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# BMJ Open

## 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.

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2  
3 1 **TITLE: A randomised controlled trial of a structured cognitive rehabilitation in patients with**  
4  
5 2 **attention deficit following mild traumatic brain injury: Study protocol**

6  
7 3 **ABSTRACT**

8  
9 4 **Objectives:** This study hypothesizes that structured cognitive rehabilitation for attention deficits  
10  
11 5 following mTBI will improve patients' cognitive function. The primary objective is to measure the change  
12  
13 6 of attention deficit between groups and the secondary objective is to examine the effect of treatment on  
14  
15 7 brain structures and daily life functions.

16  
17 8 **Design:** This is a prospective double blind, randomized controlled trial with two parallel groups.

18  
19 9 **Setting:** This trial will be conducted at a single centre, in Malaysia.

20  
21 10 **Participants:** This study will recruit adult participants with the following inclusion criteria: mTBI as a  
22  
23 11 result of road traffic accident; adult aged between 18 to 60 years old; Malaysia citizen; no previous  
24  
25 12 history of head trauma; education level minimum of nine years; abnormal cognition at three months after  
26  
27 13 mTBI; provision of informed consent, able to communicate in basic English and willingness to comply  
28  
29 14 with cognitive rehabilitation sessions. The exclusion criteria include pre-existing chronic illness that  
30  
31 15 cause neurological symptoms or complications; severe comorbid neurological or psychiatric disorder; on  
32  
33 16 long-term medication that alter or affect cognitive and psychological status; clinical evidence of substance  
34  
35 17 intoxication at the time of injury; major polytrauma and absolute contraindication for Magnetic  
36  
37 18 Resonance Imaging (metal or implant not compatible for imaging, claustrophobia). The sample size  
38  
39 19 calculation, setting an alpha level of 0.05, approximately 38 participants will provide 85% power to  
40  
41 20 detect statistical significance. Recruitment is inflated to 46 participants to enable a 20% attrition rate.

42  
43 21 **Interventions:** All potential participants with confirmed mTBI diagnosis will undergo  
44  
45 22 Neuropsychological Assessment Battery® at two weeks and at three months following injury. Participants  
46  
47 23 who fulfill study criteria will be recruited and randomised. The intervention group will receive  
48  
49 24 individualised computer-based cognitive rehabilitation known as Direct Attention Training program and  
50  
51 25 cognitive functional problem-solving training. The control group will receive best patient-centred care for  
52  
53 26 attention disorders which will include symptom management and cognitive compensatory strategies.  
54  
55 27 Therapy frequency for both groups will be one hour per week for 12 weeks.

56  
57 28 **Main outcome measures:** The primary outcome measure is the change of attention deficit between  
58  
59 29 intervention groups and healthy group via Neuropsychological Assessment Battery® scores. The

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

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

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

### 36 **Keywords:**

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

### 39 **ARTICLE SUMMARY:**

#### 40 **Strengths and limitations of this study:**

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

### 52 **BACKGROUND**

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

1  
2  
3 57 Statistically, 20 to 50 million people sustained non-fatal injuries worldwide as a result of RTA and with an  
4  
5 58 increasing rate in the developing countries[2,3].  
6

7 59 Cognitive deficit is rarely singular in mTBI. Commonly reported symptoms are attention, memory  
8  
9 60 and executive function deficits, each with varying severity and recovery pattern[5-14]. Specifically,  
10  
11 61 attention deficit is extremely common in TBI[15,16]. Attention is known to be the basis of all other  
12  
13 62 cognitive abilities[17]. About 40 to 60% of individuals with mTBI were reported to have attention deficits  
14  
15 63 in the first three months post-injury[18]. In the majority of individuals, resolution of mixed cognitive  
16  
17 64 deficits begins in the first month up to one-year post-injury[5,7,11,12,19-21]. A proportion of this  
18  
19 65 population quite often progresses to have chronic cognitive disability that is overlooked due to the initial  
20  
21 66 'mild' presentation[6,10,22-25]. At least one-third of survivors fail to return to full functional status at six  
22  
23 67 months and may continue to have neurocognitive functional deficits beyond one year of injury[5,12,25-  
24  
25 68 29].  
26

### 27 69 **Cognitive rehabilitation in mTBI**

28  
29 70 Currently, there is no standard treatment protocol for cognitive rehabilitation for the mTBI  
30  
31 71 population. The early neuropsychological model of attention has already made the assumption that  
32  
33 72 attention should be the focus of rehabilitation, before more advanced cognitive skills be treated[33]. In  
34  
35 73 the last 20 years, various cognitive treatment approaches have been reported in systematic reviews[34-  
36  
37 74 37]. These include remediation strategies,[38-49], compensatory strategies[50-57] and patient education  
38  
39 75 intervention[6,39,53,58]. These approaches are usually applied in combination, to optimise both  
40  
41 76 cognitive and functional recovery[17,27,28,30,31,33- 38]. In particular, treatment for attention deficits in  
42  
43 77 TBI was recommended at post-acute stage of trauma [28,30,34]. Methods of treatment included  
44  
45 78 multidimensional approach, and tasks with hierarchical difficulty and complexity[30,34]. Several studies  
46  
47 79 also reported improved psychological outcome and coping of symptoms on those who received patient  
48  
49 80 education and reassurance following mTBI[35,36]. However, these conclusions were based on a limited  
50  
51 81 number of high-quality clinical trials. Due to the heterogeneity of cognitive deficits, varied intervention  
52  
53 82 methodology, different reporting style and no treatment standardisation[34-37], the consensus was for  
54  
55 83 more robust clinical trials of larger sample size, well-described complex intervention and standardised  
56  
57 84 reporting method [34-37].  
58  
59  
60

1  
2  
3 85 Delivery of cognitive rehabilitation emphasizes six principles: 1) intervention that is theory-driven  
4  
5 86 and meaningful, 2) intervention is task-specific with increasing complexity relevant to individual needs,  
6  
7 87 3) the need to regularly practice skills acquired, 4) progress monitoring to tailor to individual's needs, 5)  
8  
9 88 generalisation of learnt strategies to apply in real-life skills, and 6) real-world adaptation to ensure  
10  
11 89 success[17,49,59]. A practical, widely accepted treatment approach with the application of evidence-  
12  
13 90 based treatment principles may represent a comprehensive treatment model in treating mTBI patients  
14  
15 91 with cognitive deficits. A large randomised trial is required to support this hypothesis.

