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# A randomised controlled trial of a structured cognitive rehabilitation in patients with attention deficit following mild traumatic brain injury: Study protocol



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# TITLE: A randomised controlled trial of a structured cognitive rehabilitation in patients with attention deficit following mild traumatic brain injury: Study protocol


## ABSTRACT

**Objectives:** This study hypothesizes that structured cognitive rehabilitation for attention deficits following mTBI will improve patients' cognitive function. The primary objective is to measure the change of attention deficit between groups and the secondary objective is to examine the effect of treatment on brain structures and daily life functions.

**Design:** This is a prospective double blind, randomized controlled trial with two parallel groups.

**Setting:** This trial will be conducted at a single centre, in Malaysia.

**Participants:** This study will recruit adult participants with the following inclusion criteria: mTBI as a result of road traffic accident; adult aged between 18 to 60 years old; Malaysia citizen; no previous history of head trauma; education level minimum of nine years; abnormal cognition at three months after mTBI; provision of informed consent, able to communicate in basic English and willingness to comply with cognitive rehabilitation sessions. The exclusion criteria include pre-existing chronic illness that cause neurological symptoms or complications; severe comorbid neurological or psychiatric disorder; on long-term medication that alter or affect cognitive and psychological status; clinical evidence of substance intoxication at the time of injury; major polytrauma and absolute contraindication for Magnetic Resonance Imaging (metal or implant not compatible for imaging, claustrophobia). The sample size calculation, setting an alpha level of 0.05, approximately 38 participants will provide 85% power to detect statistical significance. Recruitment is inflated to 46 participants to enable a 20% attrition rate.

**Interventions:** All potential participants with confirmed mTBI diagnosis will undergo Neuropsychological Assessment Battery® at two weeks and at three months following injury. Participants who fulfill study criteria will be recruited and randomised. The intervention group will receive individualised computer-based cognitive rehabilitation known as Direct Attention Training program and cognitive functional problem-solving training. The control group will receive best patient-centred care for attention disorders which will include symptom management and cognitive compensatory strategies. Therapy frequency for both groups will be one hour per week for 12 weeks.

**Main outcome measures:** The primary outcome measure is the change of attention deficit between intervention groups and healthy group via Neuropsychological Assessment Battery® scores. The

secondary outcome measures are microstructural white matter tract parameters and functional Goal Attainment Scaling score differences between groups.

**Conclusion:** This trial tests a complex clinical intervention, to provide evidence for the effect of cognitive rehabilitation in mTBI. The outcome measures include anatomical, clinical and functional aspects in order to establish a comprehensive evidence-based treatment model.

**Trial registration**: This study is registered with ClinicalTrials.gov ID NCT 03237676

## Keywords:

Mild traumatic brain injury, concussion, attention deficit, cognitive rehabilitation, randomised controlled trial

## ARTICLE SUMMARY:

**Strengths and limitations of this study:**

- To our knowledge, this is the first randomized control trial of cognitive intervention in adult mTBI population, conducted in a developing country, Southeast Asia region.
- A study from this region with various ethnic involvements may better represent the study population and in turn add further knowledge on the pattern of the impairment following mTBI.
- This trial incorporates technology in the treatment application consistent with the changing face of health service delivery in Malaysia, aiming at resource efficiency and treatment effectiveness, albeit tailored treatment approach suitable for the local setting.
- Owing to the paucity of scientific and clinical knowledge, this trial will also contribute to the evidence-based cognitive treatment model for mTBI population.
- We anticipate challenge in the recruitment phase and treatment compliance due to known and reported high attrition rate in traumatic brain injury population.

## BACKGROUND

Mild traumatic brain injury (mTBI) is defined as a traumatic injury that induces transient physiological disruption of the brain function[1]. Mild TBI is often used interchangeably with concussion and is a clinical diagnosis[1]. The most common aetiology in the low and middle-income countries is road traffic accident (RTAs) that disproportionately affects young men (15 to 29 years of age)[2-4].

Statistically, 20 to 50 million people sustained non-fatal injuries worldwide as a result of RTA and with an increasing rate in the developing countries[2,3].

Cognitive deficit is rarely singular in mTBI. Commonly reported symptoms are attention, memory and executive function deficits, each with varying severity and recovery pattern[5-14]. Specifically, attention deficit is extremely common in TBI[15,16]. Attention is known to be the basis of all other cognitive abilities[17]. About 40 to 60% of individuals with mTBI were reported to have attention deficits in the first three months post-injury[18]. In the majority of individuals, resolution of mixed cognitive deficits begins in the first month up to one-year post-injury[5,7,11,12,19-21]. A proportion of this population quite often progresses to have chronic cognitive disability that is overlooked due to the initial 'mild' presentation[6,10,22-25]. At least one-third of survivors fail to return to full functional status at six months and may continue to have neurocognitive functional deficits beyond one year of injury[5,12,25-29].

**Cognitive rehabilitation in mTBI**

Currently, there is no standard treatment protocol for cognitive rehabilitation for the mTBI population. The early neuropsychological model of attention has already made the assumption that attention should be the focus of rehabilitation, before more advanced cognitive skills be treated[33]. In the last 20 years, various cognitive treatment approaches have been reported in systematic reviews[34-37]. These include remediation strategies,[38-49], compensatory strategies[50-57] and patient education intervention[6,39,53,58]. These approaches are usually applied in combination, to optimise both cognitive and functional recovery[17,27,28,30,31,33- 38]. In particular, treatment for attention deficits in TBI was recommended at post-acute stage of trauma [28,30,34]. Methods of treatment included multidimensional approach, and tasks with hierarchical difficulty and complexity[30,34]. Several studies also reported improved psychologcical outcome and coping of symptoms on those who received patient education and reassurance following mTBI[35,36]. However, these conclusions were based on a limited number of high-quality clinical trials. Due to the heterogeneity of cognitive deficits, varied intervention methodology, different reporting style and no treatment standardisation[34-37], the consensus was for more robust clinical trials of larger sample size, well-described complex intervention and standardised reporting method [34-37].

Delivery of cognitive rehabilitation emphasizes six principles: 1) intervention that is theory-driven and meaningful, 2) intervention is task-specific with increasing complexity relevant to individual needs, 3) the need to regularly practice skills acquired, 4) progress monitoring to tailor to individual's needs, 5) generalisation of learnt strategies to apply in real-life skills, and 6) real-world adaptation to ensure success[17,49,59]. A practical, widely accepted treatment approach with the application of evidence-based treatment principles may represent a comprehensive treatment model in treating mTBI patients with cognitive deficits. A large randomised trial is required to support this hypothesis.

**Clinical, imaging and functional outcome measures in mTBI**

A combination of these three outcome measures is a comprehensive approach to analyse cognitive intervention that can make an impact in clinical practice. Scientific reviews and guidelines have recommended the use of neuropsychological assessment as an appropriate clinical outcome measure[17,27,28,30,31,33,34,36,37]. In adult mTBI, a test which was sensitive across various cognitive domains[21,24,41,43,44,53,57,60], specific to population study[24,40,43], had good validity and reliability[41,44,51,57,61-64], was cost effective and practical to use in a clinical setting[44,53,62-64] would be ideal.

The structural injury in mTBI however, is too miniscule for detection through routine computed tomography (CT) and Magnetic Resonance Imaging (MRI)[65-67]. Over the last 10 years, Diffusion Tensor Imaging (DTI) has become accepted as a non-invasive tool that is able to quantify microstructural brain changes in mTBI[24,65-70]. Changes in its parameters are indicative of microstructural remodelling at acute and chronic stages of injury, potentially explaining the persistence of symptoms that would otherwise be attributed to other causes [24,65-70]. A longitudinal DTI study may increase our understanding of the brain structural transformation in mTBI.

The most important outcome following mTBI is the ability for survivors to return to their previous functional state and quality of life. Common scales to measure disability and function are usually sensitive to cognitive deficits but not necessarily specific to the TBI population[39-41,52,53]. Many studies have also reported specific outcome measures for TBI that has good validity, reliability and practical in a clinical setting[71-78], such as Goal Attainment Scaling[71,72,77,78], Extended Glasgow Outcome Scale[73] and Functional Assessment Measure[74].

This trial evaluates a complex clinical intervention, to provide evidence on the effect of cognitive

rehabilitation in mTBI. We extend the outcome measures to include anatomical, clinical and functional aspects to establish a comprehensive evidence-based treatment model.

## METHODS

### Study hypothesis and objectives

We hypothesize that structured cognitive rehabilitation for attention deficits following mTBI will improve patients' cognitive function of attention compared to the standard care. The primary objective is to measure the effect of a 12-week individualized structured cognitive rehabilitation to address attention deficit. The secondary objective is to examine the effect of treatment on brain structures and function in daily life.

### Design

This will be a prospective double blind, randomized controlled trial with two parallel groups. The study design is summarized in **Fig. 1**.

### Participants and recruitment process

This trial will be conducted at a single centre, University Malaya Medical Centre (UMMC), Malaysia. We will recruit participants through the Emergency Medicine Department (ED), UMMC from 1st August 2017. This is a hospital, which provides acute service and is a tertiary referral centre in Malaysia. It is situated in the urban area of the nation's capital city Kuala Lumpur with the population of 1.76 million. ED physicians, radiologists and neurosurgeons will refer mTBI cases to a research assistant for recruitment. Potential cases will also be screened through UMMC digital medical record system. This study had obtained ethical approval from the Medical Research Ethics Committee, UMMC (MREC ID NO: 2016928-4293).

### Inclusion criteria

The inclusion criteria for this study include mTBI as a result of RTA only; adult aged between 18 to 60 years old; Malaysia citizen; no previous history of head trauma; education level minimum of nine years; abnormal NAB® Attention Domain score at three months after mTBI; provision of informed consent, able to communicate in basic English and willingness to comply with cognitive rehabilitation sessions.

**Exclusion criteria**

The exclusion criteria include pre-existing chronic illness that cause neurological symptoms or complications; severe comorbid neurological or psychiatric disorder; on long-term medication that alter or affect cognitive and psychological status; clinical evidence of substance intoxication at the time of injury; major polytrauma and absolute contraindication for MRI (metal or implant not compatible for MRI, claustrophobia).

**Intervention**

Potential participants will undergo screening before enrollment and randomization (**Figure 1)**. Education component includes reassurance on recovery, self-monitoring of symptom(s) and advice on gradual return to daily activities and physical exertion. The first medical responder i.e. ED physicians will perform this component at 72 hours of injury. At two weeks of injury, a rehabilitation medicine physician who is not involved with the study (RP-1) will repeat the same component.

At three months after injury, potential participants will undergo a repeat of clinical review and NAB-S® test. Participants with persistently abnormal Attention Domain based on the neuropsychological assessment will be enrolled in the study. However, those with other cognitive domain deficit other than Attention Domain will also receive treatment for that specific domain deficit(s). The cognitive intervention will be conducted at the Neurorehabilitation Therapy Unit, Department of Rehabilitation Medicine, UMMC in an outpatient setting. Participants will be assigned to different treatment groups via randomization process.

***Individualised structured cognitive rehabilitation group***

Intervention group participants will receive a two-part 12-week individualized structured cognitive rehabilitation. The first part is Direct Attention Training (DAT), a deficit-oriented evidenced-based computer-based attention-training program called CogniPlus[45]. Each session will be 30 minutes, once a week.

CogniPlus is a computer-based software program with interactive multimedia approach for multiple attention cognitive training modules. The training programs are ALERT (focused and sustained attention), FOCUS (focused attention), VIG (sustained attention), SELECT (selective attention) and DIVID (divided attention). Each attention-training category is designed based on real-life scenarios and the screen graphics are three-dimensional. This program has artificial intelligence capacity that can

automatically adapt to an individual's performance and alter the training difficulty level (hierarchical difficulty).

The second part of this intervention is strategy approach (metacognitive awareness and compensatory strategy) performed after CogniPlus training. It will last for 30 minutes and will involve feedback on the participant's CogniPlus performance, review of cognitive-related problem encountered in daily activities since the injury and problem-solving training. A trained and certified Occupational Therapist (OT-1) in cognitive therapy and CogniPlus will conduct all the sessions.

***Standard care group***

This group will receive the best standard care for attention disorders. This is a patient-centred cognitive therapy, which will include symptom management and compensatory strategies. The frequency of sessions will be one hour per week, for 12 weeks. A trained occupational therapist in cognitive therapy (OT-2) who is not involved with the intervention group treatment, will conduct all the sessions.

***Control group***

This will consist of healthy individuals demographically matched for age, gender and education years to the intervention groups. The data is collected for comparison purpose.

**Randomisation, consent and blinding**

Participants with mTBI who fulfill the study criteria will be randomized via computer-generated random permuted block assignment, gender-stratified into equally proportioned intervention and control group numbers. The study schedule and procedures are presented in **Table 1.**

| | | | STUDY PERIOD | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Enrolment | Enrolment | Allocation | Post-allocation | | | | | | End of treatment |
| **TIMEPOINT**** | | $-t_2$ *72 hours mTBI* | $-t_1$ *2 weeks mTBI* | **0** 3 months mTBI | $t_1$ | $t_2$ | $t_3$ | $t_4$ | $t_5$ | $t_{12}$ | $f_1$ *6 months mTBI* |
| | **Co-investigator (initials)** | ***Pre-study screening*** | ***Pre-study screening*** | ***Baseline/ Randomisation*** | ***Study Visit 1*** | ***Study visit $t_2$ onwards*** | | | | ***Last study visit*** | ***Outcome measures*** |
| **ENROLMENT:** | | | | | | | | | | | |
| **Eligibility screen** | Research assistant | X | X | | | | | | | | |
| **Informed consent** | MM | | | X | | | | | | | |
| **Allocation** | MM | | | X | | | | | | | |
| **NAB-S® Test (Form 1)** | NH | | X | | | | | | | | X |
| **NAB-S® Test (Form 2)** | NH | | | X | | | | | | | |
| **DTI test** | VN/NR | | | X | | | | | | | X |
| **DTI post processing** | TLK | | | X | | | | | | | X |
| **GAS** | NAM (OT-1) & NAMT (OT-2) | | | | X | X | X | X | X | X | X |
| **INTERVENTIONS:** | | | | | | | | | | | |
| **Education component** | ED team/RP-1 | X (ED team) | X (RP-1) | | | | | | | | |
| **Individualized structured cognitive rehabilitation** | NAM (OT-1) | | | | X | X | X | X | X | X | |
| **Best-practice standard treatment** | NAMT (OT-2) | | | | X | X | X | X | X | X | |
| **OUTCOME MEASURES:** | | | | | | | | | | | |
| **NAB-S® Test** | NH | | | X | | | | | | | X |
| **DTI** | VN/NR | | | X | | | | | | | X |
| **GAS** | NAM/NAMT (OT-1/OT-2) | | | | X | X | X | X | X | X | X |

**Table 1:** Study schedule and procedures.

**Modification, withdrawal and unblinding within the intervention**

Participants can withdraw their consent from this study at any time and for any reason. Investigators can also withdraw a participant from the study if he/she becomes non-compliant with the study procedures. We will also provide participants who require any treatment beyond the study intervention. The participant will only be withdrawn from this study if the immediate treatment violates our study criteria. In the case where unblinding of a participant is necessary (e.g. medical emergency), an investigator (MM) will be informed of the cause and stage of intervention received by the participant. He/she may continue in the study and follow all study procedures. We will retain the participant's data (although the participant is no longer blinded) or up to the point of participant's removal from the study.

**Adherence strategies**

Adherence to treatment is enabled throughout the intervention for both groups. This will be achieved by three providing: 1) participants with clear information on purpose, method and treatment goals during treatment sessions, 2) an appointment card with specific date and time of therapy sessions, and 3) a reminder through phone calls a day before each therapy appointment and a week before DTI scan date.

**Outcome measures**

All measures will be performed at baseline and at the end of the intervention. The primary outcome measure of this study is the change of attention deficit between intervention groups and direct comparison of each intervention group with the healthy control group. This will be measured by Neuropsychological Assessment Battery® (NAB®, PAR, Inc., Florida, USA)[61]. It consists of six modules: Screening Module and five Domain Specific Modules: Attention, Language, Memory, Spatial and Executive Function. This study will only apply the Screening Module (NAB-S®) because the Screening Module measures the same five functional domains similar/identical to the main NAB modules. It consists of 12 individual tests screening all five mentioned cognitive domains for adults aged 18 to 97 years, validated and sensitive for use in healthy and cognitively impaired brain injured population[24,61-64]. NAB-S® provides two parallel assessment sets (Record Form 1 and Form 2) that will be applied in an alternate fashion to participants in both groups to avoid practice effect.

The secondary outcome measures are microstructural WMT parameters and functional GAS scores. The DTI MRI scan is a Siemens Magnetom Prisma 3T MRI (Siemens AG, Muenchen, Germany). This study

will analyse Fractional Anisotropy (FA), Mean Diffusivity (MD) and Radial Diffusivity (RD) parameter changes at pre- and post-intervention[24,65-70]. These parameters quantify the direction and degree of tissue water diffusion within the WMT[65,66]. FA which measures the direction of the diffusion is an index expressed in a range from 0-1, with a higher score indicating a higher integrity of white matter consisting of highly parallel fibres[65,66]. MD measures the average magnitude of the diffusion while RD quantifies pathology in the myelin[65,66].

We will apply whole brain analysis method to identify FA, MD and RD parameters with statistically significant mean values ($p<0.05$) known as Tract-based Spatial Statistics (TBSS) which is part of the FSL (v5.0.6; University of Oxford, Oxford UK) software package. Based on TBSS findings we will also identify specific tracts via region of interest (ROI) approach utilizing the FSL (v5.0.6; University of Oxford) and AFNI (v2011_12_21_1014; National Institute of Mental Health, Bethesda, MD) software packages.

The tool to measure functional outcome is GAS[77-79]. The difficulty and importance of rehabilitation goals will be individually set according to his/her current levels of functional performance to underline a realistic expectation. The sensitivity of GAS is increased by the quantifiable set goals relevant and specific to the participant. Each goal is rated on a 5-point scale and score is given on the extent to which a patient's individual goals are achieved in the course of the intervention. The overall GAS scores calculation will generate a standardized measure (T score) (mean of 50 Standard Deviation ± 10). The details of each goal outcome will be recorded in the GAS Record Sheet[77-79] by a cognitive therapist of each study arm (OT-1 and OT-2) trained in GAS application.

**Sample size and power calculation**

We will base our sample size calculation on our objectives. The intended sample size is based on a previous study that had applied similar treatment approach and with one similar outcome measure to our study[40]. This study applied the non-commercial statistical power analysis program G*Power Version 3.1.9.2. An effect size of 0.58, which was the functional cognitive outcome of attention [40], is used to calculate the statistical power *a priori.* We applied Analysis of Variance (ANOVA): repeated measures, within-between interaction, setting an alpha level of 0.05, and approximately 10 participants will provide 89% power to detect a statistical significance. Recruitment is doubled (n=20) for both arms and inflated to 28 to enable a 40% attrition rate.

To have a bigger sample size, we, therefore, decided on a more conservative effect size value and calculated the sample size through estimation of Cohen's *d* value of 0.35. By using similar statistical power analysis program, medium effect size Cohen's *d* of 0.35, setting an alpha level of 0.05, approximately 38 participants will provide 85% power to detect statistical significance. Recruitment is inflated to 46 participants to enable a 20% attrition rate. From the multiple estimated calculations, the minimum intended sample size to secure this study sample is therefore 46 participants. Based on our UMMC local data, a 12 months data collection is sufficient to yield the target sample size.

