

11.3 Sample handling and analysis

11.3.1 Collection

11.3.2 Labelling

1. The standard labels provided by central lab should be used to label each sample.
2. Any hand-written additions to the labels should be made using indelible ink.
3. Labels should not be attached to caps.

11.3.3 Analyses

#	Test	Method
1	Biochemical Analysis	Elisa Kit, Collection of blood, Extraction of peptide from plasma,
2	TCD test	An ultrasound probe will be used non-invasively on the scalp to find the main cerebral blood vessels and blood flow velocities will be measured with a pulsed

		Doppler effect probe, which graphs velocities over time.
3	EEG Test	A conventional scalp EEG, the recording is obtained by placing electrodes on the scalp with a conductive gel based on the International 10–20 system.

12 DATA MANAGEMENT

Data management will be conducted using appropriate database and validation programmes. Accurate and reliable data collection will be assured by verification and cross-check of 100% of the CRFs against the investigator's records (source document verification). The data collected will be entered into a computer database and subject to quality assurance procedures as dictated by Standard Operating Procedures of Malaysian GCP.

1. Data entry
   All the data will be recorded into the computer programs using the Microsoft Excel 2013
2. Data validation and Data Query
   Data will be abstracted retrospectively from computerized medical records by a database query for the identified patients. These data will be validated and augmented by abstracting data from the patients' paper records.
3. Clean File and Database Lock
   The missing data will be managed by running standard data-cleaning reports, which identify missing values or missing records. Once all the data collected during the visits have been transferred and captured in the database, cleaning, reconciliation, and verification activities will be formed for smooth database lock.

Relevant bodies such as JKEUPM and RMC UPM would also have access to the study data.

13 STATISTICAL METHODS

13.1 Sample size and power considerations

The number of patients to be involved in this study is calculated by using hypothesis testing method. The null hypothesis defined is that frequency of migraine (primary outcome) is not different among group with r-TMS treatment. Alternative hypothesis defined is that the frequency of migraine is different among group with r-TMS treatment.

The sample size calculation is given below:

$$n = \frac{2\ \sigma^2[z_{1-\alpha/2} + z_{1-\beta}]^2}{(\mu_1-\mu_2)^2}$$

Where;

$z_{1-\alpha/2}$ =1.96 at α =0.05
$z_{1-\beta}$ =0.842 at 1-β = 0.80
σ^2=4.9
n=29

Title	Power	Number of groups	Number of measurements	Sample Size
High-rate repetitive transcranial magnetic stimulation in migraine prophylaxis: a randomized, placebo-controlled study	0.8	2	4	29/arm

The satisfying figure of power test in biomedical researches statistics is 80%, while above 80 Statistical power will give good study design, therefore, the power test is 80% has been selected in this study and significance level for rejecting a Null hypothesis is 5%. Therefore, the target number of participants per group is 29 with the total number of participants being 76 allowing 30% dropout rate to detect frequency between active treatment and sham.

Characteristics of the patients in each of the groups at baseline will be compared using independent t-test or Mann Whitney test for numerical variables, depending on the normality test for the variable. Chi-square or Fisher's exact will be used to compare categorical variables between the groups. For primary and other outcome measures, treatment effects will be examined based on within group effect, between group effect and within-between group effect. Repeated measure Analysis of Covariance (ANCOVA) will be used for the analysis. Compliance with treatment in each group will between compared using independent t-test or Mann Whitney test depending on the normality of the data. Frequencies of adverse events will be

compared using Chi-square or Fisher's exact test. All analysis will be done at significance level 0.05.

Assistance with analysis will be given by Dato' Professor Dr Lye Mun San, Senior Lecturer in Public Health and Epidemiology.