### 17 92 **Clinical, imaging and functional outcome measures in mTBI**

18  
19 93 A combination of these three outcome measures is a comprehensive approach to analyse cognitive  
20  
21 94 intervention that can make an impact in clinical practice. Scientific reviews and guidelines have  
22  
23 95 recommended the use of neuropsychological assessment as an appropriate clinical outcome  
24  
25 96 measure[17,27,28,30,31,33,34,36,37]. In adult mTBI, a test which was sensitive across various cognitive  
26  
27 97 domains[21,24,41,43,44,53,57,60], specific to population study[24,40,43], had good validity and  
28  
29 98 reliability[41,44,51,57,61-64], was cost effective and practical to use in a clinical setting[44,53,62-64]  
30  
31 99 would be ideal.

32  
33 100 The structural injury in mTBI however, is too miniscule for detection through routine computed  
34  
35 101 tomography (CT) and Magnetic Resonance Imaging (MRI)[65-67]. Over the last 10 years, Diffusion Tensor  
36  
37 102 Imaging (DTI) has become accepted as a non-invasive tool that is able to quantify microstructural brain  
38  
39 103 changes in mTBI[24,65-70]. Changes in its parameters are indicative of microstructural remodelling at  
40  
41 104 acute and chronic stages of injury, potentially explaining the persistence of symptoms that would  
42  
43 105 otherwise be attributed to other causes [24,65-70]. A longitudinal DTI study may increase our  
44  
45 106 understanding of the brain structural transformation in mTBI.

46  
47 107 The most important outcome following mTBI is the ability for survivors to return to their previous  
48  
49 108 functional state and quality of life. Common scales to measure disability and function are usually sensitive  
50  
51 109 to cognitive deficits but not necessarily specific to the TBI population[39-41,52,53]. Many studies have  
52  
53 110 also reported specific outcome measures for TBI that has good validity, reliability and practical in a  
54  
55 111 clinical setting[71-78], such as Goal Attainment Scaling[71,72,77,78], Extended Glasgow Outcome  
56  
57 112 Scale[73] and Functional Assessment Measure[74].

58  
59 113 This trial evaluates a complex clinical intervention, to provide evidence on the effect of cognitive  
60

1  
2  
3 114 rehabilitation in mTBI. We extend the outcome measures to include anatomical, clinical and functional  
4  
5 115 aspects to establish a comprehensive evidence-based treatment model.  
6

## 7 116 **METHODS**

### 8 9 117 **Study hypothesis and objectives**

11 118 We hypothesize that structured cognitive rehabilitation for attention deficits following mTBI will  
12  
13 119 improve patients' cognitive function of attention compared to the standard care. The primary objective is  
14  
15 120 to measure the effect of a 12-week individualized structured cognitive rehabilitation to address attention  
16  
17 121 deficit. The secondary objective is to examine the effect of treatment on brain structures and function in  
18  
19 122 daily life.  
20

### 21 123 **Design**

22 124 This will be a prospective double blind, randomized controlled trial with two parallel groups. The  
23  
24 125 study design is summarized in **Fig. 1**.  
25

### 26 126 **Participants and recruitment process**

27  
28 127 This trial will be conducted at a single centre, University Malaya Medical Centre (UMMC), Malaysia.  
29  
30 128 We will recruit participants through the Emergency Medicine Department (ED), UMMC from 1<sup>st</sup> August  
31  
32 129 2017. This is a hospital, which provides acute service and is a tertiary referral centre in Malaysia. It is  
33  
34 130 situated in the urban area of the nation's capital city Kuala Lumpur with the population of 1.76 million.  
35  
36 131 ED physicians, radiologists and neurosurgeons will refer mTBI cases to a research assistant for  
37  
38 132 recruitment. Potential cases will also be screened through UMMC digital medical record system. This  
39  
40 133 study had obtained ethical approval from the Medical Research Ethics Committee, UMMC (MREC ID NO:  
41  
42 134 2016928-4293).  
43

### 44 135 **Inclusion criteria**

45  
46 136 The inclusion criteria for this study include mTBI as a result of RTA only; adult aged between 18 to  
47  
48 137 60 years old; Malaysia citizen; no previous history of head trauma; education level minimum of nine  
49  
50 138 years; abnormal NAB® Attention Domain score at three months after mTBI; provision of informed  
51  
52 139 consent, able to communicate in basic English and willingness to comply with cognitive rehabilitation  
53  
54 140 sessions.  
55

56 141

57 142



### 143 **Exclusion criteria**

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

### 149 **Intervention**

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

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

### 162 ***Individualised structured cognitive rehabilitation group***

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

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

1  
2  
3 172 automatically adapt to an individual's performance and alter the training difficulty level (hierarchical  
4  
5 173 difficulty).

6  
7 174 The second part of this intervention is strategy approach (metacognitive awareness and  
8  
9 175 compensatory strategy) performed after CogniPlus training. It will last for 30 minutes and will involve  
10  
11 176 feedback on the participant's CogniPlus performance, review of cognitive-related problem encountered in  
12  
13 177 daily activities since the injury and problem-solving training. A trained and certified Occupational  
14  
15 178 Therapist (OT-1) in cognitive therapy and CogniPlus will conduct all the sessions.

#### 17 179 ***Standard care group***

18  
19 180 This group will receive the best standard care for attention disorders. This is a patient-centred  
20  
21 181 cognitive therapy, which will include symptom management and compensatory strategies. The frequency  
22  
23 182 of sessions will be one hour per week, for 12 weeks. A trained occupational therapist in cognitive therapy  
24  
25 183 (OT-2) who is not involved with the intervention group treatment, will conduct all the sessions.

#### 27 184 ***Control group***

28  
29 185 This will consist of healthy individuals demographically matched for age, gender and education years to  
30  
31 186 the intervention groups. The data is collected for comparison purpose.

#### 33 187 **Randomisation, consent and blinding**

34  
35 188 Participants with mTBI who fulfill the study criteria will be randomized via computer-generated  
36  
37 189 random permuted block assignment, gender-stratified into equally proportioned intervention and control  
38  
39 190 group numbers. The study schedule and procedures are presented in **Table 1**.

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

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

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

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

### 200 **Adherence strategies**

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

### 206 **Outcome measures**

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

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

1  
2  
3 220 will analyse Fractional Anisotropy (FA), Mean Diffusivity (MD) and Radial Diffusivity (RD) parameter  
4  
5 221 changes at pre- and post-intervention[24,65-70]. These parameters quantify the direction and degree of  
6  
7 222 tissue water diffusion within the WMT[65,66]. FA which measures the direction of the diffusion is an  
8  
9 223 index expressed in a range from 0-1, with a higher score indicating a higher integrity of white matter  
10  
11 224 consisting of highly parallel fibres[65,66]. MD measures the average magnitude of the diffusion while RD  
12  
13 225 quantifies pathology in the myelin[65,66].