**Patient and public involvement**

We applied the Medical Research Council (MRC) Developing and Evaluating Complex Intervention: New Guidance (2006) in our development of study intervention. The choice of deficit-to-treat is based on the relevant theoretical literature evidence whereas treatment approach is evinced through literature review, our clinical experience and practice setting of interest. We further conducted two approaches to select components in this study intervention that may require further focus, 1) a pilot study and, 2) Expert Panel review. We conducted a pilot study (approved by Medical Research Ethics Committee, UMMC, Malaysia UM/EC Ref: 947.15) on the application of cognitive treatment on mTBI survivors. mTBI patients were involved in the testing of clinical treatment method, the application practicality, fidelity of treatment and treatment compliance through their experience, feedback and outcomes. We have identified components that would require review for optimization of intervention and these components are further advised by Expert Panel review. The panels comprised of physicians and clinicians who are credentialed in cognitive rehabilitation practice and brain injury, with clinical experience minimum of 10 years in the field of interest in Malaysia. Panels are made up of seven rehabilitation medicine consultants, one neurosurgeon consultant, one neuroimaging consultant, five cognitive occupational therapists and one clinical psychologist. As established experts in the field, the focus of discussion is on feasibility of structured cognitive rehabilitation application in the mTBI patients in Malaysia. The in-depth discussion is based on each individual professional experience and knowledge and guided by the current evidence and recommendations available. All invited Expert Panels are involved in the final structured cognitive rehabilitation prior to its application in this study.

Following the commencement of this study, the input from participants will be similarly recorded through their experience, feedback and outcomes. The data and study materials belong to UMMC,

Malaysia. We will inform participants the result of the study following its completion even if he/she did not complete the study unless he/she has requested not to be contacted.

**Statistical analysis**

We will compare the descriptive data between the two intervention arms and with the healthy group. This will include descriptive analysis such as demographic distribution, mean, median and standard deviation. A $p$ value <0.05 will be considered statistically significant. We will also report any additional relevant data, which may implicate or contribute to the study outcome. This includes lifestyle modifications, legal or litigation issues and socioeconomic status.

Another descriptive analysis will include the magnitude of treatment effect. This study will measure the Cohen's $d$ effect size of all outcome measures for both treated groups. Neuropsychological and functional outcomes with moderate effect size threshold (>0.35) to large effect size (>0.65) are considered to be clinically significant. Functional GAS score of >60% post-intervention is also considered significant. We will also analyse the task difficulty level, mean response time and measurement of errors for the five CogniPlus Attention categories.

The primary analysis is the measure of treatment effect and microstructural brain changes by 1) direct comparison of each intervention group with the control group and 2) comparison between treated groups. We will analyse the mean clinical differences and the mean structural brain differences (DTI parameters) using repeated measure analysis to determine the mean differences of neuropsychological Attention, Total Screening Index scores and GAS T scores as well as DTI paramaters - FA, RD, AD and MD of selected WMT. The study fulfills the assumption of repeated measure analysis of normally distributed data sample and homogeneity of variance.

The secondary analysis is correlation between cognitive changes and structural brain changes through correlation coefficient (Pearson).

**Data management**

All data obtained for non-adherence or voluntary withdrawal of participants will also be reviewed and included in the study analysis where applicable. All study-related information will be securely kept at the study site. All participant information will be stored in locked filing cabinets with limited access. All data collection, administrative forms, reports and analysis will only have coded ID as identification of participants to avoid identification by any investigator of the study. Data entry also uses coded ID and is

performed by an appointed research assistant. Any other document that has participant's name such as consent form will be kept in a separate cabinet accessible by only one investigator (MM).

## Discussion

To our knowledge, this is the first randomized control trial of cognitive intervention in adult mTBI population, conducted in a developing country, Southeast Asia region. Previous studies have been done in the Western population with a predominantly Caucasian ethic group and limited ethnic variation. A study from this region with various ethnic involvements may better represent the study population and in turn add further knowledge on the pattern of the impairment following mTBI. Development of the intervention approach was based on existing evidence, pilot study and Focus Group panel review. We will also incorporate early involvement of relevant health professionals in the field and apply a comprehensive treatment approach and novel outcomes for both genders of the study population. This trial incorporates technology in the treatment application consistent with the changing face of health service delivery in Malaysia, aiming at resource efficiency and treatment effectiveness, albeit tailored treatment approach suitable for the local setting. The results of this study will provide a comprehensive overview on the effect of cognitive rehabilitation in mTBI. Owing to the paucity of scientific and clinical knowledge, this trial will also contribute to the evidence-based cognitive treatment model for mTBI population.

## Trial status

At the time of manuscript preparation, 30 potential participants have been recruited at three months post-injury. Fifteen participants were consented and received treatment following randomization. Recruitment is due to finish in April 2019. Data lock has not yet occurred and no analyses have been performed.

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**Trial sponsor**: University of Malaya, Malaysia

**Ethics approval:** Medical Research Ethics Committee, UMMC (MREC ID NO: 2016928-4293).

## Declarations

The authors declare that they have no competing interests.

## Acknowledgement

We wish to thank all our mTBI participants involved in the pilot control study as well as Expert Panels in involved in the review of our intervention development and study.

## Authors' contribution

NH initiated the study, applied for study funding and is the principal investigator. NH, MM, VN, NR, AD, RDN and GSY were involved in the conception, development of the intervention and design of the study. NAM and NAMT implemented the cognitive intervention. TLK provided the consultation on DTI processing and analysis. MD and NM provided important statistical contributions. All authors provided feedback on drafts of this paper, read and approved the final manuscript. NH, MM, VN and NR are the guarantors for the study and accept full responsibility for the work and /or the conduct of the study, had access to data, and controlled the decision to publish. MM is the corresponding author and attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

## Availability of data and material

The data and study materials belong to UMMC, Malaysia. Any request will have to go through Medical Record Department of UMMC, Malaysia. Dissemination of trial result is through publication.

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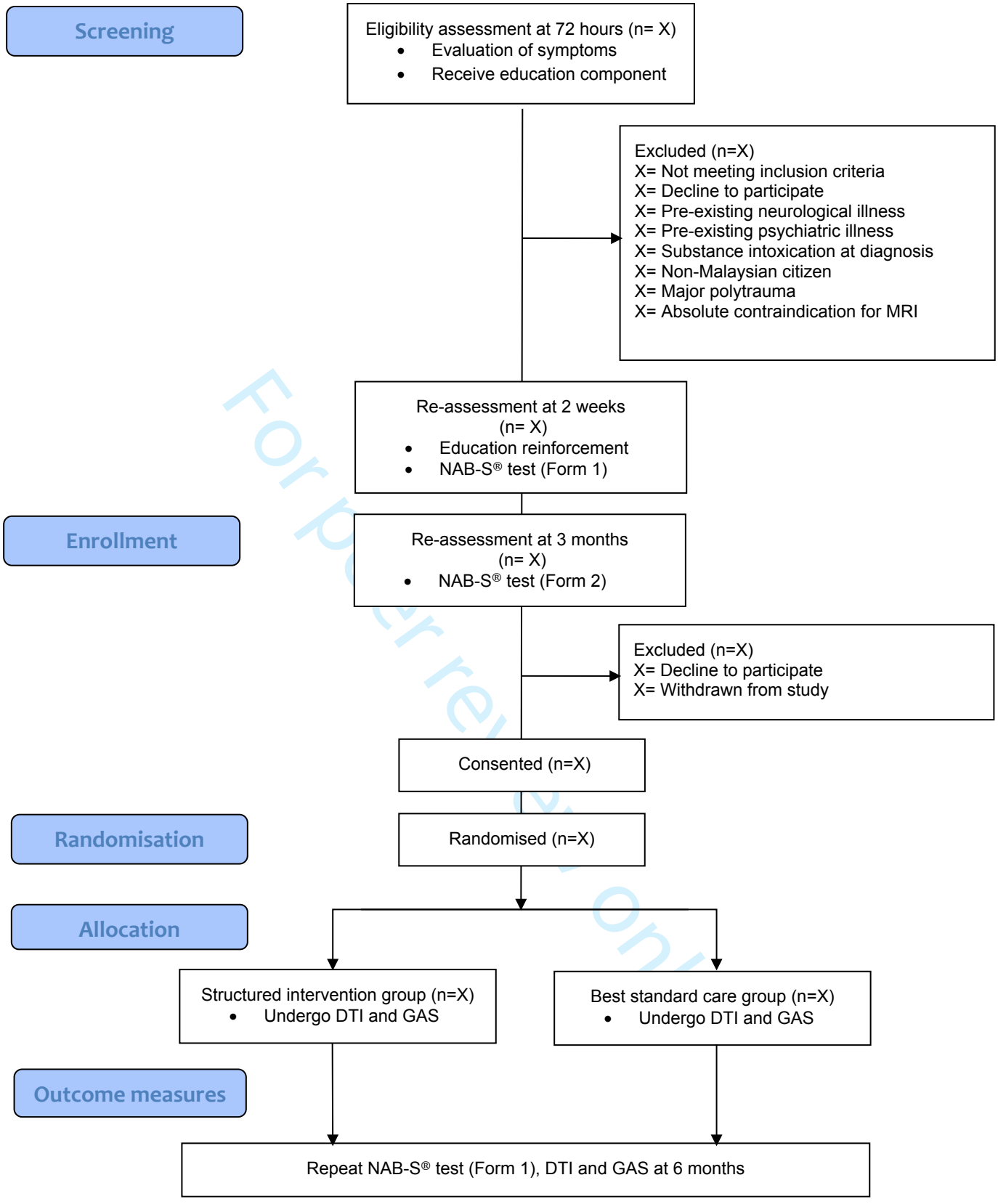


**Figure 1**: The study design

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

| Section/item | Item No | Description | Addressed on line number |
|---|---|---|---|
| **Administrative information** | | | |
| Title | 1 | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym | 1-2 |
| Trial registration | 2a | Trial identifier and registry name. If not yet registered, name of intended registry | 35, 332-336 |
| | 2b | All items from the World Health Organization Trial Registration Data Set | 332-336 |
| Protocol version | 3 | Date and version identifier | 302-309 |
| Funding | 4 | Sources and types of financial, material, and other support | 328-331 |
| Roles and responsibilities | 5a | Names, affiliations, and roles of protocol contributors | 342-350 |
| | 5b | Name and contact information for the trial sponsor | 335 |
| | 5c | Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities | NA NA |
| | 5d | Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) | NA |

| | | | |
|---|---|---|---|
| **Introduction** | | | |
| Background and rationale | 6a | Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention | 52-115 |
| | 6b | Explanation for choice of comparators | 92-115 |
| Objectives | 7 | Specific objectives or hypotheses | 117-122 |
| Trial design | 8 | Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) | 123-125; Figure 1 |
| **Methods: Participants, interventions, and outcomes** | | | |
| Study setting | 9 | Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained | 126-134 |
| Eligibility criteria | 10 | Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) | 135-148 |
| Interventions | 11a | Interventions for each group with sufficient detail to allow replication, including how and when they will be administered | 149-190; Figure 1 |
| | 11b | Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) | 191-199 |
| | 11c | Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) | 200-206 |
| | 11d | Relevant concomitant care and interventions that are permitted or prohibited during the trial | NA |
| Outcomes | 12 | Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended | 206-238 |
| Participant timeline | 13 | Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) | 187-190; Table 1 |

| | | | |
|---|---|---|---|
| Sample size | 14 | Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations | 240-255 |
| Recruitment | 15 | Strategies for achieving adequate participant enrolment to reach target sample size | 200-205; 252-255 |
| **Methods: Assignment of interventions (for controlled trials)** | | | |
| Allocation: | | | |
| Sequence generation | 16a | Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions | 187-190; Table 1 |
| Allocation concealment mechanism | 16b | Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned | 187-190 |
| Implementation | 16c | Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions | Table 1 |
| Blinding (masking) | 17a | Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how | Table 1 |
| | 17b | If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial | 191-199 |
| **Methods: Data collection, management, and analysis** | | | |
| Data collection methods | 18a | Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol | 206-238 |
| | 18b | Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols | 191-199; 200-205; 300-307 |

| | | | |
|---|---|---|---|
| Data management | 19 | Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol | 300-307 |
| Statistical methods | 20a | Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol | 279- 299 |
| | 20b | Methods for any additional analyses (eg, subgroup and adjusted analyses) | NA |
| | 20c | Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) | 191-199 |
| **Methods: Monitoring** | | | |
| Data monitoring | 21a | Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed | NA |
| | 21b | Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial | NA |
| Harms | 22 | Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct | 191-199 |
| Auditing | 23 | Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor | NA |
| **Ethics and dissemination** | | | |
| Research ethics approval | 24 | Plans for seeking research ethics committee/institutional review board (REC/IRB) approval | 133-134; 336 |
| Protocol amendments | 25 | Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) | ClinicalTrials.gov |

| | | | |
|---|---|---|---|
| Consent or assent | 26a | Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) | Table 1 |
| | 26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable | NA |
| Confidentiality | 27 | How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial | 187-199; 277-284 |
| Declaration of interests | 28 | Financial and other competing interests for principal investigators for the overall trial and each study site | 314-315 |
| Access to data | 29 | Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators | 191-199; 300-307; Table 1 |
| Ancillary and post-trial care | 30 | Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation | NA |
| Dissemination policy | 31a | Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions | 255-278 |
| | 31b | Authorship eligibility guidelines and any intended use of professional writers | BMJ guideline |
| | 31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code | NA |
| **Appendices** | | | |
| Informed consent materials | 32 | Model consent form and other related documentation given to participants and authorised surrogates | - |
| Biological specimens | 33 | Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable | NA |

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

# A randomised controlled clinical trial of a structured cognitive rehabilitation in patients with attention deficit following mild traumatic brain injury: Study protocol

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**Title:** A randomised controlled clinical trial of a structured cognitive rehabilitation in patients with attention deficit following mild traumatic brain injury: Study protocol.

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# TITLE: A randomised controlled clinical trial of a structured cognitive rehabilitation in patients with attention deficit following mild traumatic brain injury: Study protocol

## ABSTRACT

**Objectives:** Study objectives are to measure the change of attention deficits and to examine the effect of treatment on brain structures and daily life functions following intervention.

**Setting:** A single centre study, Malaysia.

**Participants:** All adult participants with the following inclusion criteria: mTBI as a result of road traffic accident; adult aged between 18 to 60 years old; no previous history of head trauma; minimum of nine years education; abnormal cognition at three months after mTBI; provision of informed consent and willingness to comply with cognitive rehabilitation program. The exclusion criteria include pre-existing chronic illness or neurological/psychiatric condition; on medication that alter or affect cognitive or psychological status; clinical evidence of substance intoxication at the time of injury; major polytrauma and absolute contraindication for Magnetic Resonance Imaging. Based on multiple estimated calculations, the minimum intended sample size to secure this study sample is 50 participants (Cohen's *d* effect size 0.35; alpha level of 0.05; 85% power to detect statistical significance; 40% attrition rate).

**Interventions:** Intervention group will receive individualised structured cognitive rehabilitation. Control group will receive best patient-centred care for attention disorders. Therapy frequency for both groups will be one hour per week for 12 weeks duration.

**Outcome measures:** S-NAB scores, Diffusion Tensor Imaging (DTI) parameters and Goal Attainment Scaling score (GAS).

**Results:** Results will include descriptive statistics of population demographics, CogniPlus Attention program and cognitive strategies. The effect of intervention will be the effect size of S-NAB scores and mean GAS T scores. DTI parameters will be compared between groups via repeated measure analysis and correlation analysis of outcome measures is via Pearson's correlation coefficient.

**Conclusion:** This is a complex clinical intervention with anatomical, clinical and functional outcome measures in order to establish a comprehensive evidence-based treatment model.

**Trial registration**: This study is registered with ClinicalTrials.gov ID NCT 03237676

## ARTICLE SUMMARY:

**Strengths and limitations of this study:**

- To our knowledge, this is the first randomized control trial of cognitive intervention in adult mTBI population, conducted in a developing country, Southeast Asia region.
- A study from this region with various ethnic involvements may better represent the study population and in turn add further knowledge on the pattern of the impairment following mTBI.
- This trial incorporates technology in the treatment application consistent with the changing face of health service delivery in Malaysia, aiming at resource efficiency and treatment effectiveness, albeit tailored treatment approach suitable for the local setting.
- Owing to the paucity of scientific and clinical knowledge, this trial will also contribute to the evidence-based cognitive treatment model for mTBI population.
- We anticipate challenge in the recruitment phase and treatment compliance due to known and reported high attrition rate in traumatic brain injury population.

## BACKGROUND

Mild traumatic brain injury (mTBI) is defined as a traumatic injury that induces transient physiological disruption of the brain function[1]. Mild TBI is often used interchangeably with concussion and is a clinical diagnosis[1]. The most common aetiology in the low and middle-income countries is road traffic accident (RTA) that disproportionately affects young men (15 to 29 years of age)[2-4]. Statistically, 20 to 50 million people sustained non-fatal injuries worldwide as a result of RTA and with an increasing rate in the developing countries[2,3].

Cognitive deficit is rarely singular in mTBI. Commonly reported symptoms are attention, memory and executive function deficits, each with varying severity and recovery pattern[5-14]. Specifically, attention deficit is extremely common in TBI[15,16]. Attention is known to be the basis of all other cognitive abilities[17]. About 40 to 60% of individuals with mTBI were reported to have attention deficits in the first three months post-injury[18]. In the majority of individuals, resolution of mixed cognitive deficits begins in the first month up to one-year post-injury[5,7,11,12,19-21]. A proportion of this population quite often progresses to have chronic cognitive disability that is overlooked due to the initial 'mild' presentation[6,10,22-25]. At least one-third of survivors fail to return to full functional status at six months and may continue to have neurocognitive functional deficits beyond one year of injury[5,12,25-29].

**Cognitive rehabilitation in mTBI**

Currently, there is no standard cognitive rehabilitation treatment for mTBI population[19]. The heterogeneity of cognitive deficits, varied intervention methodology, different reporting style and variable treatment outcomes[6,17,27,28,30-57] led to a challenge for professionals to come to an agreement on mTBI treatment[19]. The early neuropsychological model of attention has already made the assumption that attention should be the focus of rehabilitation, before more advanced cognitive skills be treated[33]. In the last 20 years, various cognitive treatment approaches have been reported in systematic reviews[34-37]. These include remediation strategies,[38-49], compensatory strategies[50-57] and patient education intervention[6,39,53,58]. These approaches are usually applied in combination, to optimise both cognitive and functional recovery[17,27,28,30,31,33- 38]. In particular, treatment for attention deficits in TBI was recommended at post-acute (3 months) stage of trauma[28,30,34,44]. Methods of treatment included multidimensional approach, and tasks with hierarchical difficulty and complexity[30,34,44]. Several studies also reported improved psychological outcome and coping of symptoms on those who received patient education and reassurance following mTBI[6,35,36]. However, these conclusions were based on a limited number of high-quality clinical trials. The consensus was for more robust clinical trials of larger sample size, well-described complex intervention and standardised reporting method [19,34-37,44,46].

Delivery of cognitive rehabilitation emphasizes six principles: 1) intervention that is theory-driven and meaningful, 2) intervention is task-specific with increasing complexity relevant to individual needs, 3) the need to regularly practice skills acquired, 4) progress monitoring to tailor to individual's needs, 5) generalisation of learnt strategies to apply in real-life skills, and 6) real-world adaptation to ensure success[17,49,59]. A practical, widely accepted treatment approach with the application of evidence-based treatment principles may represent a comprehensive treatment model in treating mTBI patients with cognitive deficits. A large randomised trial is required to support this hypothesis.

