

BMJ Open Randomised controlled clinical trial of a structured cognitive rehabilitation in patients with attention deficit following mild traumatic brain injury: study protocol

Norhamizan Hamzah,¹ Vairavan Narayanan,² Norlisah Ramli,³ Nor Atikah Mustapha,⁴ Nor Adibah Mohammad Tahir,⁴ Li Kuo Tan,³ Mahmoud Danaee,⁵ Nor Asiah Muhamad,⁶ Avril Drummond,⁷ Roshan das Nair,^{8,9} Sing Yau Goh,¹⁰ Mazlina Mazlan¹

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For numbered affiliations see end of article.

Correspondence to

Dr Mazlina Mazlan;
mazlinamazlan@ummc.edu.my

ABSTRACT

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

Setting A single centre study, Malaysia.

Participants Adults aged between 18 and 60 years with mTBI as a result of road traffic accident, with no previous history of head trauma, minimum of 9 years education and abnormal cognition at 3 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 the best patient-centred care for attention disorders. Therapy frequency for both groups will be 1 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.

Ethics and dissemination The study protocol was approved by the Medical Research Ethics Committee

Strengths and limitations of this study

- To our knowledge, this is the first randomised controlled trial of a cognitive intervention in an adult mild traumatic brain injury (mTBI) population, conducted in a low/middle-income 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, although 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.

UMMC (MREC ID NO: 2016928–4293). The findings of the trial will be disseminated through peer-reviewed journals and scientific conferences.

Trial registration number NCT03237676

BACKGROUND

Mild traumatic brain injury (mTBI) is defined as a traumatic injury that induces transient physiological disruption of the brain function.¹ mTBI is often used interchangeably with concussion and is a clinical diagnosis.¹ The most common aetiology in the low-income and middle-income countries is road traffic

accident (RTA) that disproportionately affects young men (15–29 years of age).^{2–4} Statistically, 20–50 million people sustained non-fatal injuries worldwide as a result of RTA and with an increasing rate in the low/middle-income 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%–60% of individuals with mTBI are reported to have attention deficits in the first 3 months postinjury.¹⁸ In the majority of individuals, resolution of mixed cognitive deficits begins in the first month and up to 1-year postinjury.^{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 6 months and may, indeed continue to have neurocognitive functional deficits beyond 1 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} challenge professionals in standardising 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 the 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 postacute (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 emphasises 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 patients with mTBI with cognitive deficits. A large randomised trial is required to support this hypothesis.

Clinical, imaging and functional outcome measures in mTBI

A combination of clinical, imaging and functional outcome measures is a comprehensive approach to analyse cognitive intervention that can make an impact in the 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 minuscule for detection through routine CT and 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 patients 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 (GAS),^{71 72 77–79} Extended Glasgow Outcome Scale⁷³ 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 hypothesise that structured cognitive rehabilitation for attention deficits following mTBI will improve patients’ cognitive function of attention compared with standard care.

Study objectives

The objectives are:

- ▶ To measure the clinical effect of a 12-week individualised structured cognitive rehabilitation, which addresses attention deficit and overall cognitive status.
- ▶ To analyse the effect of treatment on brain structures and functional changes.

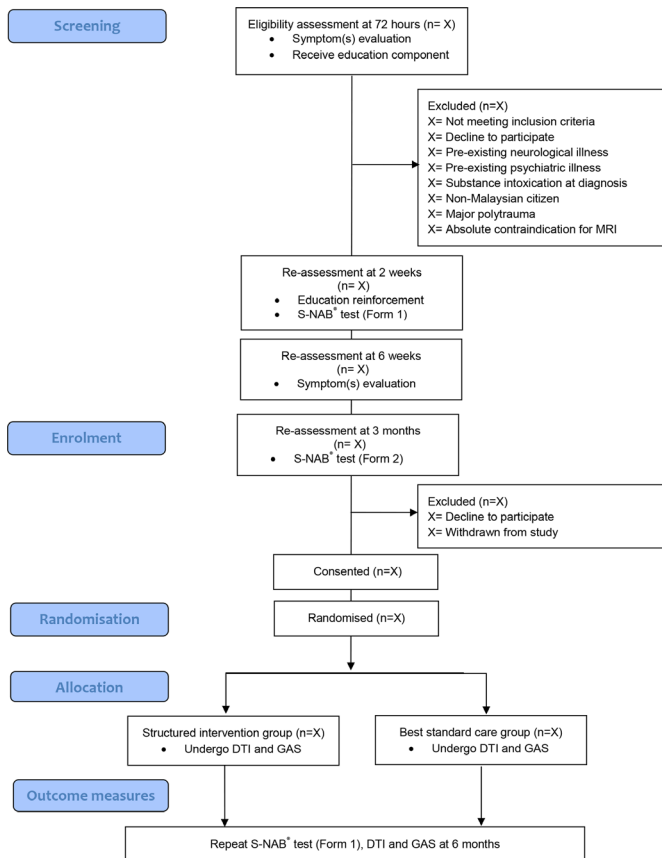


Figure 1 Flow chart showing the stages of recruitment in this study. DTI, Diffusion Tensor Imaging; GAS, Goal Attainment Scaling; S-NAB, Neuropsychological Assessment Battery-Screening Module.