14  
15 226 We will apply whole brain analysis method to identify FA, MD and RD parameters with statistically  
16  
17 227 significant mean values ( $p < 0.05$ ) known as Tract-based Spatial Statistics (TBSS) which is part of the FSL  
18  
19 228 (v5.0.6; University of Oxford, Oxford UK) software package. Based on TBSS findings we will also identify  
20  
21 229 specific tracts via region of interest (ROI) approach utilizing the FSL (v5.0.6; University of Oxford) and  
22  
23 230 AFNI (v2011\_12\_21\_1014; National Institute of Mental Health, Bethesda, MD) software packages.

24  
25 231 The tool to measure functional outcome is GAS[77-79]. The difficulty and importance of  
26  
27 232 rehabilitation goals will be individually set according to his/her current levels of functional performance  
28  
29 233 to underline a realistic expectation. The sensitivity of GAS is increased by the quantifiable set goals  
30  
31 234 relevant and specific to the participant. Each goal is rated on a 5-point scale and score is given on the  
32  
33 235 extent to which a patient's individual goals are achieved in the course of the intervention. The overall GAS  
34  
35 236 scores calculation will generate a standardized measure (T score) (mean of 50 Standard Deviation  $\pm$  10).  
36  
37 237 The details of each goal outcome will be recorded in the GAS Record Sheet[77-79] by a cognitive therapist  
38  
39 238 of each study arm (OT-1 and OT-2) trained in GAS application.

#### 40 239 **Sample size and power calculation**

41  
42  
43 240 We will base our sample size calculation on our objectives. The intended sample size is based on a  
44  
45 241 previous study that had applied similar treatment approach and with one similar outcome measure to  
46  
47 242 our study[40]. This study applied the non-commercial statistical power analysis program G\*Power  
48  
49 243 Version 3.1.9.2. An effect size of 0.58, which was the functional cognitive outcome of attention [40], is  
50  
51 244 used to calculate the statistical power *a priori*. We applied Analysis of Variance (ANOVA): repeated  
52  
53 245 measures, within-between interaction, setting an alpha level of 0.05, and approximately 10 participants  
54  
55 246 will provide 89% power to detect a statistical significance. Recruitment is doubled ( $n=20$ ) for both arms  
56  
57 247 and inflated to 28 to enable a 40% attrition rate.

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3 248 To have a bigger sample size, we, therefore, decided on a more conservative effect size value and  
4  
5 249 calculated the sample size through estimation of Cohen's *d* value of 0.35. By using similar statistical  
6  
7 250 power analysis program, medium effect size Cohen's *d* of 0.35, setting an alpha level of 0.05,  
8  
9 251 approximately 38 participants will provide 85% power to detect statistical significance. Recruitment is  
10  
11 252 inflated to 46 participants to enable a 20% attrition rate. From the multiple estimated calculations, the  
12  
13 253 minimum intended sample size to secure this study sample is therefore 46 participants. Based on our  
14  
15 254 UMMC local data, a 12 months data collection is sufficient to yield the target sample size.

### 16 17 255 **Patient and public involvement**

18  
19 256 We applied the Medical Research Council (MRC) Developing and Evaluating Complex Intervention:  
20  
21 257 New Guidance (2006) in our development of study intervention. The choice of deficit-to-treat is based on  
22  
23 258 the relevant theoretical literature evidence whereas treatment approach is evinced through literature  
24  
25 259 review, our clinical experience and practice setting of interest. We further conducted two approaches to  
26  
27 260 select components in this study intervention that may require further focus, 1) a pilot study and, 2)  
28  
29 261 Expert Panel review. We conducted a pilot study (approved by Medical Research Ethics Committee,  
30  
31 262 UMMC, Malaysia UM/EC Ref: 947.15) on the application of cognitive treatment on mTBI survivors. mTBI  
32  
33 263 patients were involved in the testing of clinical treatment method, the application practicality, fidelity of  
34  
35 264 treatment and treatment compliance through their experience, feedback and outcomes. We have  
36  
37 265 identified components that would require review for optimization of intervention and these components  
38  
39 266 are further advised by Expert Panel review. The panels comprised of physicians and clinicians who are  
40  
41 267 credentialed in cognitive rehabilitation practice and brain injury, with clinical experience minimum of 10  
42  
43 268 years in the field of interest in Malaysia. Panels are made up of seven rehabilitation medicine consultants,  
44  
45 269 one neurosurgeon consultant, one neuroimaging consultant, five cognitive occupational therapists and  
46  
47 270 one clinical psychologist. As established experts in the field, the focus of discussion is on feasibility of  
48  
49 271 structured cognitive rehabilitation application in the mTBI patients in Malaysia. The in-depth discussion  
50  
51 272 is based on each individual professional experience and knowledge and guided by the current evidence  
52  
53 273 and recommendations available. All invited Expert Panels are involved in the final structured cognitive  
54  
55 274 rehabilitation prior to its application in this study.

56 275 Following the commencement of this study, the input from participants will be similarly recorded  
57  
58 276 through their experience, feedback and outcomes. The data and study materials belong to UMMC,  
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3 277 Malaysia. We will inform participants the result of the study following its completion even if he/she did  
4  
5 278 not complete the study unless he/she has requested not to be contacted.

6  
7 279 **Statistical analysis**

8  
9 280 We will compare the descriptive data between the two intervention arms and with the healthy  
10  
11 281 group. This will include descriptive analysis such as demographic distribution, mean, median and  
12  
13 282 standard deviation. A  $p$  value  $<0.05$  will be considered statistically significant. We will also report any  
14  
15 283 additional relevant data, which may implicate or contribute to the study outcome. This includes lifestyle  
16  
17 284 modifications, legal or litigation issues and socioeconomic status.

18  
19 285 Another descriptive analysis will include the magnitude of treatment effect. This study will measure  
20  
21 286 the Cohen's  $d$  effect size of all outcome measures for both treated groups. Neuropsychological and  
22  
23 287 functional outcomes with moderate effect size threshold ( $>0.35$ ) to large effect size ( $>0.65$ ) are  
24  
25 288 considered to be clinically significant. Functional GAS score of  $>60\%$  post-intervention is also considered  
26  
27 289 significant. We will also analyse the task difficulty level, mean response time and measurement of errors  
28  
29 290 for the five CogniPlus Attention categories.