**Clinical, imaging and functional outcome measures in mTBI**

A combination of these three outcome measures is a comprehensive approach to analyse cognitive intervention that can make an impact in clinical practice. Scientific reviews and guidelines have recommended the use of neuropsychological assessment as an appropriate clinical outcome measure[17,27,28,30,31,33,34,36,37]. In adult mTBI, a test which was sensitive across various cognitive domains[21,24,41,43,53,57,60], specific to population study[24,40,43], had good validity and

reliability[41,51,57,61-64], was cost effective and practical to use in a clinical setting[53,62-64] would be ideal.

The structural injury in mTBI however, is too miniscule for detection through routine computed tomography (CT) and Magnetic Resonance Imaging (MRI)[65-67]. Over the last 10 years, Diffusion Tensor Imaging (DTI) has become accepted as a non-invasive tool that is able to quantify microstructural brain changes in mTBI[24,65-70]. Changes in its parameters are indicative of microstructural remodelling at acute and chronic stages of injury, potentially explaining the persistence of symptoms that would otherwise be attributed to other causes [24,65-70]. A longitudinal DTI study may increase our understanding of the brain structural transformation in mTBI.

The most important outcome following mTBI is the ability for survivors to return to their previous functional state and quality of life. Common scales to measure disability and function are usually sensitive to cognitive deficits but not necessarily specific to the TBI population[39-41,52,53]. Many studies have also reported specific outcome measures for TBI that has good validity, reliability and practical in a clinical setting[71-79], such as Goal Attainment Scaling[71,72,77-79], Extended Glasgow Outcome Scale[73] and Functional Assessment Measure[74].

This trial evaluates a complex clinical intervention, to provide evidence on the effect of cognitive rehabilitation in mTBI. We extend the outcome measures to include anatomical, clinical and functional aspects to establish a comprehensive evidence-based treatment model.

## METHODS

### Study hypothesis

We hypothesize that structured cognitive rehabilitation for attention deficits following mTBI will improve patients' cognitive function of attention compared to the standard care.

### Study objectives

The objectives are:

- to measure the clinical effect of a 12-week individualized structured cognitive rehabilitation to address attention deficit and overall cognitive status via S-NAB assessment
- to examine the effect of treatment on brain structures via DTI
- to analyse the functional changes following treatment via GAS and participant's feedback

- to correlate the clinical effect following cognitive rehabilitation with structural brain changes and participant's overall functional outcomes

**Design**

This will be a prospective double blind, randomized controlled trial with two parallel groups. The study design is summarized in **Figure 1**.

**Participants and recruitment process**

This trial will be conducted at a single centre, University Malaya Medical Centre (UMMC), Malaysia. UMMC is a government funded and an academic medical institution situated in the urban area of the nation's capital city Kuala Lumpur with the population of 1.76 million. Apart from providing acute medical services, this hospital is also a tertiary referral and training centre in Malaysia. UMMC also has Department of Rehabilitation Medicine that provides the facility for this study. These include main rehabilitation services (neuro-, spinal cord-, prosthetic and orthotic-, paediatric- and cardiac rehabilitation) for both inpatient and outpatient setting. Other services also include return to work/drive rehabilitation.

We will recruit participants through the Emergency Medicine Department (ED), UMMC from 1st August 2017. ED physicians, radiologists and neurosurgeons will refer mTBI cases to a research assistant for recruitment. Potential cases will also be screened through UMMC digital medical record system. Screening stages will be performed at 72 hours, two and six weeks following mTBI.

**Inclusion criteria**

Mild TBI is defined as physiological disruption of brain function as a result of trauma with symptoms of loss of consciousness 30 minutes or less, focal neurological deficit that may/may not be transient, altered mental state with Glasgow Coma Scale of 13-15 and loss of memory with post traumatic amnesia not greater than 24 hours. The inclusion criteria for this study are mTBI as a result of RTA; adult aged between 18 to 60 years old; Malaysia citizen; no previous history of head trauma; minimum of nine years education; persistently abnormal S-NAB Attention Domain score at three months of mTBI; ability to give consent and willingness to comply with cognitive rehabilitation program. Persistently abnormal S-NAB Attention Domain score is defined as Standard Score <85 (below average category) at screening phase and at enrolment phase as set by the NAB test manual (Table 1).

**Exclusion criteria**

The exclusion criteria include pre-existing chronic illness that cause neurological symptoms or complications; severe comorbid neurological or psychiatric disorder; on long-term medication that alter or affect cognitive and psychological status; clinical evidence of substance intoxication at the time of injury; major polytrauma and absolute contraindication for MRI (metal or implant not compatible for MRI, claustrophobia) (Table 1).

| Inclusion criteria | | | |
|---|---|---|---|
| **Criteria** | **IG** | **SG** | **HG** |
| 18-60 years old of age | ✓ | ✓ | ✓ |
| No previous history of head trauma | ✓ | ✓ | ✓ |
| Minimum of 9 years education | ✓ | ✓ | ✓ |
| Consented | ✓ | ✓ | ✓ |
| mTBI as a result of motor vehicle accidents only | ✓ | ✓ | |
| Abnormal S-NAB Attention Domain score at 3 months of mTBI | ✓ | ✓ | |
| Willingness to comply with rehabilitation program | | | |

| Exclusion criteria | | | |
|---|---|---|---|
| **Criteria** | **IG** | **SG** | **HG** |
| Pre-existing chronic illness or neurological or psychiatric condition | ✓ | ✓ | ✓ |
| On long term medication that can alter or affect cognitive and/or psychological status | ✓ | ✓ | ✓ |
| Clinical evidence of alcohol intoxication at the time of injury | ✓ | ✓ | |
| Major polytrauma (multiple bone fractures, nerve injury) | ✓ | ✓ | |
| Absolute contraindication for MRI | ✓ | ✓ | |

**Table 1**: The study criteria.
Note: IG-individualised structured cognitive rehabilitation group; SG- standard care group, HG- healthy control group

**Intervention**

Potential participants will undergo screening before enrolment and randomization (**Figure 1)**. Education component will include reassurance on recovery, self-monitoring of symptom(s) and advice on gradual return to daily activities and physical exertion. Symptom(s) evaluation will include clinical review of physical, cognitive and psychological status. The first medical responder i.e. ED physicians will perform this at 72 hours of injury. At two weeks and six weeks of injury, a rehabilitation medicine physician who is

not involved with the study (RP-1) will repeat the education component and symptom evaluation. Early treatment or referral to other medical speciality will be made if indicated during these reviews.

At three months after injury, potential participants will undergo a repeat of clinical review and S-NAB test. Participants with persistently abnormal Attention Domain score (standard domain score <85) will be enrolled in the study. However, those with other cognitive domain deficit(s) (standard domain score <85) other than Attention Domain will also be included in the study and will receive treatment for attention following randomization. The concomitant domain deficit(s) will also be evaluated upon completion of therapy. The cognitive intervention will be conducted at the Neurorehabilitation Therapy Unit, Department of Rehabilitation Medicine, UMMC in an outpatient setting. Participants will be assigned to different treatment groups via randomization process. Written records of intervention will be prepared and kept by the therapist of each treatment arm until treatment completion. This include participant's goals, symptom(s), cognitive strategy/method and participant's feedback.

***Individualised structured cognitive rehabilitation group***

Intervention group participants will receive a two-part 12-week individualized structured cognitive rehabilitation. The first part is Direct Attention Training (DAT), a deficit-oriented computer-based attention-training program called CogniPlus[45]. Each session will be 30 minutes, once a week.

CogniPlus is a computer-based software program with interactive multimedia approach for multiple attention cognitive training modules. The training programs are ALERT (focused and sustained attention), FOCUS (focused attention), VIG (sustained attention), SELECT (selective attention) and DIVID (divided attention). Each attention-training category is designed based on real-life scenarios and the screen graphics are three-dimensional. This program has artificial intelligence capacity that can automatically adapt to an individual's performance and alter the training difficulty level (hierarchical difficulty).

The second part of this intervention is strategy approach (metacognitive awareness and compensatory strategy) performed after CogniPlus training. Metacognitive awareness includes feedback on participant's CogniPlus performance to improve participant's awareness of impairment severity. This process is intended to regulate their learning experience and in turn instil the practise of self-monitoring and self-regulation through learning activities. Compensatory strategy component involves applying the cognitive awareness in recognizing impairment that is present in daily activities followed by the application of cognitive methods to ameliorate the deficits aiming to maximise daily functioning. A participant will

identify the deficit(s) and will apply problem-solving method(s) learnt from the therapist. Feedback and review of performance will be done again in the following therapy session. This session will last for 30 minutes and a will be conducted by a trained and certified Occupational Therapist (OT-1) in cognitive therapy and CogniPlus.

***Standard care group***

This group will receive the best standard care for attention disorders. This is a patient-centred cognitive therapy. It is based on a patient's complaint(s), symptom(s) and therapy aim(s) (self-realization of deficits or guided by therapist). Symptom(s) management may include physical (e.g. imbalance, fatigue, sleep dysregulation), psychological (e.g. mild anxiety or depression) and cognitive (e.g. forgetfulness). Referral to relevant service(s) may be required such as physiotherapy, return to work/drive rehabilitation and counselling, Compensatory strategy includes task specific training (patient-prioritised) e.g. return to drive may involve driving simulation training, visuospatial training and return to drive rehabilitation service. The frequency of sessions will be one hour per week, for 12 weeks. A trained occupational therapist in cognitive therapy (OT-2) who is not involved with the intervention group treatment, will conduct all the sessions (Table 2).

***Control group***

This will consist of healthy individuals demographically matched for age, gender and education years to the intervention groups (Table 1). The data is collected for comparison purpose.

**Randomisation, consent and blinding**

Participants with mTBI who fulfil the study criteria will be randomized via computer-generated random permuted block assignment, gender-stratified into equally proportioned intervention and control group numbers. The study schedule, procedures and blinding of co-investigators are presented in **Table 2.**

| | STUDY PERIOD | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Enrolment | Enrolment | Enrolment | Allocation | Post-allocation | | | | | | End of treatment |
| **TIMEPOINT**** | | $-t_3$ *72 hours mTBI* | $-t_2$ *2 weeks mTBI* | $-t_1$ *6 weeks mTBI* | **0** 3 months mTBI | $t_1$ | $t_2$ | $t_3$ | $t_4$ | $t_5$ | $t_{12}$ | $f_1$ *6 months mTBI* |
| | **Co-investigator (initials)** | *Pre-study screening* | *Pre-study screening* | *Pre-study screening* | *Baseline/ Randomisation* | *Study Visit 1* | *Study visit $t_2$ onwards* | | | | *Last study visit* | *Outcome measures* |
| **ENROLMENT:** | | | | | | | | | | | | |
| **Eligibility screen** | Research assistant | X | X | | | | | | | | | |
| **Informed consent** | MM | | | | X | | | | | | | |
| **Allocation** | MM | | | | X | | | | | | | |
| **S-NAB Test (Form 1)** | NH | | X | | | | | | | | | X |
| **S-NAB Test (Form 2)** | NH | | | | X | | | | | | | |
| **DTI test** | VN/NR | | | | X | | | | | | | X |
| **DTI post processing** | TLK | | | | X | | | | | | | X |
| **GAS** | NAM (OT-1) & NAMT (OT-2) | | | | | X | X | X | X | X | X | X |
| **INTERVENTIONS:** | | | | | | | | | | | | |
| **Education component/ symptom(s) evaluation** | ED team/RP-1 | X (ED team) | X (RP-1) | X (RP-1) | | | | | | | | |
| **Individualized structured cognitive rehabilitation** | NAM (OT-1) | | | | | X | X | X | X | X | X | |
| **Best standard care** | NAMT (OT-2) | | | | | X | X | X | X | X | X | |
| **OUTCOME MEASURES:** | | | | | | | | | | | | |
| **S-NAB Test** | NH | | | | X | | | | | | | X |
| **DTI** | VN/NR | | | | X | | | | | | | X |
| **GAS** | NAM/NAMT (OT-1/OT-2) | | | | | X | X | X | X | X | X | X |

**Table 2:** Study schedule and procedures.

**Modification, withdrawal and unblinding within the intervention**

Participants can withdraw their consent from this study at any time and for any reason. Investigators can also withdraw a participant from the study if he/she becomes non-compliant with the treatment protocol. This include poor treatment attendance, poor therapy participation or participant's request for withdrawal from study. We will also provide our participant who requires immediate medical attention or treatment that is otherwise not part of the study intervention throughout the study duration. In the case where unblinding of a participant is necessary (e.g. medical emergency), an investigator (MM) will be informed of the cause and stage of intervention received by the participant. He/she may continue in the study and follow all study procedures. The participant will only be withdrawn from this study if the immediate treatment violates our study criteria. We will retain all of participant's data (although the participant is no longer blinded) or up to the point of participant's removal from the study.

**Adherence strategies**

Adherence to treatment is enabled throughout the intervention for both groups. This will be achieved by providing: 1) participants with clear information on purpose, method and treatment goals during treatment sessions, 2) an appointment card with specific date and time of therapy sessions, and 3) a reminder through phone calls a day before each therapy appointment and a week before DTI scan date.

**Outcome measures**

All measures will be performed at baseline and at the end of the intervention. The primary outcome measure of this study is the change of attention deficit and other cognitive domains within intervention groups and direct comparison of each intervention group with the healthy control group. This will be measured by Neuropsychological Assessment Battery® (NAB®, PAR, Inc., Florida, USA)[61]. It consists of six modules: Screening Module and five Domain Specific Modules: Attention, Language, Memory, Spatial and Executive Function. This study will only apply the Screening Module (S-NAB) because it measures the same five functional domains similar or identical to the main NAB modules. It consists of 12 individual tests screening all five mentioned cognitive domains for adults aged 18 to 97 years, validated and sensitive for use in healthy and cognitively impaired brain injured population[24,61-64]. S-NAB also provides two parallel assessment sets (Record Form 1 and Form 2) that will be applied in an alternate fashion to participants in both groups to avoid practice effect.

S-NAB Domain Attention test items and score are interpreted as a marker of an individual's attentional capacity, working memory, psychomotor speed, selective attention, divided attention and information processing [61]. S-NAB has also been applied in our previous cohort study [24] with good validation outcome in our Malaysian mTBI population.

The secondary outcome measures are microstructural WMT parameters and functional GAS scores. The DTI MRI scan is a Siemens Magnetom Prisma 3T MRI (Siemens AG, Muenchen, Germany). This study will analyse Fractional Anisotropy (FA), Mean Diffusivity (MD) and Radial Diffusivity (RD) parameter changes at pre- and post-intervention[24,65-70]. These parameters quantify the direction and degree of tissue water diffusion within the WMT[65,66]. FA which measures the direction of the diffusion is an index expressed in a range from 0-1, with a higher score indicating a higher integrity of white matter consisting of highly parallel fibres[65,66]. MD measures the average magnitude of the diffusion while RD quantifies pathology in the myelin[65,66]. Changes in the index values of the parameters at different injury timeline will indicate the pathological changes of the WMT.

The tool to measure functional outcome is GAS[77-79]. The difficulty and importance of rehabilitation goals will be individually set according to his/her current levels of functional performance to underline a realistic expectation. The sensitivity of GAS is increased by the quantifiable set goals relevant and specific to the participant. Each goal is rated on a 5-point scale and score is given on the extent to which a patient's individual goals are achieved in the course of the intervention. The overall GAS scores calculation will generate a standardized measure (T score) (mean of 50 Standard Deviation ± 10). The details of each goal outcome will be recorded in the GAS Record Sheet[77-79] by a cognitive therapist of each study arm (OT-1 and OT-2) trained in GAS application.

Another important factor to note is participant's psychological status following mTBI. This study will also perform screening of anxiety and depression symptoms by using the Generalised Anxiety Disorder 7-item (GAD7) and Patient Health Questionnaire-9 (PHQ-9) screening tools at each study timeline. Participant's lifestyle changes will also be reviewed and recorded. Although these parameters will not be part of the study outcome measure, they however remain relevant in influencing treatment adherence and outcome.

**Sample size and power calculation**

In order to fulfil our study objectives we will base the intended sample size calculation on a previous study that had applied similar treatment approach and with one similar outcome measure to our study[40]. This study applied the non-commercial statistical power analysis program G*Power Version 3.1.9.2. An effect size of 0.58, which was the functional cognitive outcome of attention [40], is used to calculate the statistical power *a priori.* We will apply Analysis of Variance (ANOVA): repeated measures, within-between interaction, setting an alpha level of 0.05, and approximately 10 participants will provide 89% power to detect a statistical significance. Recruitment is doubled (n=20) for both arms and inflated to 28 to counter 40% attrition rate.

To have a bigger sample size, we, therefore, also decided on a more conservative effect size value and calculated the sample size through estimation of Cohen's *d* effect size value of 0.35. By using similar statistical power analysis program, medium effect size Cohen's *d* of 0.35, setting an alpha level of 0.05, approximately 38 participants will provide 85% power to detect statistical significance. Recruitment will be inflated to 50 participants to enable a 40% attrition rate.

Based on the multiple estimated calculations, the minimum intended sample size to secure this study sample is therefore 50 participants. Based on our UMMC local data, a 12 months data collection is sufficient to yield the target sample size.

**Ethics considerations**

This study was approved by Medical Research Ethics Committee, UMMC (MREC ID NO: 2016928-4293). We will obtain written consent from adult participants. During consenting, participant will be provided with Patient Information Sheet detailing the purpose of study, reason for participation, study investigation and intervention methods, withdrawal from study and contact details of investigators. Once consent is given the form and all other documents with participant's personal details will be stored immediately in a locked filing cabinet by the consent taker and is accessible only to several investigators. Study ID code will be allocated upon consenting and subsequent study documentation will only use the ID code.

Other matters also include 1) early information sharing of treatment/investigation results in the event of incidental clinical findings that requires urgent treatment by other medical speciality, 2) treatment compliance, 3) cost of investigation and treatment and 4) participant involvement in litigation issues. In

the event where information sharing is required for medical reasons, the participant will be informed immediately followed by referral to relevant professional either based at UMMC or a different centre of choice. However, cost of further investigation or treatment that is not part of this study is not funded by the study grants. Treatment compliance is achieved through our adherence strategy. We strictly adhere to the privacy and confidentiality of participant's medical information. Any information sharing with a third party for various reasons will be managed in accordance with UMMC professional and legal code of conduct.

**Patient and public involvement**

We applied the Medical Research Council (MRC) Developing and Evaluating Complex Intervention: New Guidance (2006) and Multiphase Optimization Strategy (MOST) framework to guide the development of this study. The choice of deficit to treat was based on the relevant theoretical evidence whereas treatment approach was evinced through our systematic review, clinical experience and practice setting of interest. We conducted 1) a pilot study and 2) Expert Panel review to evaluate the study design and treatment method that may require further focus.

Our pilot study was approved by Medical Research Ethics Committee, UMMC, Malaysia (UM/EC Ref: 947.15) for the application of cognitive treatment on mTBI patients. They were involved in the testing of treatment method, clinical practicality, fidelity of treatment and treatment compliance. We have identified several components required for optimization of intervention. These findings were also assessed by the Expert Panel reviewers.

The panel comprised of clinicians who were credentialed in brain injury management and cognitive rehabilitation with minimum of 10 years clinical experience in Malaysia. Panels were made up of seven rehabilitation medicine consultants, one neurosurgeon consultant, one neuroimaging consultant, five cognitive occupational therapists and one clinical psychologist. The focus of discussion was on the feasibility of structured cognitive rehabilitation for mTBI patients in Malaysia, guided by the current evidence, current practise of cognitive rehabilitation in local setting, reviewers clinical experience and our pilot study findings. A summary of the pilot study outcomes and Expert Panel recommendations are best illustrated in Table 3.