13.2 Randomisation

The participants are assigned to either an r-TMS intervention or a sham control arm in a parallel intervention mode. The principle of random allocation is employed to assign the participants to an intervention and a control arm. To achieve an unbiased comparison group and to have a balanced randomization, permuted block randomization with a varying block size is used for the study. The sample size estimated for the study is 76. Hence, there are ten blocks with a block size of four participants each and ten blocks with a block size of two participants each. One-to-one allocation ratio is used.

13.3 Analyses

13.3.1 Analyses Sets

All randomised subjects will be included in the analysis.

13.3.2 Baseline Comparability

True randomisation, concealed location and adequate sample size planned for this study will ensure enough baseline comparability between groups (r-TMS and sham). Additionally, a table of baseline characteristics of participants in each group, without between-group statistical comparisons will be included. The study team will analyse this table to decide whether any characteristics were imbalanced enough to have influenced the outcomes of the study.

13.3.3 Efficacy Analysis

Analyses were performed on an intent-to-treat basis with the last observation carried forward. The primary treatment comparisons of benefit include all eligible patients, regardless of the amount of TMS treatment sessions received. Both eligible and ineligible patients are included in the analyses and compared by treatment assignment when an intent-to-treat analysis is specifically indicated.

13.3.4 Safety Analysis

The summaries of adverse events include all patients who received any study treatment; those who did not receive study treatment are not included in these summaries. The safety population comprised all randomized patients who received at least one treatment dose and was based on the actual treatment received.

13.3.5 Handling of missing, unused and spurious data

All available data will be included in the data listings and tabulations. Where appropriate, imputations of values for missing data for primary and secondary efficacy analyses will be performed as specified in the Statistical Analysis Plan. All data recorded on the CRF will be included in the data listings that will accompany the clinical study report.

Missing data will be described, for example, by presenting the number and percentage of individuals in the missing category and will be dealt with GEE. No data will be considered spurious in the analysis since all data will be checked and cleaned before analysis

13.3.7 Planned Interim Analysis

There will be no interim analysis done in this study.

14 ADMINISTRATIVE MATTERS

14.1 Notification of regulatory authority(ies)

All necessary arrangements for the registration and approval of this study with the responsible authorities and the disposition of the required data and document will be undertaken by the Principal Investigator.

14.2 Notification of primary care physician

Investigators should ask patients if they wish for their general practitioner or primary care physician to be notified about their involvement in this study. This is so that if the patients need to see their own physician for any reason, the physician will be aware that they are taking a study drug,

14.3 Study initiation

Investigators involved in this study must not enrol any patient prior to completion of a formal meeting conducted by the Clinical Research Associate of (JKEUPM). This meeting will include an inventory of study supplies, a detailed review of the protocol and CRF, training on study procedures and other procedures required of GCP. Investigators who are not GCP certified will undergo GCP training during the study.

14.4 Protocol deviation

Any protocol deviation will be documented by the (JKEUPM) monitor with rectification as soon as possible. The investigator should be notified immediately. With the exception of emergency situations, no changes or deviations in the conduct of this protocol will be permitted without the prior approval from (JKEUPM). In the event of any emergency, the investigators will institute any medical procedures deemed appropriate. All such procedures must be promptly reported to (JKEUPM).

14.5 Study documentation

14.5.1 Essential documents

These are documents that permit evaluation of the study and the quality of the data produced. The Essential Documents are:

1. Signed protocol amendments
2. Sample CRFs
3. JKEUPM approval letter, including a dated list of JKEUPM membership and members' affiliation
4. Informed consent form
5. CV of investigator and co-investigator
6. Correspondences with sponsor and (JKEUPM)
7. Interim reports to JKEUPM
8. Investigational product accountability and shipping records
9. Site signature log
10. Monitor visit log
11. Other appropriate documents in accordance with GCP guidelines.

The investigator will maintain an Investigators Study File. This file will be used to facilitate and ensure filing of all relevant and Essential Documents during and after the study. The investigator will be responsible for keeping the Investigator's Study File updated and ensuring that all required documents are filed. The file will be inspected during monitoring visits.