30  
31 291 The primary analysis is the measure of treatment effect and microstructural brain changes by 1)  
32  
33 292 direct comparison of each intervention group with the control group and 2) comparison between treated  
34  
35 293 groups. We will analyse the mean clinical differences and the mean structural brain differences (DTI  
36  
37 294 parameters) using repeated measure analysis to determine the mean differences of neuropsychological  
38  
39 295 Attention, Total Screening Index scores and GAS T scores as well as DTI parameters - FA, RD, AD and MD  
40  
41 296 of selected WMT. The study fulfills the assumption of repeated measure analysis of normally distributed  
42  
43 297 data sample and homogeneity of variance.

44  
45 298 The secondary analysis is correlation between cognitive changes and structural brain changes  
46  
47 299 through correlation coefficient (Pearson).

48  
49 300 **Data management**

50  
51 301 All data obtained for non-adherence or voluntary withdrawal of participants will also be reviewed  
52  
53 302 and included in the study analysis where applicable. All study-related information will be securely kept  
54  
55 303 at the study site. All participant information will be stored in locked filing cabinets with limited access. All  
56  
57 304 data collection, administrative forms, reports and analysis will only have coded ID as identification of  
58  
59 305 participants to avoid identification by any investigator of the study. Data entry also uses coded ID and is  
60



1  
2  
3 306 performed by an appointed research assistant. Any other document that has participant's name such as  
4  
5 307 consent form will be kept in a separate cabinet accessible by only one investigator (MM).  
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## 7 308 **Discussion**

9 309 To our knowledge, this is the first randomized control trial of cognitive intervention in adult mTBI  
10  
11 310 population, conducted in a developing country, Southeast Asia region. Previous studies have been done in  
12  
13 311 the Western population with a predominantly Caucasian ethnic group and limited ethnic variation. A study  
14  
15 312 from this region with various ethnic involvements may better represent the study population and in turn  
16  
17 313 add further knowledge on the pattern of the impairment following mTBI. Development of the  
18  
19 314 intervention approach was based on existing evidence, pilot study and Focus Group panel review. We will  
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21 315 also incorporate early involvement of relevant health professionals in the field and apply a  
22  
23 316 comprehensive treatment approach and novel outcomes for both genders of the study population. This  
24  
25 317 trial incorporates technology in the treatment application consistent with the changing face of health  
26  
27 318 service delivery in Malaysia, aiming at resource efficiency and treatment effectiveness, albeit tailored  
28  
29 319 treatment approach suitable for the local setting. The results of this study will provide a comprehensive  
30  
31 320 overview on the effect of cognitive rehabilitation in mTBI. Owing to the paucity of scientific and clinical  
32  
33 321 knowledge, this trial will also contribute to the evidence-based cognitive treatment model for mTBI  
34  
35 322 population.  
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## 37 323 **Trial status**

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39 324 At the time of manuscript preparation, 30 potential participants have been recruited at three months  
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41 325 post-injury. Fifteen participants were consented and received treatment following randomization.  
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43 326 Recruitment is due to finish in April 2019. Data lock has not yet occurred and no analyses have been  
44  
45 327 performed.  
46

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48  
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50  
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52  
53 331 of Science and Innovation (MOSTI) grant (MOSTI Flagship Project FP0911F001)

54 332 **Protocol version identifier:** ClinicalTrials.gov ID NCT03237676

55 333 **Protocol Registered date:** 18<sup>th</sup> July 2017

56 334 **Protocol updated date:** 16<sup>th</sup> August 2017  
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335 **Trial sponsor:** University of Malaya, Malaysia

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

### 337 **Declarations**

338 The authors declare that they have no competing interests.

### 339 **Acknowledgement**

340 We wish to thank all our mTBI participants involved in the pilot control study as well as Expert Panels in

341 involved in the review of our intervention development and study.

### 342 **Authors' contribution**

343 NH initiated the study, applied for study funding and is the principal investigator. NH, MM, VN, NR, AD,

344 RDN and GSY were involved in the conception, development of the intervention and design of the study.

345 NAM and NAMT implemented the cognitive intervention. TLK provided the consultation on DTI

346 processing and analysis. MD and NM provided important statistical contributions. All authors provided

347 feedback on drafts of this paper, read and approved the final manuscript. NH, MM, VN and NR are the

348 guarantors for the study and accept full responsibility for the work and /or the conduct of the study, had

349 access to data, and controlled the decision to publish. MM is the corresponding author and attests that all

350 listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

### 351 **Availability of data and material**

352 The data and study materials belong to UMMC, Malaysia. Any request will have to go through Medical

353 Record Department of UMMC, Malaysia. Dissemination of trial result is through publication.

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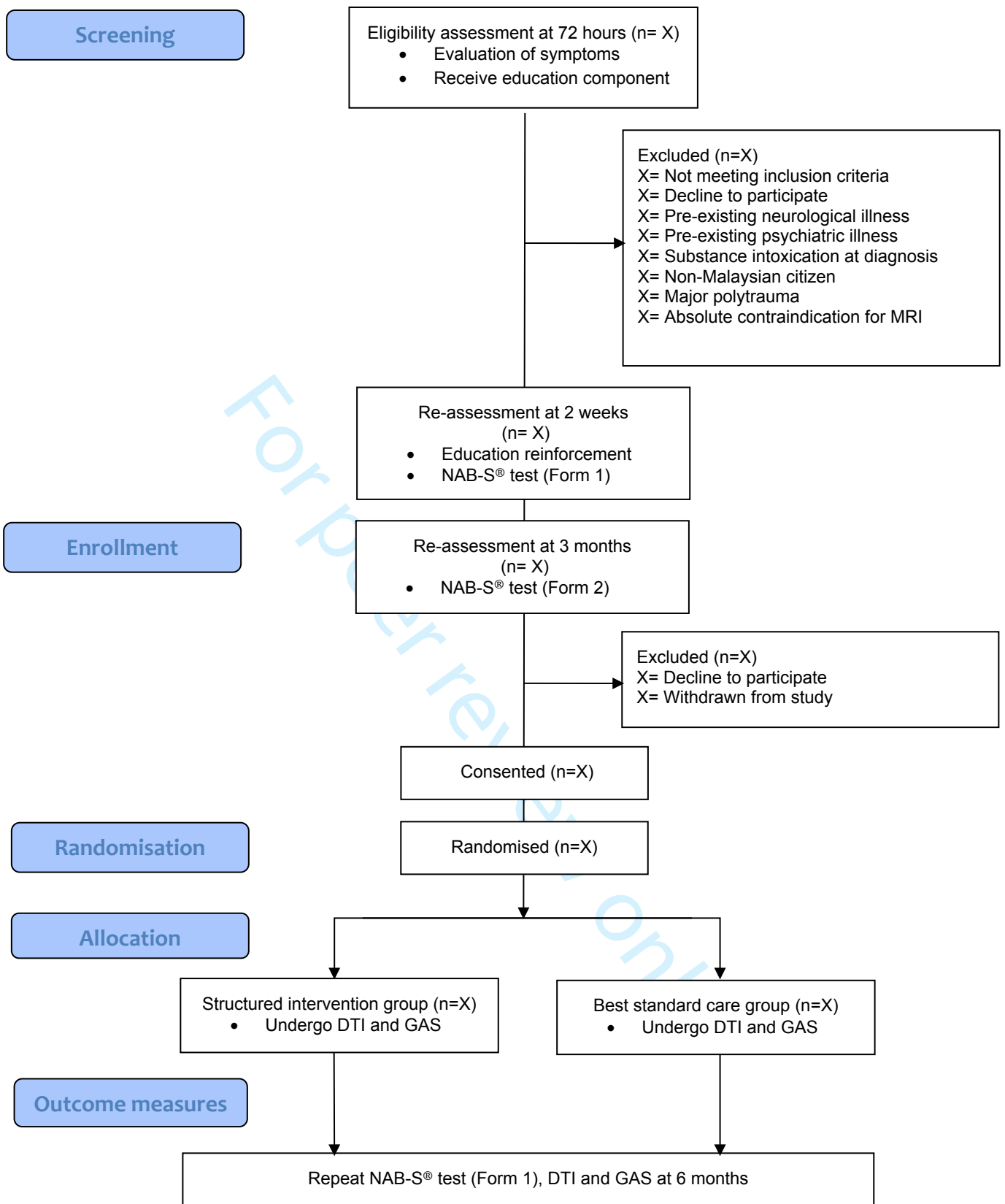
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For peer review only