Following the commencement of this study, the input from participants (experience, feedback and outcomes) will be recorded. The data and study materials belong to UMMC, Malaysia. We will inform the result of the study to our participants following its completion even if he/she did not complete the study unless he/she has requested not to be contacted.

| Pilot study | Expert panel review |
|---|---|
| Design: a case-controlled study<br>Study components:<br>**Non-randomisation** –to identify participant's willingness to attend therapy as a measure of good compliance.<br>**Treatment application** - treatment was given at early stage of injury (2 weeks post injury) to measure the treatment effect versus spontaneous' recovery.<br>**Treatment accessibility** – outpatient hospital-based treatment is feasible.<br>**Treatment compliance**–high attrition rate (50%) which compromised the treatment fidelity. Reasons for poor treatment compliance were:<br>• treatment frequency and intensity (>1 hour/weekly for the first 3 months followed by monthly session the following 3 months)<br>• mental fatigue<br>• 'unreadiness' to receive treatment<br>• treatment and transportation costs<br>• work demand (limited time off work and income lost)<br><br>**Treatment method-** clinical application of treatment was acceptable to participants.<br>**Treatment effect** - the application of effect size measurement is consistent with MOST recommendation.<br>**Outcome measure application** –S-NAB was able to measure score differences in its five domains. DTI parameters reported changes consistent with current literature evidence in mTBI population. | Design: Randomization was recommended in clinical trial design<br>Review components:<br>**Fidelity of treatment**<br>1) clear information on purpose, method and treatment goals during treatment sessions<br>2) an appointment card with specific date and time of therapy sessions<br>3) a reminder through phone calls a week and a day before each therapy<br>4) Review at 72 hours, 2 weeks, 6 weeks, and 3 months (baseline) to increase sensitivity towards participant selection, early medical intervention if required and to improve adherence.<br>**Treatment method**<br>1) as outpatient setting, with frequency 1hour/week for 12 weeks duration.<br>2) individualised treatment approach with standardization through direct attention training and metacognitive strategy<br>3) to clarify the metacognitive strategies applied in therapy such as 'self-monitoring', self-instructional procedure', 'self-evaluation', 'rehearsal', 'self-pacing', 'positive self-statement', use of internal/external strategy<br>**Outcome measure**<br>Neuropsychological assessment as a practice standard<br>Guided individualised goals (GAS application) to standardise the functional outcome measurement for both groups. |

**Table 3**: A summary of recommendations from pilot study findings and Expert Panel review

**Statistical analysis**

Descriptive statistics will be conducted on the data yielded from all groups to give a demographic overview of our study population. A $p$ value <0.05 will be considered statistically significant. We will also report additional relevant data, which may affect the study outcome. This will include lifestyle modifications, litigation cases, changes in socioeconomic status, physical symptoms and psychological status.

The measure of treatment effect is via neuropsychological assessment score changes. We will calculate the effect size of each S-NAB mean Domain Standard score (Attention, Language, Memory, Spatial and Executive Function domains) as well as the Total Index Score within each intervention group. Cohen's $d$ moderate (>0.5) to large effect size (>0.8) are considered to be clinically significant. Another treatment effect analysis also includes reporting on the CogniPlus Attention task difficulty level achieved for each program (ALERT, FOCUS, VIG, SELECT, DIVID), the change of response time and measurement of errors.

Similarly, functional changes will be measured by using the effect size calculation of mean GAS T scores obtained at pre and post intervention. We will also compare the mean change in GAS T score between groups and report on the type and preference of metacognitive strategies used by participants of both groups.

The secondary analysis will include measurement of structural brain changes following intervention. This data will be obtained from the DTI MRI scan performed at pre and post intervention, for all groups. We will identify FA, MD and RD parameters with statistically significant mean values ($p<0.05$) via whole brain analysis known as Tract-based Spatial Statistics (TBSS)[80] and region of interest (ROI) approach which is part of the FSL (v5.0.6; University of Oxford, Oxford UK) [81] and AFNI (v2011_12_21_1014; National Institute of Mental Health, Bethesda, MD) software packages. The DTI parameters of both intervention groups at three- and six months study timelines will be compared with the healthy control group by using repeated measure analysis. This is in the assumption that the study fulfils the repeated measure analysis of normally distributed data sample and homogeneity of variance.

Further analysis also includes correlation of cognitive performance with structural brain changes. We will perform Pearson's correlation coefficient between mean S-NAB Standard score of each domain and the selected WMT (with statistical significant).

**Data management**

All data obtained including from non-adherence or voluntarily withdrawn participants will also be reviewed and included in the study analysis where applicable. All study documents will be securely kept at the study site. Participant information will be stored in locked filing cabinets and will only be accessible to selected investigators. All data documents, administrative forms, reports and analysis documents will only have coded participant ID to avoid identification by any investigator of the study. Data entry will only be performed by an appointed research assistant. Any other document that has a participant's name such as consent form will be kept in a separate cabinet accessible by a selected investigator (MM).

## Discussion

To our knowledge, this is the first randomized control trial of cognitive intervention in adult mTBI population, conducted in a developing country, Southeast Asia region. Previous studies have been done in the Western population with a predominantly Caucasian ethic group and limited ethnic variation. A study from this region with various ethnic involvements of both genders may better represent the study population and in turn add further knowledge on the pattern of the impairment following mTBI. Uniquely, cultural practice and belief system may also influence treatment response and outcome. Development of the intervention approach was based on current evidence, a pilot study and Expert Panel review. This trial incorporates technology in the treatment application consistent with the changing face of health service delivery in Malaysia, aiming at resource efficiency and treatment effectiveness, albeit tailored treatment approach suitable for the local setting. The results of this study will provide a comprehensive overview on the effect of cognitive rehabilitation in mTBI. Owing to the paucity of scientific and clinical knowledge, this trial will also contribute to the evidence-based cognitive treatment model for mTBI population.

## Trial status

At the time of manuscript preparation, 30 potential participants have been recruited at three months post-injury. Fifteen participants were consented and received treatment following randomization. Recruitment is due to finish in April 2019. Data lock has not yet occurred and no analyses have been performed.

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## Declarations

The authors declare that they have no competing interests.

## Acknowledgement

We wish to thank all our mTBI participants involved in the pilot control study as well as Expert Panels in involved in the review of our intervention development and study.

## Authors' contribution

NH initiated the study, applied for study funding and is the principal investigator. NH, MM, VN, NR, AD, RDN and GSY were involved in the conception, development of the intervention and design of the study. NAM and NAMT implemented the cognitive intervention. TLK provided the consultation on DTI processing and analysis. MD and NM provided important statistical contributions. All authors provided feedback on drafts of this paper, read and approved the final manuscript. NH, MM, VN and NR are the guarantors for the study and accept full responsibility for the work and /or the conduct of the study, had access to data, and controlled the decision to publish. MM is the corresponding author and attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

## Availability of data and material

The data and study materials belong to UMMC, Malaysia. Any request will have to go through Medical Record Department of UMMC, Malaysia. Dissemination of trial result is through publication.

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**Figure 1**: Flowchart showing the stages of recruitment in this study.

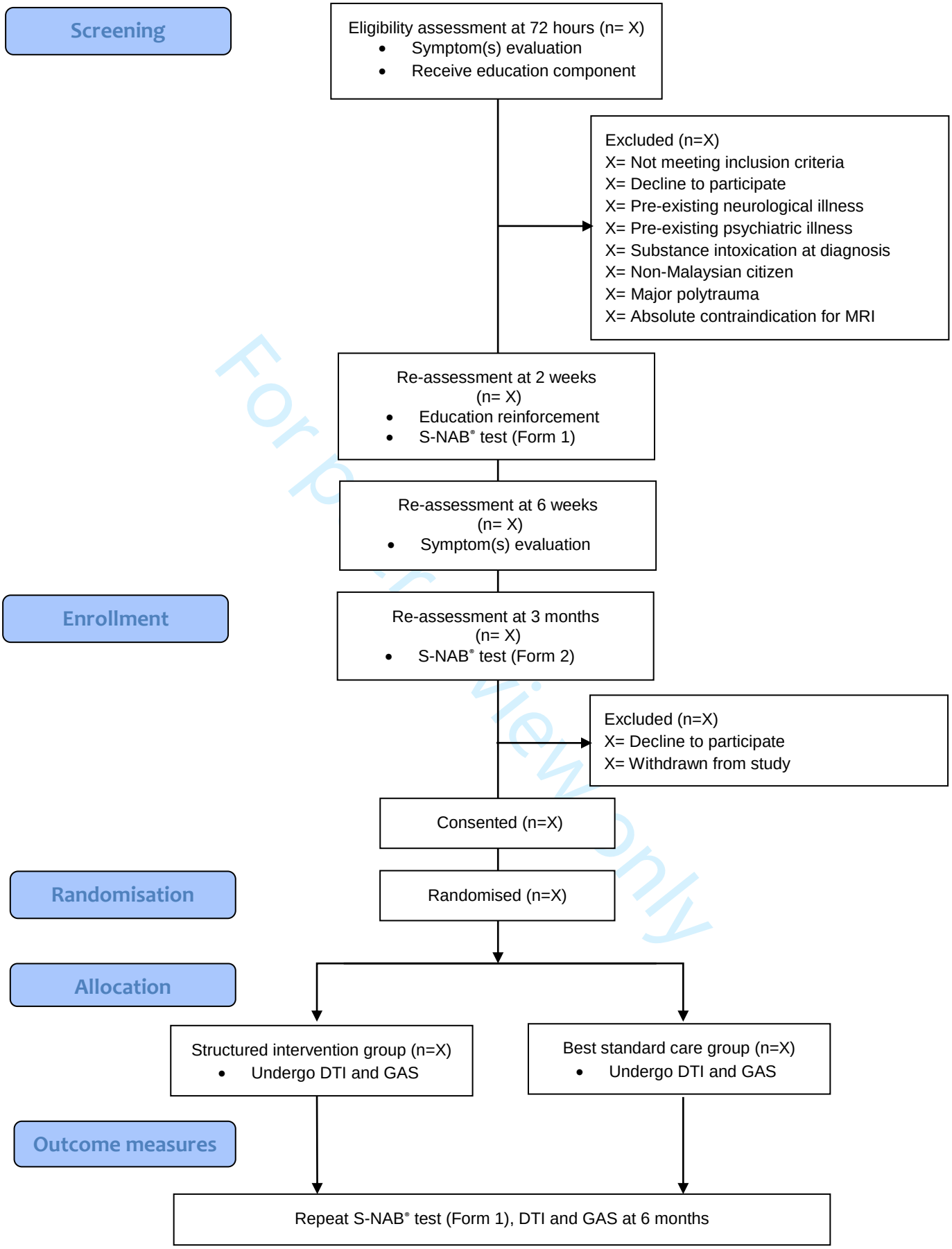


**Figure 1**: PRISMA flowchart showing the stages of recruitment in this study.

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

| Section/item | Item No | Description | Addressed on line number |
|---|---|---|---|
| **Administrative information** | | | |
| Title | 1 | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym | 1-2 |
| Trial registration | 2a | Trial identifier and registry name. If not yet registered, name of intended registry | 380-383 |
| | 2b | All items from the World Health Organization Trial Registration Data Set | 376-383 |
| Protocol version | 3 | Date and version identifier | 380-383 |
| Funding | 4 | Sources and types of financial, material, and other support | 376-379 |
| Roles and responsibilities | 5a | Names, affiliations, and roles of protocol contributors | 389-397 |
| | 5b | Name and contact information for the trial sponsor | 383 |
| | 5c | Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities | NA<br>NA |
| | 5d | Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) | NA |

| | | | |
|---|---|---|---|
| **Introduction** | | | |
| Background and rationale | 6a | Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention | 44-105 |
| | 6b | Explanation for choice of comparators | 44-105 |
| Objectives | 7 | Specific objectives or hypotheses | 107-117 |
| Trial design | 8 | Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) | 118-132; Figure 1 |
| **Methods: Participants, interventions, and outcomes** | | | |
| Study setting | 9 | Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained | 122-128 |
| Eligibility criteria | 10 | Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) | 133-150, Table 1 |
| Interventions | 11a | Interventions for each group with sufficient detail to allow replication, including how and when they will be administered | 151-203; Figure 1 |
| | 11b | Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) | 208-218 |
| | 11c | Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) | 219-223 |
| | 11d | Relevant concomitant care and interventions that are permitted or prohibited during the trial | NA |
| Outcomes | 12 | Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended | 224-262 |
| Participant timeline | 13 | Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) | 204-207; Table 2 |

| | | | |
|---|---|---|---|
| Sample size | 14 | Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations | 263-279 |
| Recruitment | 15 | Strategies for achieving adequate participant enrolment to reach target sample size | 219-223; 263-279 |
| **Methods: Assignment of interventions (for controlled trials)** | | | |
| Allocation: | | | |
| Sequence generation | 16a | Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions | 204-207; Table 2 |
| Allocation concealment mechanism | 16b | Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned | 204-207; Table 2 |
| Implementation | 16c | Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions | Table 2 |
| Blinding (masking) | 17a | Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how | Table 2 |
| | 17b | If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial | 208-218 |
| **Methods: Data collection, management, and analysis** | | | |
| Data collection methods | 18a | Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol | Figure 1;204-207; Table 2; 208-262;298-321;Table 3 |
| | 18b | Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols | 208-223 |

| | | | |
|---|---|---|---|
| Data management | 19 | Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol | 350-357 |
| Statistical methods | 20a | Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol | 322-349 |
| | 20b | Methods for any additional analyses (eg, subgroup and adjusted analyses) | NA |
| | 20c | Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) | 208-218 |
| **Methods: Monitoring** | | | |
| Data monitoring | 21a | Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed | NA |
| | 21b | Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial | NA |
| Harms | 22 | Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct | 208-218 |
| Auditing | 23 | Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor | NA |
| **Ethics and dissemination** | | | |
| Research ethics approval | 24 | Plans for seeking research ethics committee/institutional review board (REC/IRB) approval | 280-297 |
| Protocol amendments | 25 | Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) | ClinicalTrials.gov |

| | | | |
|---|---|---|---|
| Consent or assent | 26a | Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) | Table 2 |
| | 26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable | NA |
| Confidentiality | 27 | How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial | 208-218;350-357 |
| Declaration of interests | 28 | Financial and other competing interests for principal investigators for the overall trial and each study site | 376-385 |
| Access to data | 29 | Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators | 350-357;Table 2 |
| Ancillary and post-trial care | 30 | Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation | NA |
| Dissemination policy | 31a | Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions | 298-321 |
| | 31b | Authorship eligibility guidelines and any intended use of professional writers | BMJ guideline |
| | 31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code | NA |
| **Appendices** | | | |
| Informed consent materials | 32 | Model consent form and other related documentation given to participants and authorised surrogates | - |
| Biological specimens | 33 | Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable | NA |

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

# A randomised controlled clinical trial of a structured cognitive rehabilitation in patients with attention deficit following mild traumatic brain injury: Study protocol

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| | |

**Title:** A randomised controlled clinical trial of a structured cognitive rehabilitation in patients with attention deficit following mild traumatic brain injury: Study protocol.

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**Word count: 4802**

# TITLE: A randomised controlled clinical trial of a structured cognitive rehabilitation in patients with attention deficit following mild traumatic brain injury: Study protocol

## ABSTRACT

**Objectives:** To measure the clinical, structural and functional changes of an individualized structured cognitive rehabilitation in mild traumatic brain injury (mTBI) population.

**Setting:** A single centre study, Malaysia.

**Participants:** Adults aged between 18 to 60 years with mTBI as a result of road traffic accident, with no previous history of head trauma, minimum of nine years education and abnormal cognition at three months will be included. The exclusion criteria include pre-existing chronic illness or neurological/psychiatric condition, long-term medication that affects cognitive/psychological status, clinical evidence of substance intoxication at the time of injury and major polytrauma. Based on multiple estimated calculations, the minimum intended sample size is 50 participants (Cohen's *d* effect size 0.35; alpha level of 0.05; 85% power to detect statistical significance; 40% attrition rate).

**Interventions:** Intervention group will receive individualised structured cognitive rehabilitation. Control group will receive best patient-centred care for attention disorders. Therapy frequency for both groups will be one hour per week for 12 weeks.

**Outcome measures:** *Primary*: Neuropsychological Assessment Battery-Screening Module (S-NAB) scores. *Secondary:* Diffusion Tensor Imaging (DTI) parameters and Goal Attainment Scaling score (GAS).

**Results:** Results will include descriptive statistics of population demographics, CogniPlus cognitive program and metacognitive strategies. The effect of intervention will be the effect size of S-NAB scores and mean GAS T scores. DTI parameters will be compared between groups via repeated measure analysis. Correlation analysis of outcome measures will be calculated using Pearson's correlation coefficient.

**Conclusion:** This is a complex clinical intervention with multiple outcome measures to provide a comprehensive evidence-based treatment model.

**Trial registration**: This study is registered with ClinicalTrials.gov ID NCT 03237676

**Ethics and Dissemination:** The study protocol was approved by the Medical Research Ethics Committee, UMMC (MREC ID NO: 2016928-4293). The findings of the trial will be disseminated through peer-reviewed journals and scientific conferences.

## ARTICLE SUMMARY:

**Strengths and limitations of this study:**

- To our knowledge, this is the first randomized controlled trial of cognitive intervention in an adult mTBI population, conducted in a developing country (Southeast Asia region).
- A study from this region with various ethnic groups may better represent the study population and in turn add further knowledge on the pattern of the impairment following mTBI.
- This trial incorporates technology in the intervention arm consistent with the changing face of health service delivery in Malaysia, aiming at resource efficiency and treatment effectiveness, albeit the tailored treatment approachis suitable for the local setting.
- Owing to the paucity of scientific and clinical knowledge, this trial will also contribute to the evidence-based cognitive treatment model for mTBI population.
- We anticipate challenge in the recruitment phase and treatment compliance due to known and reported high attrition rate in the traumatic brain injury population.

## BACKGROUND

Mild traumatic brain injury (mTBI) is defined as a traumatic injury that induces transient physiological disruption of the brain function[1]. Mild TBI is often used interchangeably with concussion and is a clinical diagnosis[1]. The most common aetiology in the low and middle-income countries is road traffic accident (RTA) that disproportionately affects young men (15 to 29 years of age)[2-4]. Statistically, 20 to 50 million people sustained non-fatal injuries worldwide as a result of RTA and with an increasing rate in the developing countries[2,3].

Cognitive deficit is rarely singular in mTBI. Commonly reported symptoms are attention, memory and executive function deficits, each with varying severity and recovery pattern[5-14]. Specifically, attention deficit is extremely common in TBI[15,16]. Attention is known to be the basis of all other cognitive abilities[17]. About 40 to 60% of individuals with mTBI were reported to have attention deficits in the first three months post-injury[18]. In the majority of individuals, resolution of mixed cognitive deficits begins in the first month up to one-year post-injury[5,7,11,12,19-21]. A proportion of this population quite often progresses to have chronic cognitive disability that is overlooked due to the initial 'mild' presentation[6,10,22-25]. At least one-third of survivors fail to return to full functional status at six months and may continue to have neurocognitive functional deficits beyond one year of injury[5,12,25-29].