14.5.2 Source documents

These are original hospital records, clinical charts, subject screening checklist, original laboratory reports, memoranda, recorded data from automated instruments, transcriptions certified after verification as being accurate, microfiches, photographic negatives, microfilm, magnetic or electronic media, x-rays, subjects' files, and records kept at the pharmacy, at the laboratories and at medico-legal departments involved in the study.

The investigator must maintain source documents for each patient in the study. All information on CRFs must be traceable to these source documents:

1. Patient identification list
2. Curriculum vitae
3. Site signature/authorization log

14.6 Patient identification list/Enrolment log

The investigator has to maintain a list of all enrolled patients containing the full name, date of birth, date of enrolment, and the randomization number. The list must show an unequivocal study identification number. The list will be filed in the Investigator's Study File on site.

14.7 Curriculum vitae

The investigator will provide curriculum vitae showing his/her experience in the area of the proposed study. These should be filed at (JKEUPM) as well as in the Investigator's Study File on site.

14.8 Site signature/authorization log

The investigator must maintain a Signature Log to document signatures and initials of all staff authorized to make entries and/or corrections on CRFs and other study related records or documents. The log will be filed in the Investigator's Study File.

14.9 Retention of documents

The investigator shall arrange for the retention of all study documents and records, including subject records, CRFs, drug inventory/accountability log, signed informed consent forms and the patient identification list for at least 3 years after completion or discontinuation of the study.

If the investigator moves or retires, he/she must nominate someone in writing to be responsible for archiving. Archived data may be held in microfiche or electronic record, provided a backup exists and a hard copy can be obtained from it if required.

If the investigator cannot guarantee this archiving requirement at the study site for any or all the documents, special arrangements must be made with the sponsor or (JKEUPM) to store these in a sealed container(s) outside of the site so that they can be returned sealed to the investigator in case of a regular audit. Where source documents are required for the continued care of the subject, appropriate copies should be made for storage outside of the site.

For the biospecimens, patients will be asked for informed consent for future study of the samples for other indications. A separate informed consent will be signed for patients who agree for the future biospecimens testing. Another ethical board approval will be obtained for any other test. Samples will be stored securely at the Universiti Putra Malaysia and will be destroyed after 5 years of storage.

14.10 Finance

UPM Putra Grant from the Research Management Centre (RMC) UPM (Grant id: GPB/2017/9585500) will support the work of the investigator and supply the required investigational product for the study.

14.11 Study Termination and Site Closure

The sponsor and (JKEUPM) reserve the right to terminate this study and remove all study materials from the study site at any time. Reasons that may require termination of the study include:

1. It becomes apparent that patient enrolment is unsatisfactory with respect to quality or quantity.
2. Date recording is inaccurate and/or incomplete
3. Deliberate violation of the signed protocol

4. The incidence and/or severity of adverse events in this or other studies indicate a potential health hazard caused by the treatments under trial.

Should (JKEUPM) or the sponsor decide to terminate the study, the investigator will complete the CRFs as far as possible. The completed CRFs and any study material will then be collected by (JKEUPM).

14.12 Confidentially

The investigator agrees that all information communicated to him/her is the exclusive property of the Sponsor or (JKEUPM), and ensure that the same will be kept strictly confidential by the investigator or any person connected with the work and shall not be disclosed to any third party without the prior written consent of the sponsor and (JKEUPM).

14.13 Anticipated subject accrual and duration of the study

This study is expected to start in December 2018.The projected study timetable for the study is as follows:

1. First patient enrolled is expected in January 2019
2. Last patient enrolled is expected in December 2019
3. The last patient enrolled is projected to complete the study period in April 2020.

   These accrual rates are based on reasonable planning expectations. The investigator should however continually compare the actual and expected accrual rates, and make every effort to ensure that they are as closely matched as possible. If the investigator anticipates major problems with recruitment, or delay in the expected completion date, he/she should discuss this with the (JKEUPM) staff as early as possible.

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