**Figure 1:** The study design



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 |
|-----------------------------------|---------|--|--------------------------|
| <b>Administrative information</b> |         |  |                          |
| 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<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                       |

## 1 Introduction

|    |                |    |   |
|----|----------------|----|---|
| 2  |                |    |   |
| 3  | Background and | 6a | Description of research question and justification for undertaking the trial, including summary of relevant   |
| 4  | rationale      |    | studies (published and unpublished) examining benefits and harms for each intervention                        |
| 5  |                |    |   |
| 6  |                | 6b | Explanation for choice of comparators   |
| 7  |                |    |   |
| 8  | Objectives     | 7  | Specific objectives or hypotheses   |
| 9  |                |    |   |
| 10 | Trial design   | 8  | Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), |
| 11 |                |    | allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)                   |
| 12 |                |    |   |
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## 14 Methods: Participants, interventions, and outcomes

|    |                      |     |   |
|----|----------------------|-----|---|
| 16 | Study setting        | 9   | Description of study settings (eg, community clinic, academic hospital) and list of countries where data will |
| 17 |                      |     | be collected. Reference to where list of study sites can be obtained  |
| 18 |                      |     |   |
| 19 | Eligibility criteria | 10  | Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and  |
| 20 |                      |     | individuals who will perform the interventions (eg, surgeons, psychotherapists)                               |
| 21 |                      |     |   |
| 22 | Interventions        | 11a | Interventions for each group with sufficient detail to allow replication, including how and when they will be |
| 23 |                      |     | administered  |
| 24 |                      |     |   |
| 25 |                      |     |   |
| 26 |                      | 11b | Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose  |
| 27 |                      |     | change in response to harms, participant request, or improving/worsening disease)                             |
| 28 |                      |     |   |
| 29 |                      | 11c | Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence        |
| 30 |                      |     | (eg, drug tablet return, laboratory tests)  |
| 31 |                      |     |   |
| 32 |                      | 11d | Relevant concomitant care and interventions that are permitted or prohibited during the trial                 |
| 33 |                      |     |   |
| 34 | Outcomes             | 12  | Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood       |
| 35 |                      |     | pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, |
| 36 |                      |     | median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen         |
| 37 |                      |     | efficacy and harm outcomes is strongly recommended  |
| 38 |                      |     |   |
| 39 |                      |     |   |
| 40 | Participant timeline | 13  | Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for   |
| 41 |                      |     | participants. A schematic diagram is highly recommended (see Figure)  |
| 42 |                      |     |   |
| 43 |                      |     |   |
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|   |             |    |   |                  |
|---|-------------|----|---|------------------|
| 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          |
| 2 |             |    |   |                  |
| 3 |             |    |   |                  |
| 4 | Recruitment | 15 | Strategies for achieving adequate participant enrolment to reach target sample size   | 200-205; 252-255 |
| 5 |             |    |   |                  |

6 **Methods: Assignment of interventions (for controlled trials)**

7 Allocation:

|    |                                  |     |  |                  |
|----|----------------------------------|-----|--|------------------|
| 8  |                                  |     |  |                  |
| 9  |                                  |     |  |                  |
| 10 | 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 |
| 11 |                                  |     |  |                  |
| 12 |                                  |     |  |                  |
| 13 |                                  |     |  |                  |
| 14 |                                  |     |  |                  |
| 15 |                                  |     |  |                  |
| 16 | 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          |
| 17 |                                  |     |  |                  |
| 18 |                                  |     |  |                  |
| 19 |                                  |     |  |                  |
| 20 | Implementation                   | 16c | Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions  | Table 1          |
| 21 |                                  |     |  |                  |
| 22 |                                  |     |  |                  |
| 23 |                                  |     |  |                  |
| 24 | Blinding (masking)               | 17a | Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how  | Table 1          |
| 25 |                                  |     |  |                  |
| 26 |                                  |     |  |                  |
| 27 |                                  | 17b | If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial   | 191-199          |
| 28 |                                  |     |  |                  |
| 29 |                                  |     |  |                  |
| 30 |                                  |     |  |                  |