**Cognitive rehabilitation in mTBI**

Currently, there is no standard cognitive rehabilitation treatment for mTBI population[19]. The heterogeneity of cognitive deficits, varied intervention methodology, different reporting style and variable treatment outcomes[6,17,27,28,30-57] led to a challenge for professionals to come to an agreement on mTBI treatment[19]. The early neuropsychological model of attention has already made the assumption that attention should be the focus of rehabilitation, before more advanced cognitive skills be treated[33]. In the last 20 years, various cognitive treatment approaches have been reported in systematic reviews[34-37]. These include remediation strategies,[38-49], compensatory strategies[50-57] and patient education intervention[6,39,53,58]. These approaches are usually applied in combination, to optimise both cognitive and functional recovery[17,27,28,30,31,33- 38]. In particular, treatment for attention deficits in TBI was recommended at post-acute (3 months) stage of trauma[28,30,34,44]. Methods of treatment included multidimensional approach, and tasks with hierarchical difficulty and complexity[30,34,44]. Several studies also reported improved psychological outcome and coping of symptoms on those who received patient education and reassurance following mTBI[6,35,36]. However, these conclusions were based on a limited number of high-quality clinical trials. The consensus was for more robust clinical trials of larger sample size, well-described complex intervention and standardised reporting method [19,34-37,44,46].

Delivery of cognitive rehabilitation emphasizes six principles: 1) intervention that is theory-driven and meaningful, 2) intervention is task-specific with increasing complexity relevant to individual needs, 3) the need to regularly practice skills acquired, 4) progress monitoring to tailor to individual's needs, 5) generalisation of learnt strategies to apply in real-life skills, and 6) real-world adaptation to ensure success[17,49,59]. A practical, widely accepted treatment approach with the application of evidence-based treatment principles may represent a comprehensive treatment model in treating mTBI patients with cognitive deficits. A large randomised trial is required to support this hypothesis.

**Clinical, imaging and functional outcome measures in mTBI**

A combination of these three outcome measures is a comprehensive approach to analyse cognitive intervention that can make an impact in clinical practice. Scientific reviews and guidelines have recommended the use of neuropsychological assessment as an appropriate clinical outcome measure[17,27,28,30,31,33,34,36,37]. In adult mTBI, a test that is sensitive across various cognitive domains[21,24,41,43,53,57,60], specific to population study[24,40,43], has good validity and

reliability[41,51,57,61-64], was cost effective and practical to use in a clinical setting[53,62-64] would be ideal.

The structural injury in mTBI however, is too miniscule for detection through routine computed tomography (CT) and Magnetic Resonance Imaging (MRI)[65-67]. Over the last ten years, Diffusion Tensor Imaging (DTI) has become accepted as a non-invasive tool that is able to quantify microstructural brain changes in mTBI[24,65-70]. Changes in its parameters are indicative of microstructural remodelling at acute and chronic stages of injury, potentially explaining the persistence of symptoms that would otherwise be attributed to other causes [24,65-70]. A longitudinal DTI study may increase our understanding of the brain structural transformation in mTBI.

The most important outcome following mTBI is the ability for survivors to return to their previous functional state and quality of life. Commonly used scales to measure disability and function are usually sensitive to cognitive deficits but not necessarily specific to the TBI population[39-41,52,53]. Many studies have also reported specific outcome measures for TBI that has good validity, reliability and practical in a clinical setting[71-79], such as Goal Attainment Scaling[71,72,77-79], Extended Glasgow Outcome Scale[73] and Functional Assessment Measure[74].

This trial evaluates a complex clinical intervention, to provide evidence on the effect of cognitive rehabilitation in mTBI. The outcome measures include anatomical, clinical and functional aspects to provide a comprehensive evidence-based treatment model.

## METHODS

### Study hypothesis

We hypothesize that structured cognitive rehabilitation for attention deficits following mTBI will improve patients' cognitive function of attention compared to standard care.

### Study objectives

The objectives are:

- to measure the clinical effect of a 12-week individualized structured cognitive rehabilitation which addresses attention deficit and overall cognitive status
- to analyse the effect of treatment on brain structures and functional changes
- to correlate clinical effects following cognitive rehabilitation with structural brain changes and participants' overall functional outcomes

**Design**

This will be a prospective double blind, randomized controlled trial with two parallel groups. The study design is summarized in **Figure 1**.

**Participants and recruitment process**

This trial will be conducted at a single centre, University Malaya Medical Centre (UMMC), Malaysia. UMMC is a government funded academic medical institution situated in the urban area of the nation's capital city Kuala Lumpur with a population of 1.76 million. Apart from providing acute medical services, this hospital is also a tertiary referral and training centre in Malaysia. UMMC also houses Department of Rehabilitation Medicine that provides the facility for this study. This department includes the main rehabilitation services (neuro-, spinal cord-, prosthetic and orthotic-, paediatric- and cardiac rehabilitation) for both inpatient and outpatient setting. Other services also include return to work/driving rehabilitation.

We will recruit participants through the Emergency Medicine Department (ED), UMMC from 1st August 2017. ED physicians, radiologists and neurosurgeons will refer mTBI cases to a research assistant for recruitment. Potential cases will also be screened through the UMMC digital medical record system. Screening stages will be performed at 72 hours, two and six weeks following mTBI.

**Inclusion criteria**

Mild TBI is defined as physiological disruption of brain function as a result of trauma with symptoms of loss of consciousness 30 minutes or less, focal neurological deficit that may/may not be transient, altered mental state with Glasgow Coma Scale of 13-15 and loss of memory with post traumatic amnesia not greater than 24 hours. The inclusion criteria for this study are mTBI as a result of RTA; adult aged between 18 to 60 years old; Malaysian resident; no previous history of head trauma; minimum of nine years education; persistently abnormal S-NAB Attention Domain score at three months of mTBI; ability to give consent and willingness to comply with cognitive rehabilitation program. Persistently abnormal S-NAB Attention Domain score is defined as Standard Score <85 (below average category) at screening phase and at enrolment phase as set by the NAB test manual (Table 1).

**Exclusion criteria**

The exclusion criteria include pre-existing chronic illness that causes neurological symptoms or complications; severe comorbid neurological or psychiatric disorder; on long-term medication that alters

or affects cognitive and psychological status; clinical evidence of substance intoxication at the time of injury; major polytrauma and absolute contraindications for MRI (metal or implant not compatible for MRI, claustrophobia) (Table 1).

| Inclusion criteria | | | |
|---|---|---|---|
| **Criteria** | **IG** | **SG** | **HG** |
| 18-60 years old of age | ✓ | ✓ | ✓ |
| No previous history of head trauma | ✓ | ✓ | ✓ |
| Minimum of 9 years education | ✓ | ✓ | ✓ |
| Consented | ✓ | ✓ | ✓ |
| mTBI as a result of motor vehicle accidents only | ✓ | ✓ | |
| Abnormal S-NAB Attention Domain score at 3 months of mTBI | ✓ | ✓ | |
| Willingness to comply with rehabilitation program | | | |

| Exclusion criteria | | | |
|---|---|---|---|
| **Criteria** | **IG** | **SG** | **HG** |
| Pre-existing chronic illness or neurological or psychiatric condition | ✓ | ✓ | ✓ |
| On long term medication that can alter or affect cognitive and/or psychological status | ✓ | ✓ | ✓ |
| Clinical evidence of alcohol intoxication at the time of injury | ✓ | ✓ | |
| Major polytrauma (multiple bone fractures, nerve injury) | ✓ | ✓ | |
| Absolute contraindication for MRI | ✓ | ✓ | |

**Table 1**: The study criteria.
Note: IG-individualised structured cognitive rehabilitation group; SG- standard care group, HG- healthy control group

**Intervention**

Potential participants will undergo screening before enrolment and randomization (**Figure 1)**. The education component will include reassurance on recovery, self-monitoring of symptom(s) and advice on gradual return to daily activities and physical exertion. Symptom(s) evaluation will include clinical review of physical, cognitive and psychological status. The first medical responder i.e. ED physicians will perform this review at 72 hours of injury. At two weeks and six weeks after injury, a rehabilitation medicine physician who is not involved with the study (RP-1) will repeat the education component and symptom evaluation. Early treatment or referral to other medical speciality will be made if indicated during these reviews.

At three months after injury, potential participants will undergo a repeat of clinical review and S-NAB test. Participants with persistently abnormal Attention Domain scores (standard domain score <85) will be enrolled in the study. However, participants with deficits of cognition of more than one domain involvement (standard domain score <85) other than in the Attention domain, will also be included and will receive treatment for attention following randomization. The concomitant domain deficit(s) will also be evaluated upon completion of therapy. The cognitive intervention will be conducted at the Neurorehabilitation Therapy Unit, Department of Rehabilitation Medicine, UMMC in an outpatient setting. Participants will be assigned to different treatment groups via the randomization process. Written records of the intervention will be recorded and kept by the therapist of each treatment arm until treatment completion. This will include the participant's goals, symptom(s), cognitive strategy/method and participant's feedback.

***Individualised structured cognitive rehabilitation group***

Intervention group participants will receive a two-part 12-week individualized structured cognitive rehabilitation. The first part will be Direct Attention Training (DAT), a deficit-oriented computer-based attention-training program called CogniPlus[45]. Each session last 30 minutes, once a week.

CogniPlus is a computer-based software program with interactive multimedia approach for multiple attention cognitive training modules. The training programs are ALERT (focused and sustained attention), FOCUS (focused attention), VIG (sustained attention), SELECT (selective attention) and DIVID (divided attention). Each attention-training category is designed based on real-life scenarios. The screen graphics are three-dimensional. This program has an artificial intelligence capacity that can automatically adapt to an individual's performance and alter the training difficulty level (hierarchical difficulty).

The second part of this intervention will be strategy approach (metacognitive awareness and compensatory strategy) performed after CogniPlus training. Metacognitive awareness includes feedback on the participant's CogniPlus performance to improve their awareness of impairment severity. This process is intended to regulate learning experience and in turn instil the practise of self-monitoring and self-regulation through learning activities. Compensatory strategy component involves instilling cognitive awareness in recognizing impairment that is present in daily activities. This will be followed by the application of cognitive methods to ameliorate the deficit to maximise daily functioning. A participant will identify the deficit(s) and will apply problem-solving method(s) learnt from the therapist. Feedback and

review of performance will be done again in the following therapy session. This session will last for 30 minutes and a will be conducted by a trained and certified Occupational Therapist (OT-1) in cognitive therapy and CogniPlus.

***Standard care group***

This group will receive the best standard care for attention disorders. This is a patient-centred cognitive therapy. It is based on a patient's complaint(s), symptom(s) and therapy aim(s) (self-realization of deficits or guided by therapist). Symptom(s) management may include physical (e.g. imbalance, fatigue, sleep dysregulation), psychological (e.g. mild anxiety or depression) and cognitive (e.g. forgetfulness). Referral to relevant service(s) may be required such as physiotherapy, return to work/driving rehabilitation and counselling. Compensatory strategy includes task specific training (patient-prioritised) e.g. return to driving may involve driving simulation training, visuospatial training and return to drive rehabilitation service. The frequency of sessions will be one hour per week, for 12 weeks. A trained occupational therapist in cognitive therapy (OT-2) who is not involved with the intervention group treatment, will conduct all the sessions (Table 2).

***Control group***

This will consist of healthy individuals demographically matched for age, gender and education years to the intervention groups (Table 1). They will undergo S-NAB assessment battery, DTI imaging and psychological screening tools which will include the Generalised Anxiety Disorder 7-item (GAD7) and Patient Health Questionnaire-9 (PHQ-9). Their lifestyle aspects will also be reviewed and recorded (spiritual practice, diet, physical exercise, occupation and driving). The data will be collected for comparison purpose.

**Randomisation, consent and blinding**

Participants with mTBI who fulfil the study criteria will be randomized via computer-generated random permuted block assignment, gender-stratified into equally proportioned intervention and control group numbers. The study schedule, procedures and blinding of co-investigators are presented in **Table 2.**

| | STUDY PERIOD | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Enrolment | Enrolment | Enrolment | Allocation | Post-allocation | | | | | | End of treatment |
| **TIMEPOINT**** | | $-t_3$ *72 hours mTBI* | $-t_2$ *2 weeks mTBI* | $-t_1$ *6 weeks mTBI* | **0** 3 months mTBI | $t_1$ | $t_2$ | $t_3$ | $t_4$ | $t_5$ | $t_{12}$ | $f_1$ *6 months mTBI* |
| | **Co-investigator (initials)** | *Pre-study screening* | *Pre-study screening* | *Pre-study screening* | *Baseline/ Randomisation* | *Study Visit 1* | *Study visit $t_2$ onwards* | | | | *Last study visit* | *Outcome measures* |
| **ENROLMENT:** | | | | | | | | | | | | |
| **Eligibility screen** | Research assistant | X | X | | | | | | | | | |
| **Informed consent** | MM | | | | X | | | | | | | |
| **Allocation** | MM | | | | X | | | | | | | |
| **S-NAB Test (Form 1)** | NH | | X | | | | | | | | | X |
| **S-NAB Test (Form 2)** | NH | | | | X | | | | | | | |
| **DTI test** | VN/NR | | | | X | | | | | | | X |
| **DTI post processing** | TLK | | | | X | | | | | | | X |
| **GAS** | NAM (OT-1) & NAMT (OT-2) | | | | | X | X | X | X | X | X | X |
| **INTERVENTIONS:** | | | | | | | | | | | | |
| **Education component/ symptom(s) evaluation** | ED team/RP-1 | X (ED team) | X (RP-1) | X (RP-1) | | | | | | | | |
| **Individualized structured cognitive rehabilitation** | NAM (OT-1) | | | | | X | X | X | X | X | X | |
| **Best standard care** | NAMT (OT-2) | | | | | X | X | X | X | X | X | |
| **OUTCOME MEASURES:** | | | | | | | | | | | | |
| **S-NAB Test** | NH | | | | X | | | | | | | X |
| **DTI** | VN/NR | | | | X | | | | | | | X |
| **GAS** | NAM/NAMT (OT-1/OT-2) | | | | | X | X | X | X | X | X | X |

**Table 2:** Study schedule and procedures.

**Modification, withdrawal and unblinding within the intervention**

Participants can withdraw their consent from this study at any time and for any reason. Investigators can also withdraw a participant from the study if he/she becomes non-compliant with the treatment protocol. This includes poor treatment attendance (non-attendance of >50% of total therapy sessions) or the participant's request for withdrawal from the study. We will also provide participants who require immediate medical attention or treatment that is otherwise not part of the study intervention with this throughout the study duration. In the case where unblinding of a participant is necessary (e.g. medical emergency), an investigator (MM) will be informed of the cause and stage of intervention. He/she may continue in the study and follow all study procedures. The participant will only be withdrawn from this study if the immediate treatment violates our study criteria. We will retain all of participant's data (although the participant is no longer blinded) up to the point of participant's removal from the study.

**Adherence strategies**

Adherence to treatment is encouraged throughout for both groups. This will be achieved by providing: 1) participants with clear information on purpose, method and treatment goals during treatment sessions, 2) an appointment card with specific date and time of therapy sessions, and 3) a reminder through phone calls a day before each therapy appointment and a week before DTI scan date.

**Outcome measures**

All measures will be performed at baseline and at 12 weeks of intervention after randomisation. The primary outcome measure for this study is the change in attention deficit and other cognitive domains within intervention groups and direct comparison of each intervention group with the healthy control group. This will be measured by Neuropsychological Assessment Battery® (NAB®, PAR, Inc., Florida, USA)[61]. It consists of six modules: Screening Module and five Domain Specific Modules: Attention, Language, Memory, Spatial and Executive Function. This study will only apply the Screening Module (S-NAB) because it measures the same five functional domains similar or identical to the main NAB modules. It consists of 12 individual tests screening all five mentioned cognitive domains for adults aged 18 to 97 years, validated and sensitive for use in healthy and cognitively impaired brain injured population[24,61-64]. S-NAB also provides two parallel assessment sets (Record Form 1 and Form 2) that will be applied in an alternate fashion to participants in both groups to avoid practice effect.

S-NAB Domain Attention test items and score are interpreted as a marker of an individual's attentional capacity, working memory, psychomotor speed, selective attention, divided attention and information processing [61]. S-NAB has also been applied in our previous cohort study [24] with good validation outcome in our Malaysian mTBI population.

The secondary outcome measures are microstructural WMT parameters and GAS scores. The DTI MRI scan is a Siemens Magnetom Prisma 3T MRI (Siemens AG, Muenchen, Germany). This study will analyse Fractional Anisotropy (FA), Mean Diffusivity (MD) and Radial Diffusivity (RD) parameter changes at pre- and post-intervention[24,65-70]. These parameters quantify the direction and degree of tissue water diffusion within the WMT[65,66]. FA which measures the direction of the diffusion is an index expressed in a range from 0-1, with a higher score indicating a higher integrity of white matter consisting of highly parallel fibres[65,66]. MD measures the average magnitude of the diffusion while RD quantifies pathology in the myelin[65,66]. Changes in the index values of the parameters at different injury timeline will indicate the pathological changes of the WMT.

The tool to measure functional goal outcome will be the GAS[77-79]. The difficulty and importance of rehabilitation goals will be individually set according to his/her current levels of functional performance to reinforce realistic expectations. The sensitivity of GAS is increased by the quantifiable set goals relevant and specific to the participant. Each goal is rated on a 5-point scale and score is given on the extent to which a patient's individual goals are achieved in the course of the intervention. The overall GAS scores calculation will generate a standardized measure (T score) (mean of 50 Standard Deviation ± 10). The details of each goal outcome will be recorded in the GAS Record Sheet[77-79] by a cognitive therapist of each study arm (OT-1 and OT-2) trained in GAS application.

Another important factor to note is the participant's psychological status following mTBI. This study will also perform a screening of anxiety and depression symptoms by using GAD7 and PHQ-9 screening tools at each study timeline. Participant's lifestyle changes/modifications such as spiritual practice, diet change, physical exercise, return to work/education, return to driving, litigation issues and insurance claims will also be reviewed and recorded. Although these parameters will not be part of the study outcome measure, they however remain relevant in influencing treatment adherence and outcome.

**Sample size and power calculation**

In order to fulfil our study objectives we will base the intended sample size calculation on a previous study that had applied a similar treatment approach and which had a similar outcome measure to our study[40]. This study applied the non-commercial statistical power analysis program G*Power Version 3.1.9.2. An effect size of 0.58, which was the functional cognitive outcome of attention [40], is used to calculate the statistical power *a priori.* We will apply Analysis of Variance (ANOVA): repeated measures, within-between interaction, setting an alpha level of 0.05, and approximately 10 participants will provide 89% power to detect a statistical significance. Recruitment is doubled (n=20) for both arms and inflated to 28 to counter 40% attrition rate.

To have a bigger sample size, we, therefore, also decided on a more conservative effect size value and calculated the sample size through estimation of Cohen's *d* effect size value of 0.35. By using similar statistical power analysis program, medium effect size Cohen's *d* of 0.35, setting an alpha level of 0.05, approximately 38 participants will provide 85% power to detect statistical significance. Recruitment will be inflated to 50 participants to enable a 40% attrition rate.

Based on the multiple estimated calculations, the minimum intended sample size is therefore 50 participants. Based on our UMMC local data, a 12 months data collection is sufficient to yield the target sample size.

**Ethics considerations**

This study was approved by Medical Research Ethics Committee, UMMC (MREC ID NO: 2016928-4293). We will obtain written consent from participants. During consenting, participant will be provided with Patient Information Sheet detailing the purpose of study, reason for participation, study investigation and intervention methods, withdrawal from study and contact details of investigators. Once consent is given the form and all other documents with the participant's personal details will be stored immediately in a locked filing cabinet by the consent taker. This will be accessible only to a small number of investigators. Study ID codes will be allocated after consent is obtained and subsequent study documentation will only use the ID code.