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

Design

This will be a prospective double blind, randomised controlled trial with two parallel groups. The study design is summarised 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 (neurorehabilitation, spinal cord rehabilitation, prosthetic rehabilitation and orthotic rehabilitation, paediatric rehabilitation 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 1 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, 2 and 6 weeks following mTBI.

Inclusion criteria

mTBI is defined as physiological disruption of brain function as a result of trauma with symptoms of loss of consciousness 30 min 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 and 60 years old; Malaysian resident; no previous history of head trauma; minimum of 9 years education; persistently abnormal Neuropsychological Assessment Battery-Screening Module (S-NAB) Attention Domain score at 3 months of mTBI; ability to give consent and willingness to comply with cognitive rehabilitation programme. 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](#)).

Intervention

Potential participants will undergo screening before enrolment and randomisation ([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, that is, ED physicians will perform this review at 72 hours of injury. At 2 and 6 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 specialty will be made if indicated during these reviews.

At 3 months after injury, potential participants will undergo a repeat of clinical review and S-NAB test. Eligibility criteria will include (1) an abnormal S-NAB Attention Domain score at 3 months post-mTBI or (2) deficits in more than one S-NAB domain, not including the attention domain. The concomitant domain deficit(s) will also

Table 1 The study criteria

Criteria	IG	SG	HG
Inclusion criteria			
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 programme			
Exclusion criteria			
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	✓	✓	

IG-individualised structured cognitive rehabilitation group.

HG, healthy control group; mTBI, mild traumatic brain injury; SG, standard care group; S-NAB, Neuropsychological Assessment Battery-Screening Module.

be evaluated on completion of therapy. The cognitive intervention will be conducted at the Neurorehabilitation Therapy Unit, Department of Rehabilitation Medicine, UMMC as an outpatient setting. Participants will be assigned to different treatment groups via the randomisation 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 2-part 12-week individualised structured cognitive rehabilitation. The first part will be Direct Attention Training, a deficit-oriented computer-based attention-training programme called CogniPlus.⁴⁵ Each session last 30 min, once a week.

CogniPlus is a computer-based software programme 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 recognising 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 min 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-realisation of deficits or guided by therapist). Symptom(s) management may include physical (eg, imbalance, fatigue and sleep dysregulation), psychological (eg, mild anxiety or depression) and cognitive (eg, 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), for

example, return to driving may involve driving simulation training, and visuospatial training. The frequency of sessions will be 1 hour per week, for 12 weeks. A trained OT 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, DTI imaging and psychological screening tools, which will include the Generalised Anxiety Disorder 7-item (GAD-7) 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 randomised via computer-generated random permuted block assignment, gender stratified into equally proportioned intervention and control group numbers. The study schedule, procedures and blinding of coinvestigators are presented in table 2.

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 necessary treatment to participants who require immediate medical attention that is otherwise not part of the study intervention throughout the study duration. In the case where unblinding of a participant is necessary (eg, 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 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 NAB (PAR, 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 18–97 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 study²⁴ with good validation outcome in our Malaysian mTBI population.

The secondary outcome measures are microstructural white matter tract (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-intervention 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 to 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 standardised measure (T score) (mean of 50 SD ±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.

Table 2 Study schedule and procedures

		Study period										End of treatment	
Time point	Coinvestigator (initials)	Enrolment		Enrolment		Enrolment		Allocation		Postallocation		Last study visit	Outcome measures
		$-t_3$ 72 hours mTBI	$-t_2$ 2 weeks mTBI	$-t_1$ 6 weeks mTBI	0 3 months mTBI	t_1 Study visit 1	t_2 Study visit 1	t_3 Study visit 2 onwards	t_4 Study visit 2 onwards	t_5 Study visit 2 onwards	t_{12} Last study visit		
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	LKT					X							X
GAS	NAM (OT-1) and NAMT (OT-2)						X	X	X	X	X	X	X
Interventions:													
Education component/symptom(s) evaluation	ED team/RP-1 (ED team)	X	X (RP-1)	X (RP-1)									
Individualised structured cognitive rehabilitation	NAM (OT-1)					X	X	X	X	X	X	X	
Best standard care	NAMT (OT-2)					X	X	X	X	X	X	X	
Outcome measures:													
S-NAB test	NH						X						X
DTI	VN/NR						X						X

Continued

(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 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.