31 **Methods: Data collection, management, and analysis**

|    |                         |     |  |                           |
|----|-------------------------|-----|--|---------------------------|
| 32 |                         |     |  |                           |
| 33 | 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                   |
| 34 |                         |     |  |                           |
| 35 |                         |     |  |                           |
| 36 |                         |     |  |                           |
| 37 |                         |     |  |                           |
| 38 |                         |     |  |                           |
| 39 |                         | 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 |
| 40 |                         |     |  |                           |
| 41 |                         |     |  |                           |
| 42 |                         |     |  |                           |

|    |                                 |     |   |                    |
|----|---------------------------------|-----|---|--------------------|
| 1  | 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            |
| 2  |                                 |     |   |                    |
| 3  |                                 |     |   |                    |
| 4  |                                 |     |   |                    |
| 5  | 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           |
| 6  |                                 |     |   |                    |
| 7  |                                 |     |   |                    |
| 8  |                                 | 20b | Methods for any additional analyses (eg, subgroup and adjusted analyses)  | NA                 |
| 9  |                                 |     |   |                    |
| 10 |                                 | 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            |
| 11 |                                 |     |   |                    |
| 12 |                                 |     |   |                    |
| 13 |                                 |     |   |                    |
| 14 | <b>Methods: Monitoring</b>      |     |   |                    |
| 15 |                                 |     |   |                    |
| 16 | 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                 |
| 17 |                                 |     |   |                    |
| 18 |                                 |     |   |                    |
| 19 |                                 |     |   |                    |
| 20 |                                 |     |   |                    |
| 21 |                                 |     |   |                    |
| 22 |                                 | 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                 |
| 23 |                                 |     |   |                    |
| 24 |                                 |     |   |                    |
| 25 | 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            |
| 26 |                                 |     |   |                    |
| 27 |                                 |     |   |                    |
| 28 | Auditing                        | 23  | Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor   | NA                 |
| 29 |                                 |     |   |                    |
| 30 |                                 |     |   |                    |
| 31 |                                 |     |   |                    |
| 32 | <b>Ethics and dissemination</b> |     |   |                    |
| 33 |                                 |     |   |                    |
| 34 | Research ethics approval        | 24  | Plans for seeking research ethics committee/institutional review board (REC/IRB) approval   | 133-134; 336       |
| 35 |                                 |     |   |                    |
| 36 |                                 |     |   |                    |
| 37 | 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 |
| 38 |                                 |     |   |                    |
| 39 |                                 |     |   |                    |
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|    |                               |     |   |                           |
|----|-------------------------------|-----|---|---------------------------|
| 1  | 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                   |
| 2  |                               |     |   |                           |
| 3  |                               |     |   |                           |
| 4  |                               | 26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable   | NA                        |
| 5  |                               |     |   |                           |
| 6  |                               |     |   |                           |
| 7  | 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          |
| 8  |                               |     |   |                           |
| 9  |                               |     |   |                           |
| 10 | Declaration of interests      | 28  | Financial and other competing interests for principal investigators for the overall trial and each study site   | 314-315                   |
| 11 |                               |     |   |                           |
| 12 |                               |     |   |                           |
| 13 | 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 |
| 14 |                               |     |   |                           |
| 15 |                               |     |   |                           |
| 16 | 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                        |
| 17 |                               |     |   |                           |
| 18 |                               |     |   |                           |
| 19 |                               |     |   |                           |
| 20 | 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                   |
| 21 |                               |     |   |                           |
| 22 |                               |     |   |                           |
| 23 |                               |     |   |                           |
| 24 |                               | 31b | Authorship eligibility guidelines and any intended use of professional writers  | BMJ guideline             |
| 25 |                               |     |   |                           |
| 26 |                               | 31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code   | NA                        |
| 27 |                               |     |   |                           |
| 28 |                               |     |   |                           |
| 29 | <b>Appendices</b>             |     |   |                           |
| 30 |                               |     |   |                           |
| 31 | Informed consent materials    | 32  | Model consent form and other related documentation given to participants and authorised surrogates  | -                         |
| 32 |                               |     |   |                           |
| 33 |                               |     |   |                           |
| 34 | 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                        |
| 35 |                               |     |   |                           |
| 36 |                               |     |   |                           |

\*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”](https://creativecommons.org/licenses/by/4.0/) 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

|                                 |  |
|---------------------------------|--|
| Journal:                        | <i>BMJ Open</i>  |
| Manuscript ID                   | bmjopen-2018-028711.R1   |
| Article Type:                   | Research   |
| Date Submitted by the Author:   | 28-May-2019  |
| Complete List of Authors:       | Hamzah, Norhamizan; University of Malaya, Rehabilitation Medicine<br>Narayanan, Vairavan; University of Malaya, Surgery<br>Ramli, Norlisah; University of Malaya, Biomedical Imaging<br>Mustapha, Nor Atikah ; University of Malaya Medical Centre, Rehabilitation Medicine<br>Mohammad Tahir, Nor Adibah; University of Malaya Medical Centre, Dept of Rehabilitation Medicine<br>Tan, Li Kuo; University of Malaya, Biomedical Imaging<br>Danaee, Mahmoud ; University of Malaya, Department of Social and Preventive Medicine, Faculty of Medicine<br>Muhamad, Nor Asiah; Ministry of Health Malaysia, Institute of Public Health<br>Drummond, Avril; University of Nottingham Faculty of Medicine and Health Sciences<br>dasNair, Roshan; University of Nottingham Faculty of Medicine and Health Sciences<br>Goh , Sing Yau; Universiti Tunku Abdul Rahman, Lee Kong Chian Faculty of Engineering and Science<br>Mazlan, Mazlina; University of Malaya, Rehabilitation Medicine |
| <b>Primary Subject Heading</b>: | Rehabilitation medicine  |
| Secondary Subject Heading:      | Rehabilitation medicine, Research methods  |
| Keywords:                       | mild traumatic brain injury, concussion, attention deficit, cognitive rehabilitation, randomised controlled trial  |
|                                 |  |

SCHOLARONE™  
Manuscripts

**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: 5091**

1  
2  
3 1 **TITLE: A randomised controlled clinical trial of a structured cognitive rehabilitation in patients**  
4  
5 2 **with attention deficit following mild traumatic brain injury: Study protocol**  
6

7 3 **ABSTRACT**

8 4 **Objectives:** Study objectives are to measure the change of attention deficits and to examine the effect of  
9  
10 5 treatment on brain structures and daily life functions following intervention.  
11

12 6 **Setting:** A single centre study, Malaysia.  
13

14 7 **Participants:** All adult participants with the following inclusion criteria: mTBI as a result of road traffic  
15  
16 8 accident; adult aged between 18 to 60 years old; no previous history of head trauma; minimum of nine  
17  
18 9 years education; abnormal cognition at three months after mTBI; provision of informed consent and  
19  
20 10 willingness to comply with cognitive rehabilitation program. The exclusion criteria include pre-existing  
21  
22 11 chronic illness or neurological/psychiatric condition; on medication that alter or affect cognitive or  
23  
24 12 psychological status; clinical evidence of substance intoxication at the time of injury; major polytrauma and  
25  
26 13 absolute contraindication for Magnetic Resonance Imaging. Based on multiple estimated calculations, the  
27  
28 14 minimum intended sample size to secure this study sample is 50 participants (Cohen's *d* effect size 0.35;  
29  
30 15 alpha level of 0.05; 85% power to detect statistical significance; 40% attrition rate).  
31