Other issues included will be 1) early information sharing of treatment/investigation results in the event of incidental clinical findings that requires urgent treatment by other medical speciality, 2) treatment compliance, 3) cost of investigation and treatment and 4) participant involvement in litigation issues. In

the event of information sharing being required for medical reasons, the participant will be informed immediately followed by referral to the relevant professional either based at UMMC or a different centre of choice. However, costs of further investigation or treatment that is not part of this study will not be funded from the study grants. Treatment compliance will be achieved through our adherence strategy. We strictly adhere to the privacy and confidentiality of participant's medical information. Any information sharing with a third party for various reasons will be managed in accordance with UMMC professional and legal code of conduct.

**Patient and public involvement**

We applied the Medical Research Council's (MRC) Developing and Evaluating Complex Intervention: New Guidance (2006) and Multiphase Optimization Strategy (MOST) framework to guide the development and design of this study. The treatment approach was based on the relevant theoretical evidence whereas treatment approach was evinced through our systematic review, clinical experience and practice setting of interest. We conducted 1) a pilot study and 2) Expert Panel review to evaluate the study design and treatment method that may require further focus.

Our pilot study was approved by Medical Research Ethics Committee, UMMC, Malaysia (UM/EC Ref: 947.15) for the application of cognitive treatment on mTBI patients. They were involved in the testing of treatment method, clinical practicality, fidelity of treatment and treatment compliance. We have identified several components required for optimization of intervention. These findings were also assessed by the Expert Panel reviewers.

The panel comprised of clinicians who were credentialed in brain injury management and cognitive rehabilitation with minimum of ten years clinical experience working in Malaysia. Panels were made up of seven rehabilitation medicine consultants, one neurosurgeon consultant, one neuroimaging consultant, five cognitive occupational therapists and one clinical psychologist. The focus of discussion was on the feasibility of structured cognitive rehabilitation for mTBI patients in Malaysia, guided by the current evidence, current practise of cognitive rehabilitation in local setting, reviewers clinical experience and our pilot study findings. A summary of the pilot study outcomes and Expert Panel recommendations are best illustrated in Table 3.

Following the commencement of this study, the input from participants (experience, feedback and outcomes) will be recorded. The data and study materials will belong to UMMC, Malaysia. We will inform

our participants of the result of the study to following completion even if he/she did not complete the study unless he/she has requested no contact.

| Pilot study | Expert panel review |
|---|---|
| Design: a case-controlled study<br>Study components:<br>**Non-randomisation** –to identify participant's willingness to attend therapy as a measure of good compliance.<br>**Treatment application** - treatment was given at early stage of injury (2 weeks post injury) to measure the treatment effect versus spontaneous' recovery.<br>**Treatment accessibility** – outpatient hospital-based treatment is feasible.<br>**Treatment compliance**–high attrition rate (50%) which compromised the treatment fidelity. Reasons for poor treatment compliance were:<br>• treatment frequency and intensity (>1 hour/weekly for the first 3 months followed by monthly session the following 3 months)<br>• mental fatigue<br>• 'unreadiness' to receive treatment<br>• treatment and transportation costs<br>• work demand (limited time off work and income lost)<br><br>**Treatment method-** clinical application of treatment was acceptable to participants.<br>**Treatment effect** - the application of effect size measurement is consistent with MOST recommendation.<br>**Outcome measure application** –S-NAB was able to measure score differences in its five domains. DTI parameters reported changes consistent with current literature evidence in mTBI population. | Design: Randomization was recommended in clinical trial design<br>Review components:<br>**Fidelity of treatment**<br>1) clear information on purpose, method and treatment goals during treatment sessions<br>2) an appointment card with specific date and time of therapy sessions<br>3) a reminder through phone calls a week and a day before each therapy<br>4) Review at 72 hours, 2 weeks, 6 weeks, and 3 months (baseline) to increase sensitivity towards participant selection, early medical intervention if required and to improve adherence.<br>**Treatment method**<br>1) as outpatient setting, with frequency 1hour/week for 12 weeks duration.<br>2) individualised treatment approach with standardization through direct attention training and metacognitive strategy<br>3) to clarify the metacognitive strategies applied in therapy such as 'self-monitoring', self-instructional procedure', 'self-evaluation', 'rehearsal', 'self-pacing', 'positive self-statement', use of internal/external strategy<br>**Outcome measure**<br>Neuropsychological assessment as a practice standard<br>Guided individualised goals (GAS application) to standardise the functional goal outcome measurement for both groups. |

**Table 3**: A summary of recommendations from pilot study findings and Expert Panel review

**Statistical analysis**

Descriptive statistics will be conducted on the data obtained from all groups to give a demographic overview of our study population. A $p$ value <0.05 will be considered statistically significant. We will also report additional relevant data, which may affect the study outcome. This will include lifestyle modifications, litigation cases, changes in socioeconomic status, physical symptoms and psychological status.

The measure of treatment effect is changes in neuropsychological assessment scores. We will calculate the effect size of each S-NAB mean Domain Standard score (Attention, Language, Memory, Spatial and Executive Function domains) as well as the Total Index Score within each intervention group. Cohen's $d$ moderate (>0.5) to large effect size (>0.8) are considered to be clinically significant. Another treatment effect analysis also includes reporting on the CogniPlus Attention task difficulty level achieved for each program (ALERT, FOCUS, VIG, SELECT, DIVID), the change of response time and measurement of errors.

Similarly, functional changes will be measured by using the effect size calculation of mean GAS T scores obtained at pre and post intervention. We will also compare the mean change in GAS T score between groups and report on the type and preference of metacognitive strategies used by participants of both groups. The metacognitive strategies applied will be obtained and recorded in writing during the participant's feedback sessions.

The secondary analysis will include measurement of structural brain changes following intervention. This data will be obtained from the DTI MRI scan performed at pre and post intervention, for all groups. We will identify FA, MD and RD parameters with statistically significant mean values ($p<0.05$) via whole brain analysis known as Tract-based Spatial Statistics (TBSS)[80] and region of interest (ROI) approach which is part of the FSL (v5.0.6; University of Oxford, Oxford UK) [81] and AFNI (v2011_12_21_1014; National Institute of Mental Health, Bethesda, MD) software packages. The DTI parameters of both intervention groups at three- and six months study timelines will be compared with the healthy control group by using repeated measure analysis. This is in the assumption that the study fulfils the repeated measure analysis of normally distributed data sample and homogeneity of variance.

Further analysis also includes correlation of cognitive performance with structural brain changes. We will perform Pearson's correlation coefficient between mean S-NAB Standard score of each domain and the selected WMT (with statistical significant).

**Data management**

All data obtained including from non-adherence or voluntarily withdrawn participants will also be reviewed and included in the study analysis where applicable. All study documents will be securely kept at the study site. Participant information will be stored in locked filing cabinets and will only be accessible to selected investigators. All data documents, administrative forms, reports and analysis documents will only have coded participant ID to avoid identification by any investigator of the study. Data entry will only be performed by an appointed research assistant. Any other document that has a participant's name such as consent form will be kept in a separate cabinet accessible by a selected investigator (MM).

## Discussion

To our knowledge, this is the first randomized control trial of cognitive intervention in adult mTBI population, conducted in a developing country, Southeast Asia region. Previous studies have been done conducted in the Western population with a predominantly Caucasian ethic group and limited ethnic variation. A study from this region with various ethnic group involvements of both genders may better represent the study population and in turn add further knowledge on the pattern of the impairment following mTBI. Uniquely, cultural practice and belief system may also influence treatment response and outcome. Development of the intervention approach was based on current evidence, a pilot study and Expert Panel review. This trial incorporates technology in the treatment application consistent with the changing face of health service delivery in Malaysia, aiming at resource efficiency and treatment effectiveness, albeit tailored treatment approach suitable for the local setting. The results of this study will provide a comprehensive overview on the effect of cognitive rehabilitation in mTBI. Owing to the paucity of scientific and clinical knowledge, this trial will also contribute to the evidence-based cognitive treatment model for mTBI population.

## Trial status

At the time of manuscript preparation, 30 potential participants have been recruited at three months post-injury. Fifteen participants were consented and received treatment following randomization. Recruitment is due to finish in April 2019. Data lock has not yet occurred and no analyses have been performed.

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**Competing interest:** none declared

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We wish to thank all our mTBI participants involved in the pilot control study as well as Expert Panels in involved in the review of our intervention development and study.

## Authors' contribution

NH initiated the study, applied for study funding and is the principal investigator. NH, MM, VN, NR, AD, RDN and GSY were involved in the conception, development of the intervention and design of the study. NAM and NAMT implemented the cognitive intervention. TLK provided the consultation on DTI processing and analysis. MD and NM provided important statistical contributions. All authors provided feedback on drafts of this paper, read and approved the final manuscript. NH, MM, VN and NR are the guarantors for the study and accept full responsibility for the work and /or the conduct of the study, had access to data, and controlled the decision to publish. MM is the corresponding author and attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

## Availability of data and material

The data and study materials belong to UMMC, Malaysia. Any request will have to go through Medical Record Department of UMMC, Malaysia. Dissemination of trial result is through publication.

## Ethics and Dissemination

The study protocol was approved by the Medical Research Ethics Committee, UMMC (MREC ID NO: 2016928-4293). The findings of the trial will be disseminated through peer-reviewed journals and scientific conferences.

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**Figure 1**: Flowchart showing the stages of recruitment in this study.

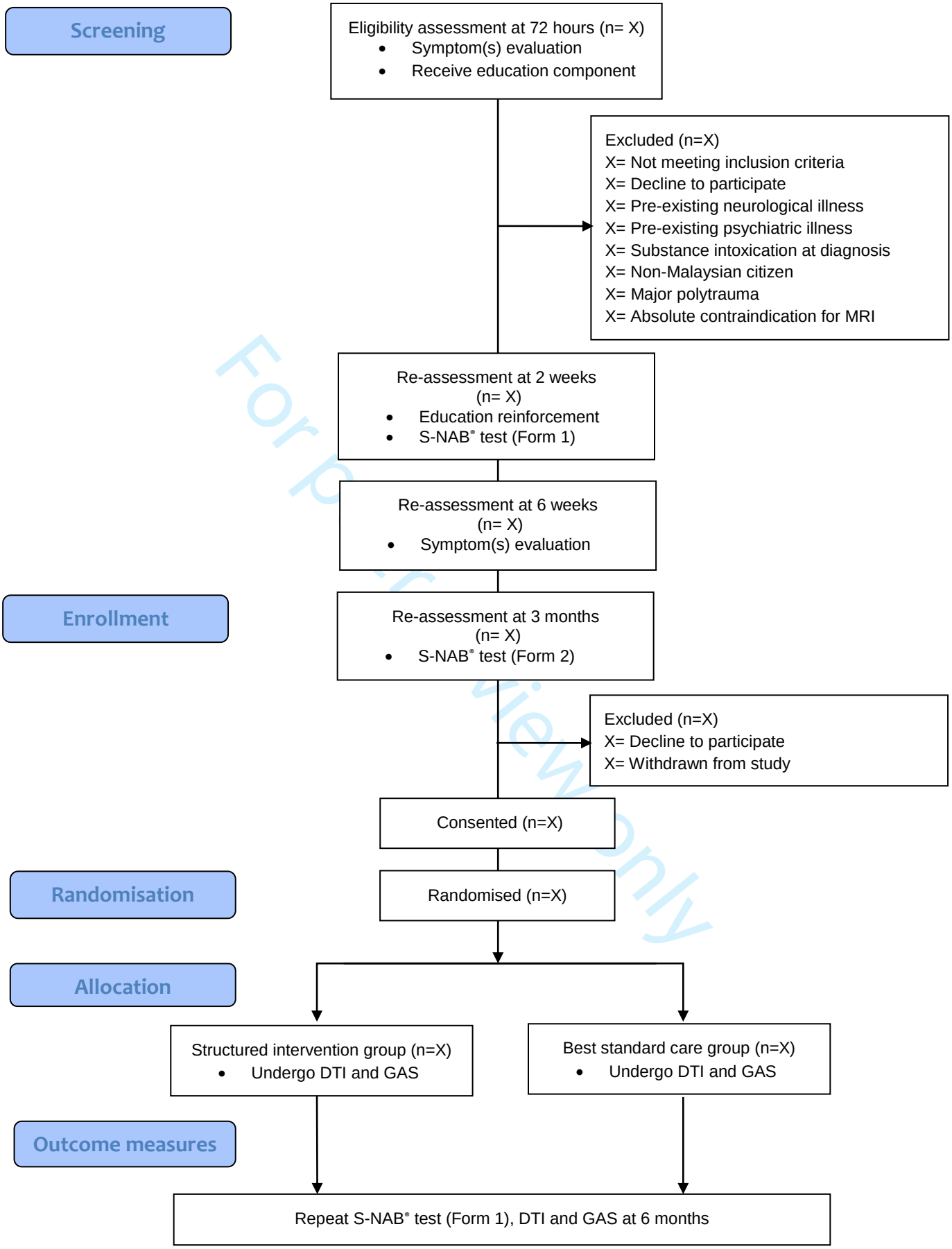


**Figure 1**: Flowchart showing the stages of recruitment in this study.


SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

| Section/item | Item No | Description | Addressed on line number |
|---|---|---|---|
| **Administrative information** | | | |
| Title | 1 | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym | 1-2 |
| Trial registration | 2a | Trial identifier and registry name. If not yet registered, name of intended registry | 380-383 |
| | 2b | All items from the World Health Organization Trial Registration Data Set | 376-383 |
| Protocol version | 3 | Date and version identifier | 380-383 |
| Funding | 4 | Sources and types of financial, material, and other support | 376-379 |
| Roles and responsibilities | 5a | Names, affiliations, and roles of protocol contributors | 389-397 |
| | 5b | Name and contact information for the trial sponsor | 383 |
| | 5c | Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities | NA NA |
| | 5d | Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) | NA |

| | | | |
|---|---|---|---|
| **Introduction** | | | |
| Background and rationale | 6a | Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention | 44-105 |
| | 6b | Explanation for choice of comparators | 44-105 |
| Objectives | 7 | Specific objectives or hypotheses | 107-117 |
| Trial design | 8 | Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) | 118-132; Figure 1 |
| **Methods: Participants, interventions, and outcomes** | | | |
| Study setting | 9 | Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained | 122-128 |
| Eligibility criteria | 10 | Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) | 133-150, Table 1 |
| Interventions | 11a | Interventions for each group with sufficient detail to allow replication, including how and when they will be administered | 151-203; Figure 1 |
| | 11b | Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) | 208-218 |
| | 11c | Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) | 219-223 |
| | 11d | Relevant concomitant care and interventions that are permitted or prohibited during the trial | NA |
| Outcomes | 12 | Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended | 224-262 |
| Participant timeline | 13 | Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) | 204-207; Table 2 |

| | | | |
|---|---|---|---|
| Sample size | 14 | Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations | 263-279 |
| Recruitment | 15 | Strategies for achieving adequate participant enrolment to reach target sample size | 219-223; 263-279 |
| **Methods: Assignment of interventions (for controlled trials)** | | | |
| Allocation: | | | |
| Sequence generation | 16a | Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions | 204-207; Table 2 |
| Allocation concealment mechanism | 16b | Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned | 204-207; Table 2 |
| Implementation | 16c | Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions | Table 2 |
| Blinding (masking) | 17a | Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how | Table 2 |
| | 17b | If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial | 208-218 |
| **Methods: Data collection, management, and analysis** | | | |
| Data collection methods | 18a | Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol | Figure 1;204-207; Table 2; 208-262;298-321;Table 3 |
| | 18b | Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols | 208-223 |

| | | | |
|---|---|---|---|
| Data management | 19 | Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol | 350-357 |
| Statistical methods | 20a | Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol | 322-349 |
| | 20b | Methods for any additional analyses (eg, subgroup and adjusted analyses) | NA |
| | 20c | Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) | 208-218 |
| **Methods: Monitoring** | | | |
| Data monitoring | 21a | Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed | NA |
| | 21b | Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial | NA |
| Harms | 22 | Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct | 208-218 |
| Auditing | 23 | Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor | NA |
| **Ethics and dissemination** | | | |
| Research ethics approval | 24 | Plans for seeking research ethics committee/institutional review board (REC/IRB) approval | 280-297 |
| Protocol amendments | 25 | Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) | ClinicalTrials.gov |

| | | | |
|---|---|---|---|
| Consent or assent | 26a | Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) | Table 2 |
| | 26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable | NA |
| Confidentiality | 27 | How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial | 208-218;350-357 |
| Declaration of interests | 28 | Financial and other competing interests for principal investigators for the overall trial and each study site | 376-385 |
| Access to data | 29 | Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators | 350-357;Table 2 |
| Ancillary and post-trial care | 30 | Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation | NA |
| Dissemination policy | 31a | Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions | 298-321 |
| | 31b | Authorship eligibility guidelines and any intended use of professional writers | BMJ guideline |
| | 31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code | NA |
| **Appendices** | | | |
| Informed consent materials | 32 | Model consent form and other related documentation given to participants and authorised surrogates | - |
| Biological specimens | 33 | Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable | NA |

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

# A randomised controlled clinical trial of a structured cognitive rehabilitation in patients with attention deficit following mild traumatic brain injury: Study protocol

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| | |

**Title:** A randomised controlled clinical trial of a structured cognitive rehabilitation in patients with attention deficit following mild traumatic brain injury: Study protocol.

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# TITLE: A randomised controlled clinical trial of a structured cognitive rehabilitation in patients with attention deficit following mild traumatic brain injury: Study protocol

## ABSTRACT

**Objectives:** To measure the clinical, structural and functional changes of an individualized structured cognitive rehabilitation in mild traumatic brain injury (mTBI) population.

**Setting:** A single centre study, Malaysia.

**Participants:** Adults aged between 18 to 60 years with mTBI as a result of road traffic accident, with no previous history of head trauma, minimum of nine years education and abnormal cognition at three months will be included. The exclusion criteria include pre-existing chronic illness or neurological/psychiatric condition, long-term medication that affects cognitive/psychological status, clinical evidence of substance intoxication at the time of injury and major polytrauma. Based on multiple estimated calculations, the minimum intended sample size is 50 participants (Cohen's *d* effect size 0.35; alpha level of 0.05; 85% power to detect statistical significance; 40% attrition rate).

**Interventions:** Intervention group will receive individualised structured cognitive rehabilitation. Control group will receive best patient-centred care for attention disorders. Therapy frequency for both groups will be one hour per week for 12 weeks.

**Outcome measures:** *Primary*: Neuropsychological Assessment Battery-Screening Module (S-NAB) scores. *Secondary:* Diffusion Tensor Imaging (DTI) parameters and Goal Attainment Scaling score (GAS).

**Results:** Results will include descriptive statistics of population demographics, CogniPlus cognitive program and metacognitive strategies. The effect of intervention will be the effect size of S-NAB scores and mean GAS T scores. DTI parameters will be compared between groups via repeated measure analysis. Correlation analysis of outcome measures will be calculated using Pearson's correlation coefficient.

**Conclusion:** This is a complex clinical intervention with multiple outcome measures to provide a comprehensive evidence-based treatment model.

**Trial registration**: This study is registered with ClinicalTrials.gov ID NCT 03237676

**Ethics and Dissemination:** The study protocol was approved by the Medical Research Ethics Committee UMMC (MREC ID NO: 2016928-4293). The findings of the trial will be disseminated through peer-reviewed journals and scientific conferences.