Participants in the pilot study 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 optimisation 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 10 years clinical experience working in Malaysia. Panels were made up of seven rehabilitation medicine consultants, one neurosurgeon consultant, one neuroimaging consultant, five cognitive OT and one clinical psychologist. The focus of discussion was on the feasibility of structured cognitive rehabilitation for patients with mTBI 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](#).

Table 3 A summary of recommendations from pilot study findings and expert panel review

Pilot study	Expert panel review
<p>Design: a case–controlled study</p> <p>Study components:</p> <p>Non-randomisation—to identify participant's willingness to attend therapy as a measure of good compliance.</p> <p>Treatment application—treatment was given at early stage of injury (2 weeks postinjury) to measure the treatment effect vs spontaneous recovery.</p> <p>Treatment accessibility—outpatient hospital-based treatment is feasible.</p> <p>Treatment compliance—high attrition rate (50%), which compromised the treatment fidelity. Reasons for poor treatment compliance were:</p> <ul style="list-style-type: none"> ▶ Treatment frequency and intensity (>1 hour/weekly for the first 3 months followed by monthly session the following 3 months) ▶ Mental fatigue. ▶ 'Unreadiness' to receive treatment. ▶ Treatment and transportation costs. ▶ Work demand (limited time off work and income lost). <p>Treatment method—clinical application of treatment was acceptable to participants.</p> <p>Treatment effect—the application of effect size measurement is consistent with MOST recommendation.</p> <p>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.</p>	<p>Design: Randomisation was recommended in clinical trial design</p> <p>Review components:</p> <p>Fidelity of treatment</p> <ol style="list-style-type: none"> 1. Clear information on purpose, method and treatment goals during treatment sessions. 2. An appointment card with specific date and time of therapy sessions. 3. A reminder through phone calls a week and a day before each therapy 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. <p>Treatment method</p> <ol style="list-style-type: none"> 1. As outpatient setting, with frequency 1 hour/week for 12 weeks duration. 2. Individualised treatment approach with standardisation through direct attention training and metacognitive strategy 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. <p>Outcome measure</p> <p>Neuropsychological assessment as a practice standard</p> <p>Guided individualised goals (GAS application) to standardise the functional goal outcome measurement for both groups.</p>

DTI, Diffusion Tensor Imaging; GAS, Goal Attainment Scaling; MOST, Multiphase Optimisation Strategy; mTBI, mild traumatic brain injury; S-NAB, Neuropsychological Assessment Battery-Screening Module.

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 following its completion, even if he/she did not complete the study unless he/she has requested no contact.

Statistical analysis

Descriptive statistics will be conducted on the data obtained from all groups to provide a demographic overview of our study population. A $p < 0.05$ 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 and 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 preintervention and postintervention. We will also compare the mean change in GAS T score between groups and report on the type and preference of meta-cognitive strategies used by participants of both groups.

The secondary analysis will include measurement of structural brain changes following intervention. These data will be obtained from the DTI MRI scan performed at preintervention and postintervention, 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 approach which is part of the FSL (V.5.0.6; University of Oxford, Oxford UK)⁸¹ and AFNI (V.2011_12_21_1014; National Institute of Mental Health, Bethesda, Maryland, USA) software packages. The DTI parameters of both intervention groups at 3 and 6 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 randomised control trial of cognitive intervention in adult mTBI population, conducted in a low/middle-income country, Southeast Asia region. Previous studies have been conducted in the Western population with a predominantly Caucasian ethnic 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, although 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 3 months post-injury. Fifteen participants were consented and received treatment following randomisation. Recruitment is due to finish in April 2019. Data lock has not yet occurred and no analyses have been performed.

Author affiliations

¹Department of Rehabilitation Medicine, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia

²Department of Surgery, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia

³Department of Biomedical Imaging, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia

⁴Department of Rehabilitation Medicine, University of Malaya Medical Centre, Kuala Lumpur, Malaysia

⁵Department of Social and Preventive Medicine, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia

⁶Institute for Public Health, National Institutes of Health, Ministry of Health, Setia Alam, Malaysia
⁷Faculty of Medicine and Health Sciences, University of Nottingham, Nottingham, United Kingdom
⁸School of Medicine, University of Nottingham, Nottingham, United Kingdom
⁹Institute of Mental Health, Nottinghamshire Healthcare Trust, Nottingham, United Kingdom
¹⁰Lee Kong Chian Faculty of Engineering and Science, Universiti Tunku Abdul Rahman, Sungai Long Campus, Malaysia

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