32 16 **Interventions:** Intervention group will receive individualised structured cognitive rehabilitation. Control  
33  
34 17 group will receive best patient-centred care for attention disorders. Therapy frequency for both groups  
35  
36 18 will be one hour per week for 12 weeks duration.  
37

38 19 **Outcome measures:** S-NAB scores, Diffusion Tensor Imaging (DTI) parameters and Goal Attainment  
39  
40 20 Scaling score (GAS).  
41

42 21 **Results:** Results will include descriptive statistics of population demographics, CogniPlus Attention  
43  
44 22 program and cognitive strategies. The effect of intervention will be the effect size of S-NAB scores and mean  
45  
46 23 GAS T scores. DTI parameters will be compared between groups via repeated measure analysis and  
47  
48 24 correlation analysis of outcome measures is via Pearson's correlation coefficient.  
49

50 25 **Conclusion:** This is a complex clinical intervention with anatomical, clinical and functional outcome  
51  
52 26 measures in order to establish a comprehensive evidence-based treatment model.  
53

54 27 **Trial registration:** This study is registered with ClinicalTrials.gov ID NCT 03237676  
55  
56 28  
57  
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## 30 **ARTICLE SUMMARY:**

### 31 **Strengths and limitations of this study:**

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

## 43 **BACKGROUND**

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

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

## 59 **Cognitive rehabilitation in mTBI**

60 Currently, there is no standard cognitive rehabilitation treatment for mTBI population[19]. The  
61 heterogeneity of cognitive deficits, varied intervention methodology, different reporting style and variable  
62 treatment outcomes[6,17,27,28,30-57] led to a challenge for professionals to come to an agreement on  
63 mTBI treatment[19]. The early neuropsychological model of attention has already made the assumption  
64 that attention should be the focus of rehabilitation, before more advanced cognitive skills be treated[33].  
65 In the last 20 years, various cognitive treatment approaches have been reported in systematic reviews[34-  
66 37]. These include remediation strategies,[38-49], compensatory strategies[50-57] and patient education  
67 intervention[6,39,53,58]. These approaches are usually applied in combination, to optimise both cognitive  
68 and functional recovery[17,27,28,30,31,33- 38]. In particular, treatment for attention deficits in TBI was  
69 recommended at post-acute (3 months) stage of trauma[28,30,34,44]. Methods of treatment included  
70 multidimensional approach, and tasks with hierarchical difficulty and complexity[30,34,44]. Several  
71 studies also reported improved psychological outcome and coping of symptoms on those who received  
72 patient education and reassurance following mTBI[6,35,36]. However, these conclusions were based on a  
73 limited number of high-quality clinical trials. The consensus was for more robust clinical trials of larger  
74 sample size, well-described complex intervention and standardised reporting method [19,34-37,44,46].

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

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

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

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3 88 reliability[41,51,57,61-64], was cost effective and practical to use in a clinical setting[53,62-64] would be  
4  
5 89 ideal.

6  
7 90 The structural injury in mTBI however, is too miniscule for detection through routine computed  
8  
9 91 tomography (CT) and Magnetic Resonance Imaging (MRI)[65-67]. Over the last 10 years, Diffusion Tensor  
10  
11 92 Imaging (DTI) has become accepted as a non-invasive tool that is able to quantify microstructural brain  
12  
13 93 changes in mTBI[24,65-70]. Changes in its parameters are indicative of microstructural remodelling at  
14  
15 94 acute and chronic stages of injury, potentially explaining the persistence of symptoms that would otherwise  
16  
17 95 be attributed to other causes [24,65-70]. A longitudinal DTI study may increase our understanding of the  
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19 96 brain structural transformation in mTBI.

20  
21 97 The most important outcome following mTBI is the ability for survivors to return to their previous  
22  
23 98 functional state and quality of life. Common scales to measure disability and function are usually sensitive  
24  
25 99 to cognitive deficits but not necessarily specific to the TBI population[39-41,52,53]. Many studies have also  
26  
27 100 reported specific outcome measures for TBI that has good validity, reliability and practical in a clinical  
28  
29 101 setting[71-79], such as Goal Attainment Scaling[71,72,77-79], Extended Glasgow Outcome Scale[73] and  
30  
31 102 Functional Assessment Measure[74].

32  
33 103 This trial evaluates a complex clinical intervention, to provide evidence on the effect of cognitive  
34  
35 104 rehabilitation in mTBI. We extend the outcome measures to include anatomical, clinical and functional  
36  
37 105 aspects to establish a comprehensive evidence-based treatment model.

## 38 39 106 **METHODS**

### 40 41 107 **Study hypothesis**

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43 108 We hypothesize that structured cognitive rehabilitation for attention deficits following mTBI will  
44  
45 109 improve patients' cognitive function of attention compared to the standard care.

### 46 47 110 **Study objectives**

48  
49 111 The objectives are:

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51  
52 112 • to measure the clinical effect of a 12-week individualized structured cognitive rehabilitation to  
53  
54 113 address attention deficit and overall cognitive status via S-NAB assessment
- 55  
56 114 • to examine the effect of treatment on brain structures via DTI
- 57  
58 115 • to analyse the functional changes following treatment via GAS and participant's feedback
- 59  
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3 116 • to correlate the clinical effect following cognitive rehabilitation with structural brain changes and  
4  
5 117 participant's overall functional outcomes  
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7 118 **Design**  
8

9 119 This will be a prospective double blind, randomized controlled trial with two parallel groups. The  
10  
11 120 study design is summarized in **Figure 1**.  
12

13 121 **Participants and recruitment process**  
14

15 122 This trial will be conducted at a single centre, University Malaya Medical Centre (UMMC), Malaysia.  
16  
17 123 UMMC is a government funded and an academic medical institution situated in the urban area of the  
18  
19 124 nation's capital city Kuala Lumpur with the population of 1.76 million. Apart from providing acute medical  
20  
21 125 services, this hospital is also a tertiary referral and training centre in Malaysia. UMMC also has Department  
22  
23 126 of Rehabilitation Medicine that provides the facility for this study. These include main rehabilitation  
24  
25 127 services (neuro-, spinal cord-, prosthetic and orthotic-, paediatric- and cardiac rehabilitation) for both  
26  
27 128 inpatient and outpatient setting. Other services also include return to work/drive rehabilitation.  
28