## ARTICLE SUMMARY:

**Strengths and limitations of this study:**

- To our knowledge, this is the first randomized controlled trial of a cognitive intervention in an adult mTBI population, conducted in a developing country (Southeast Asia region).
- A study from this region, with various ethnic groups may better represent the study population and in turn add further knowledge on the pattern of the impairment following mTBI.
- This trial incorporates technology in the intervention arm consistent with the changing face of health service delivery in Malaysia, aiming at both resource efficiency and treatment effectiveness, albeit the tailored treatment approach is appropriate for the local setting.
- Owing to the paucity of scientific and clinical knowledge, this trial will also contribute to the evidence-based cognitive treatment model for the mTBI population.
- We anticipate challenges in the recruitment phase and with treatment compliance due to known and reported high attrition rate in the traumatic brain injury population.

## BACKGROUND

Mild traumatic brain injury (mTBI) is defined as a traumatic injury that induces transient physiological disruption of the brain function [1]. Mild TBI is often used interchangeably with concussion and is a clinical diagnosis [1]. The most common aetiology in the low and middle-income countries is road traffic accident (RTA) that disproportionately affects young men (15 to 29 years of age) [2-4]. Statistically, 20 to 50 million people sustained non-fatal injuries worldwide as a result of RTA and with an increasing rate in the developing countries [2,3].

Cognitive deficit is rarely singular in mTBI. Commonly reported symptoms are attention, memory and executive function deficits, each with varying severity and recovery pattern [5-14]. Specifically, attention deficit is extremely common in TBI [15,16]. Attention is known to be the basis of all other cognitive abilities [17]. About 40 to 60% of individuals with mTBI are reported to have attention deficits in the first three months post-injury [18]. In the majority of individuals, resolution of mixed cognitive deficits begins in the first month and up to one-year post-injury [5,7,11,12,19-21]. A proportion of this population often progresses to have chronic cognitive disability that is overlooked due to the initial 'mild' presentation[6,10,22-25]. At least one-third of survivors fail to return to full functional status at six

months and may, indeed continue to have neurocognitive functional deficits beyond one year of injury [5,12,25-29].

**Cognitive rehabilitation in mTBI**

Currently, there is no standard cognitive rehabilitation treatment for mTBI population [19]. The heterogeneity of cognitive deficits, varied intervention methodology, different reporting style and variable treatment outcomes [6,17,27,28,30-57] lead to a challenge for professionals in agreeing mTBI treatment[19]. The early neuropsychological model of attention has already made the assumption that attention should be the focus of rehabilitation, even before more advanced cognitive skills are treated[33]. In the last 20 years, various cognitive treatment approaches have been reported in systematic reviews [34-37]. These include remediation strategies,[38-49], compensatory strategies[50-57] and patient education intervention[6,39,53,58]. These approaches are usually applied in combination, in order to optimise both cognitive and functional recovery [17,27,28,30,31,33-38]. In particular, treatment for attention deficits in TBI has been recommended at post-acute (3 months) stage of trauma [28,30,34,44]. Methods of treatment included multidimensional approach, and tasks with hierarchical difficulty and complexity [30,34,44]. Several studies also reported improved psychological outcome and coping of symptoms on those who received patient education and reassurance following mTBI [6,35,36]. However, these conclusions were based on a limited number of high-quality clinical trials. The consensus was for more robust clinical trials with larger sample sizes, with well-described complex intervention and standardised reporting methods [19,34-37,44,46].

Delivery of cognitive rehabilitation emphasizes six principles: 1) intervention that is theory-driven and meaningful, 2) intervention is task-specific with increasing complexity relevant to individual needs, 3) the need to regularly practice skills acquired, 4) progress monitoring to tailor to individual's needs, 5) generalisation of learnt strategies to apply in real-life skills, and 6) real-world adaptation to ensure success [17,49,59]. A practical, widely accepted treatment approach with the application of evidence-based treatment principles may represent a comprehensive treatment model in treating mTBI patients with cognitive deficits. A large randomised trial is required to support this hypothesis.

**Clinical, imaging and functional outcome measures in mTBI**

A combination of these three outcome measures is a comprehensive approach to analyse cognitive intervention that can make an impact in clinical practice. Scientific reviews and guidelines have

recommended the use of neuropsychological assessment as an appropriate clinical outcome measure [17,27,28,30,31,33,34,36,37]. In adult mTBI, a test that is sensitive across various cognitive domains [21,24,41,43,53,57,60], specific to population study [24,40,43], has good validity and reliability [41,51,57,61-64], is cost effective and practical to use in a clinical setting[53,62-64] would be ideal.

The structural injury in mTBI however, is too miniscule for detection through routine computed tomography (CT) and Magnetic Resonance Imaging (MRI)[65-67]. Over the last ten years, Diffusion Tensor Imaging (DTI) has become accepted as a non-invasive tool that is able to quantify microstructural brain changes in mTBI [24,65-70]. Changes in its parameters are indicative of microstructural remodelling at acute and chronic stages of injury, potentially explaining the persistence of symptoms that would otherwise be attributed to other causes [24,65-70]. A longitudinal DTI study may increase our understanding of the brain structural transformation in mTBI.

The most important outcome following mTBI is the ability for survivors to return to their previous functional state and quality of life. Commonly used scales to measure disability and function are usually sensitive to cognitive deficits but not necessarily specific to the TBI population [39-41,52,53]. Many studies have also reported specific outcome measures for TBI that has good validity, reliability and practical in a clinical setting [71-79], such as Goal Attainment Scaling [71,72,77-79], Extended Glasgow Outcome Scale [73] and Functional Assessment Measure[74].

This trial evaluates a complex clinical intervention which will provide evidence on the effect of cognitive rehabilitation in mTBI. The outcome measures include anatomical, clinical and functional aspects to provide a comprehensive evidence-based treatment model.

## METHODS

### Study hypothesis

We hypothesize that structured cognitive rehabilitation for attention deficits following mTBI will improve patients' cognitive function of attention compared to standard care.

### Study objectives

The objectives are:

- to measure the clinical effect of a 12-week individualized structured cognitive rehabilitation which addresses attention deficit and overall cognitive status
- to analyse the effect of treatment on brain structures and functional changes

- to correlate clinical effects following cognitive rehabilitation with structural brain changes and participants' overall functional outcomes

**Design**

This will be a prospective double blind, randomized controlled trial with two parallel groups. The study design is summarized in **Figure 1**.

**Participants and recruitment process**

This trial will be conducted at a single centre, University Malaya Medical Centre (UMMC), Malaysia. UMMC is a government funded academic medical institution situated in the urban area of the nation's capital city Kuala Lumpur with a population of 1.76 million. Apart from providing acute medical services, this hospital is also a tertiary referral and training centre in Malaysia. UMMC also houses Department of Rehabilitation Medicine that provides the facility for this study. This department includes the main rehabilitation services (neuro-, spinal cord-, prosthetic and orthotic-, paediatric- and cardiac rehabilitation) for both inpatient and outpatient setting. Other services also include return to work/driving rehabilitation.

We will recruit participants through the Emergency Medicine Department (ED), UMMC from 1st August 2017. ED physicians, radiologists and neurosurgeons will refer mTBI cases to a research assistant for recruitment. Potential cases will also be screened through the UMMC digital medical record system. Screening stages will be performed at 72 hours, two and six weeks following mTBI.

**Inclusion criteria**

Mild TBI is defined as physiological disruption of brain function as a result of trauma with symptoms of loss of consciousness 30 minutes or less, focal neurological deficit that may/may not be transient, altered mental state with Glasgow Coma Scale of 13-15 and loss of memory with post traumatic amnesia not greater than 24 hours. The inclusion criteria for this study are mTBI as a result of RTA; adult aged between 18 to 60 years old; Malaysian resident; no previous history of head trauma; minimum of nine years education; persistently abnormal S-NAB Attention Domain score at three months of mTBI; ability to give consent and willingness to comply with cognitive rehabilitation program. Persistently abnormal S-NAB Attention Domain score is defined as Standard Score <85 (below average category) at screening phase and at enrolment phase as set by the NAB test manual (Table 1).

**Exclusion criteria**

The exclusion criteria include pre-existing chronic illness that causes neurological symptoms or complications; severe comorbid neurological or psychiatric disorder; on long-term medication that alters or affects cognitive and psychological status; clinical evidence of substance intoxication at the time of injury; major polytrauma and absolute contraindications for MRI (metal or implant not compatible for MRI, claustrophobia) (Table 1).

| Inclusion criteria | | | |
|---|---|---|---|
| **Criteria** | **IG** | **SG** | **HG** |
| 18-60 years old of age | ✓ | ✓ | ✓ |
| No previous history of head trauma | ✓ | ✓ | ✓ |
| Minimum of 9 years education | ✓ | ✓ | ✓ |
| Consented | ✓ | ✓ | ✓ |
| mTBI as a result of motor vehicle accidents only | ✓ | ✓ | |
| Abnormal S-NAB Attention Domain score at 3 months of mTBI | ✓ | ✓ | |
| Willingness to comply with rehabilitation program | | | |

| Exclusion criteria | | | |
|---|---|---|---|
| **Criteria** | **IG** | **SG** | **HG** |
| Pre-existing chronic illness or neurological or psychiatric condition | ✓ | ✓ | ✓ |
| On long term medication that can alter or affect cognitive and/or psychological status | ✓ | ✓ | ✓ |
| Clinical evidence of alcohol intoxication at the time of injury | ✓ | ✓ | |
| Major polytrauma (multiple bone fractures, nerve injury) | ✓ | ✓ | |
| Absolute contraindication for MRI | ✓ | ✓ | |

**Table 1**: The study criteria.
Note: IG-individualised structured cognitive rehabilitation group; SG- standard care group, HG- healthy control group

**Intervention**

Potential participants will undergo screening before enrolment and randomization (**Figure 1)**. The education component will include reassurance on recovery, self-monitoring of symptom(s) and advice on gradual return to daily activities and physical exertion. Symptom(s) evaluation will include clinical review of physical, cognitive and psychological status. The first medical responder i.e. ED physicians will perform this review at 72 hours of injury. At two weeks and six weeks after injury, a rehabilitation medicine physician who is not involved with the study (RP-1) will repeat the education component and

symptom evaluation. Early treatment or referral to other medical speciality will be made if indicated during these reviews.

At three months after injury, potential participants will undergo a repeat of clinical review and S-NAB test. Eligibility criteria will include i) an abnormal S-NAB Attention Domain score at 3 months post-mTBI, or ii) deficits in more than one S-NAB domain, not including the attention domain. The concomitant domain deficit(s) will also be evaluated upon completion of therapy. The cognitive intervention will be conducted at the Neurorehabilitation Therapy Unit, Department of Rehabilitation Medicine, UMMC in an outpatient setting. Participants will be assigned to different treatment groups via the randomization process. Written records of the intervention will be recorded and kept by the therapist of each treatment arm until treatment completion. This will include the participant's goals, symptom(s), cognitive strategy/method and participant's feedback.

***Individualised structured cognitive rehabilitation group***

Intervention group participants will receive a two-part 12-week individualized structured cognitive rehabilitation. The first part will be Direct Attention Training (DAT), a deficit-oriented computer-based attention-training program called CogniPlus [45]. Each session last 30 minutes, once a week.

CogniPlus is a computer-based software program with interactive multimedia approach for multiple attention cognitive training modules. The training programs are ALERT (focused and sustained attention), FOCUS (focused attention), VIG (sustained attention), SELECT (selective attention) and DIVID (divided attention). Each attention-training category is designed based on real-life scenarios. The screen graphics are three-dimensional. This program has an artificial intelligence capacity that can automatically adapt to an individual's performance and alter the training difficulty level (hierarchical difficulty).

The second part of this intervention will be strategy approach (metacognitive awareness and compensatory strategy) performed after CogniPlus training. Metacognitive awareness includes feedback on the participant's CogniPlus performance to improve their awareness of impairment severity. This process is intended to regulate learning experience and in turn instil the practise of self-monitoring and self-regulation through learning activities. Compensatory strategy component involves instilling cognitive awareness in recognizing impairment that is present in daily activities. This will be followed by the application of cognitive methods to ameliorate the deficit to maximise daily functioning. A participant will identify the deficit(s) and will apply problem-solving method(s) learnt from the therapist. Feedback and

review of performance will be repeated in the next following therapy session. The metacognitive strategies applied will also be recorded in writing during the participant's feedback sessions. This session will last for 30 minutes and a will be conducted by a trained and certified Occupational Therapist (OT-1) in cognitive therapy and CogniPlus.

***Standard care group***

This group will receive the best standard care for attention disorders. This is a patient-centred cognitive therapy. It is based on a patient's complaint(s), symptom(s) and therapy aim(s) (self-realization of deficits or guided by therapist). Symptom(s) management may include physical (e.g. imbalance, fatigue, sleep dysregulation), psychological (e.g. mild anxiety or depression) and cognitive (e.g. forgetfulness). Referral to relevant service(s) may be required such as physiotherapy, return to work/driving rehabilitation and counselling. Compensatory strategy includes task specific training (patient-prioritised) e.g. return to driving may involve driving simulation training, visuospatial training and return to drive rehabilitation service. The frequency of sessions will be one hour per week, for 12 weeks. A trained occupational therapist in cognitive therapy (OT-2) who is not involved with the intervention group treatment, will conduct all the sessions (Table 2).

***Control group***

This will consist of healthy individuals demographically matched for age, gender and education years to the intervention groups (Table 1). They will undergo S-NAB assessment battery, DTI imaging and psychological screening tools, which will include the Generalised Anxiety Disorder 7-item (GAD7) and Patient Health Questionnaire-9 (PHQ-9). Their lifestyle aspects will also be reviewed and recorded (spiritual practice, diet, physical exercise, occupation and driving). The data will be collected for comparison purpose.

**Randomisation, consent and blinding**

Participants with mTBI who fulfil the study criteria will be randomized via computer-generated random permuted block assignment, gender-stratified into equally proportioned intervention and control group numbers. The study schedule, procedures and blinding of co-investigators are presented in **Table 2.**

| | | STUDY PERIOD | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Enrolment | Enrolment | Enrolment | Allocation | Post-allocation | | | | | | End of treatment |
| **TIMEPOINT**** | | $-t_3$ *72 hours mTBI* | $-t_2$ *2 weeks mTBI* | $-t_1$ *6 weeks mTBI* | **0** 3 months mTBI | $t_1$ | $t_2$ | $t_3$ | $t_4$ | $t_5$ | $t_{12}$ | $f_1$ *6 months mTBI* |
| | **Co-investigator (initials)** | ***Pre-study screening*** | ***Pre-study screening*** | ***Pre-study screening*** | ***Baseline/ Randomisation*** | ***Study Visit 1*** | ***Study visit $t_2$ onwards*** | | | | ***Last study visit*** | ***Outcome measures*** |
| **ENROLMENT:** | | | | | | | | | | | | |
| **Eligibility screen** | Research assistant | X | X | | | | | | | | | |
| **Informed consent** | MM | | | | X | | | | | | | |
| **Allocation** | MM | | | | X | | | | | | | |
| **S-NAB Test (Form 1)** | NH | | X | | | | | | | | | X |
| **S-NAB Test (Form 2)** | NH | | | | X | | | | | | | |
| **DTI test** | VN/NR | | | | X | | | | | | | X |
| **DTI post processing** | TLK | | | | X | | | | | | | X |
| **GAS** | NAM (OT-1) & NAMT (OT-2) | | | | | X | X | X | X | X | X | X |
| **INTERVENTIONS:** | | | | | | | | | | | | |
| **Education component/ symptom(s) evaluation** | ED team/RP-1 | X (ED team) | X (RP-1) | X (RP-1) | | | | | | | | |
| **Individualized structured cognitive rehabilitation** | NAM (OT-1) | | | | | X | X | X | X | X | X | |
| **Best standard care** | NAMT (OT-2) | | | | | X | X | X | X | X | X | |
| **OUTCOME MEASURES:** | | | | | | | | | | | | |
| **S-NAB Test** | NH | | | | X | | | | | | | X |
| **DTI** | VN/NR | | | | X | | | | | | | X |
| **GAS** | NAM/NAMT (OT-1/OT-2) | | | | | X | X | X | X | X | X | X |

**Table 2:** Study schedule and procedures.

**Modification, withdrawal and unblinding within the intervention**

Participants can withdraw their consent from this study at any time and for any reason. Investigators can also withdraw a participant from the study if he/she becomes non-compliant with the treatment protocol. This includes poor treatment attendance (non-attendance of >50% of total therapy sessions) or the participant's request for withdrawal from the study. We will also provide participants who require immediate medical attention or treatment that is otherwise not part of the study intervention with this throughout the study duration. In the case where unblinding of a participant is necessary (e.g. medical emergency), an investigator (MM) will be informed of the cause and stage of intervention. He/she may continue in the study and follow all study procedures. The participant will only be withdrawn from this study if the immediate treatment violates the study criteria. We will retain all of participant's data (although the participant is no longer blinded) up to the point of participant's removal from the study.

**Adherence strategies**

Adherence to treatment is encouraged throughout for both groups. This will be achieved by providing: 1) participants with clear information on purpose, method and treatment goals during treatment sessions, 2) an appointment card with specific date and time of therapy sessions, and 3) a reminder through phone calls a day before each therapy appointment and a week before DTI scan date.

**Outcome measures**

All measures will be performed at baseline and at 12 weeks of intervention after randomisation. The primary outcome measure for this study is the change in attention deficit and other cognitive domains within intervention groups and direct comparison of each intervention group with the healthy control group. This will be measured by Neuropsychological Assessment Battery® (NAB®, PAR, Inc., Florida, USA)[61]. It consists of six modules: Screening Module and five Domain Specific Modules: Attention, Language, Memory, Spatial and Executive Function. This study will only apply the Screening Module (S-NAB) because it measures the same five functional domains similar or identical to the main NAB modules. It consists of 12 individual tests screening all five mentioned cognitive domains for adults aged 18 to 97 years, validated and sensitive for use in healthy and cognitively impaired brain injured population [24,61-64]. S-NAB also provides two parallel assessment sets (Record Form 1 and Form 2) that will be applied in an alternate fashion to participants in both groups to avoid practice effect.

S-NAB Domain Attention test items and score are interpreted as a marker of an individual's attentional capacity, working memory, psychomotor speed, selective attention, divided attention and information processing [61]. S-NAB has also been applied in our previous cohort study [24] with good validation outcome in our Malaysian mTBI population.

The secondary outcome measures are microstructural WMT parameters and GAS scores. The DTI MRI scan is a Siemens Magnetom Prisma 3T MRI (Siemens AG, Muenchen, Germany). This study will analyse Fractional Anisotropy (FA), Mean Diffusivity (MD) and Radial Diffusivity (RD) parameter changes at pre- and post-intervention [24,65-70]. These parameters quantify the direction and degree of tissue water diffusion within the WMT [65,66]. FA which measures the direction of the diffusion is an index expressed in a range from 0-1, with a higher score indicating a higher integrity of white matter consisting of highly parallel fibres [65,66]. MD measures the average magnitude of the diffusion while RD quantifies pathology in the myelin [65,66]. Changes in the index values of the parameters at different injury timeline will indicate the pathological changes of the WMT.

The tool to measure functional goal outcome will be the GAS [77-79]. The difficulty and importance of rehabilitation goals will be individually set according to his/her current levels of functional performance to reinforce realistic expectations. The sensitivity of GAS is increased by the quantifiable set goals relevant and specific to the participant. Each goal is rated on a 5-point scale and score is given on the extent to which a patient's individual goals are achieved in the course of the intervention. The overall GAS scores calculation will generate a standardized measure (T score) (mean of 50 Standard Deviation ± 10). The details of each goal outcome will be recorded in the GAS Record Sheet [77-79] by a cognitive therapist from each study arm (OT-1 and OT-2) trained in GAS application.

Another important factor to note is the participant's psychological status following mTBI. This study will also perform a screening of anxiety and depression symptoms by using GAD7 and PHQ-9 screening tools at each study timeline. Participant's lifestyle changes/modifications such as spiritual practice, diet change, physical exercise, return to work/education, return to driving, litigation issues and insurance claims will also be reviewed and recorded. Although these parameters will not be part of the study outcome measure, they however remain relevant in influencing treatment adherence and outcome.

**Sample size and power calculation**

In order to fulfil our study objectives we will base the intended sample size calculation on a previous study that had applied a similar treatment approach and which had a similar outcome measure to our study[40]. This study applied the non-commercial statistical power analysis program G*Power Version 3.1.9.2. An effect size of 0.58, which was the functional cognitive outcome of attention [40], is used to calculate the statistical power *a priori.* We will apply Analysis of Variance (ANOVA): repeated measures, within-between interaction, setting an alpha level of 0.05, and approximately 10 participants will provide 89% power to detect a statistical significance. Recruitment is doubled (n=20) for both arms and inflated to 28 to counter 40% attrition rate.

To have a bigger sample size, we, therefore, also decided on a more conservative effect size value and calculated the sample size through estimation of Cohen's *d* effect size value of 0.35. By using similar statistical power analysis program, medium effect size Cohen's *d* of 0.35, setting an alpha level of 0.05, approximately 38 participants will provide 85% power to detect statistical significance. Recruitment will be inflated to 50 participants to enable a 40% attrition rate.

Based on the multiple estimated calculations, the minimum intended sample size is therefore 50 participants. Based on UMMC local data, a 12 months data collection is sufficient to yield the target sample size.

**Ethics considerations**

This study is approved by Medical Research Ethics Committee UMMC (MREC ID NO: 2016928-4293). We will obtain written consent from participants. During consenting, participant will be provided with a Patient Information Sheet detailing the purpose of study, reason for participation, study investigation and intervention methods, withdrawal from the study and contact details of investigators. Once consent is given the form and all other documents with the participant's personal details will be stored immediately in a locked filing cabinet by the consent taker. This will be accessible only to a small number of investigators. Study ID codes will be allocated after consent is obtained and subsequent study documentation will only use the ID code.

Other issues included will be 1) early information sharing of treatment/investigation results in the event of incidental clinical findings that requires urgent treatment by other medical speciality, 2) treatment compliance, 3) cost of investigation and treatment and 4) participant involvement in litigation

issues. In the event of information sharing being required for medical reasons, the participant will be informed immediately followed by referral to the relevant professional either based at UMMC or a different centre of choice. However, costs of further investigation or treatment that is not part of this study will not be funded from the study grants. Treatment compliance will be achieved through our adherence strategy. We strictly adhere to the privacy and confidentiality of participant's medical information. Any information sharing with a third party for various reasons will be managed in accordance with UMMC professional and legal code of conduct.

**Patient and public involvement**

We applied the Medical Research Council's (MRC) Developing and Evaluating Complex Intervention: New Guidance (2006) and Multiphase Optimization Strategy (MOST) framework to guide the development and design of this study. The treatment approach was based on the relevant theoretical evidence whereas treatment approach was evinced through our systematic review, clinical experience and practice setting of interest. We conducted 1) a pilot study and 2) Expert Panel review to evaluate the study design and treatment method that may require further focus.

Our pilot study was approved by Medical Research Ethics Committee, UMMC, Malaysia (UM/EC Ref: 947.15) for the application of cognitive treatment on mTBI patients. They were recruited in the testing of the treatment method, clinical practicality, fidelity of treatment and treatment compliance. We have additionally identified several components required for the optimization of the intervention. These findings were also assessed by the Expert Panel reviewers.

The panel comprised of clinicians who were credentialed in brain injury management and cognitive rehabilitation with minimum of ten years clinical experience working in Malaysia. Panels were made up of seven rehabilitation medicine consultants, one neurosurgeon consultant, one neuroimaging consultant, five cognitive occupational therapists and one clinical psychologist. The focus of discussion was on the feasibility of structured cognitive rehabilitation for mTBI patients in Malaysia, guided by the current evidence, current practise of cognitive rehabilitation in local setting, reviewers' clinical experience and our pilot study findings. A summary of the pilot study outcomes and Expert Panel recommendations are best illustrated in Table 3.

Following the commencement of this study, the input from participants (experience, feedback and outcomes) will be recorded. The data and study materials will belong to UMMC, Malaysia. We will inform

our participants of the result of the study to following completion even if he/she did not complete the study unless he/she has requested no contact.

| Pilot study | Expert panel review |
|---|---|
| Design: a case-controlled study<br>Study components:<br>**Non-randomisation** –to identify participant's willingness to attend therapy as a measure of good compliance.<br>**Treatment application** - treatment was given at early stage of injury (2 weeks post injury) to measure the treatment effect versus spontaneous' recovery.<br>**Treatment accessibility** – outpatient hospital-based treatment is feasible.<br>**Treatment compliance**–high attrition rate (50%), which compromised the treatment fidelity. Reasons for poor treatment compliance were:<br>• Treatment frequency and intensity (>1 hour/weekly for the first 3 months followed by monthly session the following 3 months)<br>• Mental fatigue<br>• 'Unreadiness' to receive treatment<br>• Treatment and transportation costs<br>• Work demand (limited time off work and income lost)<br><br>**Treatment method-** clinical application of treatment was acceptable to participants.<br>**Treatment effect** - the application of effect size measurement is consistent with MOST recommendation.<br>**Outcome measure application** –S-NAB was able to measure score differences in its five domains. DTI parameters reported changes consistent with current literature evidence in mTBI population. | Design: Randomization was recommended in clinical trial design<br>Review components:<br>**Fidelity of treatment**<br>1) Clear information on purpose, method and treatment goals during treatment sessions<br>2) An appointment card with specific date and time of therapy sessions<br>3) A reminder through phone calls a week and a day before each therapy<br>4) Review at 72 hours, 2 weeks, 6 weeks, and 3 months (baseline) to increase sensitivity towards participant selection, early medical intervention if required and to improve adherence.<br>**Treatment method**<br>1) As outpatient setting, with frequency 1hour/week for 12 weeks duration.<br>2) Individualised treatment approach with standardization through direct attention training and metacognitive strategy<br>3) To clarify the metacognitive strategies applied in therapy such as 'self-monitoring', self-instructional procedure', 'self-evaluation', 'rehearsal', 'self-pacing', 'positive self-statement', use of internal/external strategy<br>**Outcome measure**<br>Neuropsychological assessment as a practice standard<br>Guided individualised goals (GAS application) to standardise the functional goal outcome measurement for both groups. |

**Table 3**: A summary of recommendations from pilot study findings and Expert Panel review

**Statistical analysis**

Descriptive statistics will be conducted on the data obtained from all groups to provide a demographic overview of our study population. A $p$ value <0.05 will be considered statistically significant. We will also report additional relevant data, which may affect the study outcome. This will include lifestyle modifications, litigation cases, changes in socioeconomic status, physical symptoms and psychological status.

The measure of treatment effect will be changes in neuropsychological assessment scores. We will calculate the effect size of each S-NAB mean Domain Standard score (Attention, Language, Memory, Spatial and Executive Function domains) as well as the Total Index Score within each intervention group. Cohen's $d$ moderate (>0.5) to large effect size (>0.8) is considered to be clinically significant. Another treatment effect analysis will include reporting on the CogniPlus Attention task difficulty level achieved for each program (ALERT, FOCUS, VIG, SELECT, DIVID), the change of response time and measurement of errors.

Similarly, functional changes will be measured by using the effect size calculation of mean GAS T scores obtained at pre and post intervention. We will also compare the mean change in GAS T score between groups and report on the type and preference of metacognitive strategies used by participants of both groups.

The secondary analysis will include measurement of structural brain changes following intervention. This data will be obtained from the DTI MRI scan performed at pre and post intervention, for all groups. We will identify FA, MD and RD parameters with statistically significant mean values ($p<0.05$) via whole brain analysis known as Tract-based Spatial Statistics (TBSS)[80] and region of interest (ROI) approach which is part of the FSL (v5.0.6; University of Oxford, Oxford UK) [81] and AFNI (v2011_12_21_1014; National Institute of Mental Health, Bethesda, MD) software packages. The DTI parameters of both intervention groups at three- and six months study timelines will be compared with the healthy control group by using repeated measure analysis. This is in the assumption that the study fulfils the repeated measure analysis of normally distributed data sample and homogeneity of variance.

Further analysis also includes correlation of cognitive performance with structural brain changes. We will perform Pearson's correlation coefficient between mean S-NAB Standard score of each domain and the selected WMT (with statistical significant).

**Data management**

All data obtained including from non-adherence or voluntarily withdrawn participants will also be reviewed and included in the study analysis where applicable. All study documents will be securely kept at the study site. Participant information will be stored in locked filing cabinets and will only be accessible to selected investigators. All data documents, administrative forms, reports and analysis documents will only have coded participant ID to avoid identification by any investigator of the study. Data entry will only be performed by an appointed research assistant. Any other document that has a participant's name such as consent form will be kept in a separate cabinet accessible by a selected investigator (MM).

## Discussion

To our knowledge, this is the first randomized control trial of cognitive intervention in adult mTBI population, conducted in a developing country, Southeast Asia region. Previous studies have been conducted in the Western population with a predominantly Caucasian ethic group and limited ethnic variation. A study from this region with various ethnic group involvements of both genders, may better represent the study population and in turn add further knowledge on the pattern of impairment following mTBI. Uniquely, cultural practice and belief system may also influence treatment response and outcome. Development of the intervention approach was based on current evidence, a pilot study and Expert Panel review. This trial incorporates technology in the treatment application consistent with the changing face of health service delivery in Malaysia, aiming at resource efficiency and treatment effectiveness, albeit using a tailored treatment approach appropriate for the local setting. The results of this study will provide a comprehensive overview on the effect of cognitive rehabilitation in mTBI. Owing to the paucity of scientific and clinical knowledge, this trial will also contribute to the evidence-based cognitive treatment model for mTBI population.

## Trial status

At the time of manuscript preparation, 30 potential participants have been recruited at three months post-injury. Fifteen participants were consented and received treatment following randomization. Recruitment is due to finish in April 2019. Data lock has not yet occurred and no analyses have been performed.

## Funding

This study is partially funded by High Impact Research Grant UM.C/625/1/HIR/MOHE/CHAN/12 and fully funded by Post Graduate Research Grant (IPPP) PPPC/C1-2016/DGJ/01 and Malaysian Ministry of Science and Innovation (MOSTI) grant (MOSTI Flagship Project FP0911F001)

**Protocol version identifier**: ClinicalTrials.gov ID NCT03237676

**Protocol Registered date**: 18th July 2017

**Protocol updated date**: 16th August 2017

**Trial sponsor**: University of Malaya, Malaysia

**Competing interest:** none declared

## Acknowledgement

We wish to thank all our mTBI participants involved in the pilot control study as well as Expert Panels in involved in the review of our intervention development and study.

## Authors' contribution

NH initiated the study, applied for study funding and is the principal investigator. NH, MM, VN, NR, AD, RDN and GSY were involved in the conception, development of the intervention and design of the study. NAM and NAMT implemented the cognitive intervention. TLK provided the consultation on DTI processing and analysis. MD and NM provided important statistical contributions. All authors provided feedback on drafts of this paper, read and approved the final manuscript. NH, MM, VN and NR are the guarantors for the study and accept full responsibility for the work and /or the conduct of the study, had access to data, and controlled the decision to publish. MM is the corresponding author and attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

## Availability of data and material

The data and study materials belong to UMMC, Malaysia. Any request will have to go through Medical Record Department of UMMC, Malaysia. Dissemination of trial result is through publication.

## Ethics and Dissemination

The study protocol is approved by the Medical Research Ethics Committee UMMC (MREC ID NO: 2016928-4293). The findings of the trial will be disseminated through peer-reviewed journals and scientific conferences.

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**Figure 1**: Flowchart showing the stages of recruitment in this study.

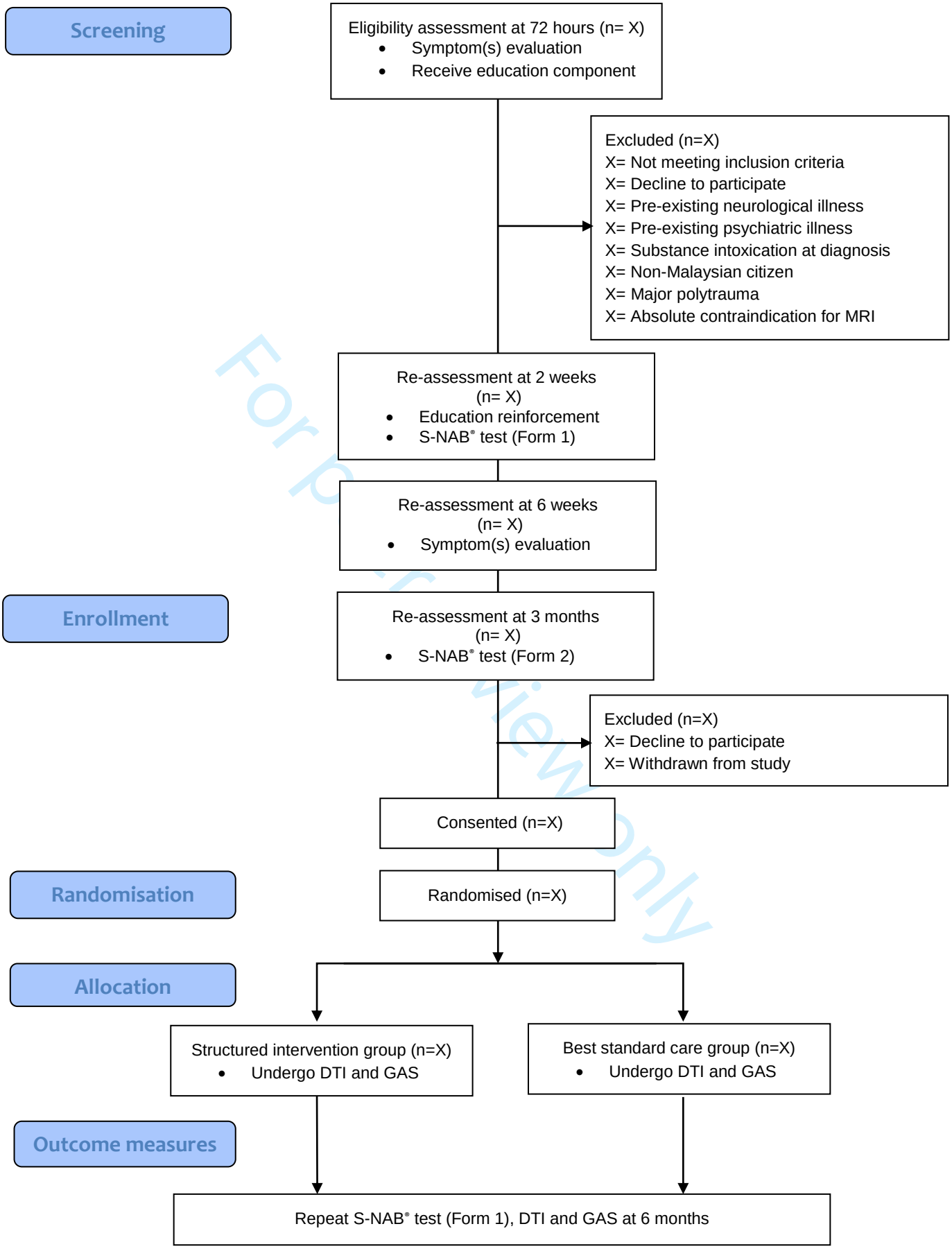


**Figure 1**: Flowchart showing the stages of recruitment in this study.


SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

| Section/item | Item No | Description | Addressed on line number |
|---|---|---|---|
| **Administrative information** | | | |
| Title | 1 | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym | 1-2 |
| Trial registration | 2a | Trial identifier and registry name. If not yet registered, name of intended registry | 380-383 |
| | 2b | All items from the World Health Organization Trial Registration Data Set | 376-383 |
| Protocol version | 3 | Date and version identifier | 380-383 |
| Funding | 4 | Sources and types of financial, material, and other support | 376-379 |
| Roles and responsibilities | 5a | Names, affiliations, and roles of protocol contributors | 389-397 |
| | 5b | Name and contact information for the trial sponsor | 383 |
| | 5c | Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities | NA NA |
| | 5d | Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) | NA |

| | | | |
|---|---|---|---|
| **Introduction** | | | |
| Background and rationale | 6a | Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention | 44-105 |
| | 6b | Explanation for choice of comparators | 44-105 |
| Objectives | 7 | Specific objectives or hypotheses | 107-117 |
| Trial design | 8 | Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) | 118-132; Figure 1 |
| **Methods: Participants, interventions, and outcomes** | | | |
| Study setting | 9 | Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained | 122-128 |
| Eligibility criteria | 10 | Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) | 133-150, Table 1 |
| Interventions | 11a | Interventions for each group with sufficient detail to allow replication, including how and when they will be administered | 151-203; Figure 1 |
| | 11b | Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) | 208-218 |
| | 11c | Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) | 219-223 |
| | 11d | Relevant concomitant care and interventions that are permitted or prohibited during the trial | NA |
| Outcomes | 12 | Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended | 224-262 |
| Participant timeline | 13 | Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) | 204-207; Table 2 |

| | | | |
|---|---|---|---|
| Sample size | 14 | Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations | 263-279 |
| Recruitment | 15 | Strategies for achieving adequate participant enrolment to reach target sample size | 219-223; 263-279 |
| **Methods: Assignment of interventions (for controlled trials)** | | | |
| Allocation: | | | |
| Sequence generation | 16a | Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions | 204-207; Table 2 |
| Allocation concealment mechanism | 16b | Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned | 204-207; Table 2 |
| Implementation | 16c | Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions | Table 2 |
| Blinding (masking) | 17a | Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how | Table 2 |
| | 17b | If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial | 208-218 |
| **Methods: Data collection, management, and analysis** | | | |
| Data collection methods | 18a | Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol | Figure 1;204-207; Table 2; 208-262;298-321;Table 3 |
| | 18b | Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols | 208-223 |

| | | | |
|---|---|---|---|
| Data management | 19 | Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol | 350-357 |
| Statistical methods | 20a | Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol | 322-349 |
| | 20b | Methods for any additional analyses (eg, subgroup and adjusted analyses) | NA |
| | 20c | Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) | 208-218 |
| **Methods: Monitoring** | | | |
| Data monitoring | 21a | Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed | NA |
| | 21b | Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial | NA |
| Harms | 22 | Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct | 208-218 |
| Auditing | 23 | Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor | NA |
| **Ethics and dissemination** | | | |
| Research ethics approval | 24 | Plans for seeking research ethics committee/institutional review board (REC/IRB) approval | 280-297 |
| Protocol amendments | 25 | Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) | ClinicalTrials.gov |

| | | | |
|---|---|---|---|
| Consent or assent | 26a | Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) | Table 2 |
| | 26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable | NA |
| Confidentiality | 27 | How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial | 208-218;350-357 |
| Declaration of interests | 28 | Financial and other competing interests for principal investigators for the overall trial and each study site | 376-385 |
| Access to data | 29 | Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators | 350-357;Table 2 |
| Ancillary and post-trial care | 30 | Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation | NA |
| Dissemination policy | 31a | Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions | 298-321 |
| | 31b | Authorship eligibility guidelines and any intended use of professional writers | BMJ guideline |
| | 31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code | NA |
| **Appendices** | | | |
| Informed consent materials | 32 | Model consent form and other related documentation given to participants and authorised surrogates | - |
| Biological specimens | 33 | Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable | NA |

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.