29 129 We will recruit participants through the Emergency Medicine Department (ED), UMMC from 1<sup>st</sup>  
30  
31 130 August 2017. ED physicians, radiologists and neurosurgeons will refer mTBI cases to a research assistant  
32  
33 131 for recruitment. Potential cases will also be screened through UMMC digital medical record system.  
34  
35 132 Screening stages will be performed at 72 hours, two and six weeks following mTBI.  
36

37 133 **Inclusion criteria**  
38

39 134 Mild TBI is defined as physiological disruption of brain function as a result of trauma with symptoms  
40  
41 135 of loss of consciousness 30 minutes or less, focal neurological deficit that may/may not be transient, altered  
42  
43 136 mental state with Glasgow Coma Scale of 13-15 and loss of memory with post traumatic amnesia not  
44  
45 137 greater than 24 hours. The inclusion criteria for this study are mTBI as a result of RTA; adult aged between  
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47 138 18 to 60 years old; Malaysia citizen; no previous history of head trauma; minimum of nine years education;  
48  
49 139 persistently abnormal S-NAB Attention Domain score at three months of mTBI; ability to give consent and  
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51 140 willingness to comply with cognitive rehabilitation program. Persistently abnormal S-NAB Attention  
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53 141 Domain score is defined as Standard Score <85 (below average category) at screening phase and at  
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55 142 enrolment phase as set by the NAB test manual (Table 1).  
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3 **145 Exclusion criteria**

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5 **146** The exclusion criteria include pre-existing chronic illness that cause neurological symptoms or  
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7 **147** complications; severe comorbid neurological or psychiatric disorder; on long-term medication that alter  
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9 **148** or affect cognitive and psychological status; clinical evidence of substance intoxication at the time of injury;  
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11 **149** major polytrauma and absolute contraindication for MRI (metal or implant not compatible for MRI,  
12  
13 **150** claustrophobia) (Table 1).  
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| Inclusion criteria  |    |    |    | Exclusion criteria   |    |    |    |
|---|----|----|----|--|----|----|----|
| Criteria  | IG | SG | HG | Criteria   | IG | SG | HG |
| 18-60 years old of age                                    | ✓  | ✓  | ✓  | Pre-existing chronic illness or neurological or psychiatric condition                  | ✓  | ✓  | ✓  |
| No previous history of head trauma                        | ✓  | ✓  | ✓  | On long term medication that can alter or affect cognitive and/or psychological status | ✓  | ✓  | ✓  |
| Minimum of 9 years education                              | ✓  | ✓  | ✓  | Clinical evidence of alcohol intoxication at the time of injury                        | ✓  | ✓  |    |
| Consented   | ✓  | ✓  | ✓  | Major polytrauma (multiple bone fractures, nerve injury)                               | ✓  | ✓  |    |
| mTBI as a result of motor vehicle accidents only          | ✓  | ✓  |    | Absolute contraindication for MRI  | ✓  | ✓  |    |
| Abnormal S-NAB Attention Domain score at 3 months of mTBI | ✓  | ✓  |    |  |    |    |    |
| Willingness to comply with rehabilitation program         |    |    |    |  |    |    |    |

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42 **Table 1:** The study criteria.

43 Note: IG-individualised structured cognitive rehabilitation group; SG- standard care group, HG- healthy control group  
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46 **151 Intervention**

47  
48 **152** Potential participants will undergo screening before enrolment and randomization (**Figure 1**).  
49  
50 **153** Education component will include reassurance on recovery, self-monitoring of symptom(s) and advice on  
51  
52 **154** gradual return to daily activities and physical exertion. Symptom(s) evaluation will include clinical review  
53  
54 **155** of physical, cognitive and psychological status. The first medical responder i.e. ED physicians will perform  
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56 **156** this at 72 hours of injury. At two weeks and six weeks of injury, a rehabilitation medicine physician who is  
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3 157 not involved with the study (RP-1) will repeat the education component and symptom evaluation. Early  
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5 158 treatment or referral to other medical speciality will be made if indicated during these reviews.  
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7 159 At three months after injury, potential participants will undergo a repeat of clinical review and S-NAB  
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9 160 test. Participants with persistently abnormal Attention Domain score (standard domain score <85) will be  
10  
11 161 enrolled in the study. However, those with other cognitive domain deficit(s) (standard domain score <85)  
12  
13 162 other than Attention Domain will also be included in the study and will receive treatment for attention  
14  
15 163 following randomization. The concomitant domain deficit(s) will also be evaluated upon completion of  
16  
17 164 therapy. The cognitive intervention will be conducted at the Neurorehabilitation Therapy Unit,  
18  
19 165 Department of Rehabilitation Medicine, UMMC in an outpatient setting. Participants will be assigned to  
20  
21 166 different treatment groups via randomization process. Written records of intervention will be prepared  
22  
23 167 and kept by the therapist of each treatment arm until treatment completion. This include participant's  
24  
25 168 goals, symptom(s), cognitive strategy/method and participant's feedback.  
26

### 27 169 ***Individualised structured cognitive rehabilitation group***

28  
29 170 Intervention group participants will receive a two-part 12-week individualized structured cognitive  
30  
31 171 rehabilitation. The first part is Direct Attention Training (DAT), a deficit-oriented computer-based  
32  
33 172 attention-training program called CogniPlus[45]. Each session will be 30 minutes, once a week.  
34

35 173 CogniPlus is a computer-based software program with interactive multimedia approach for multiple  
36  
37 174 attention cognitive training modules. The training programs are ALERT (focused and sustained attention),  
38  
39 175 FOCUS (focused attention), VIG (sustained attention), SELECT (selective attention) and DIVID (divided  
40  
41 176 attention). Each attention-training category is designed based on real-life scenarios and the screen  
42  
43 177 graphics are three-dimensional. This program has artificial intelligence capacity that can automatically  
44  
45 178 adapt to an individual's performance and alter the training difficulty level (hierarchical difficulty).  
46

47 179 The second part of this intervention is strategy approach (metacognitive awareness and compensatory  
48  
49 180 strategy) performed after CogniPlus training. Metacognitive awareness includes feedback on participant's  
50  
51 181 CogniPlus performance to improve participant's awareness of impairment severity. This process is  
52  
53 182 intended to regulate their learning experience and in turn instil the practise of self-monitoring and self-  
54  
55 183 regulation through learning activities. Compensatory strategy component involves applying the cognitive  
56  
57 184 awareness in recognizing impairment that is present in daily activities followed by the application of  
58  
59 185 cognitive methods to ameliorate the deficits aiming to maximise daily functioning. A participant will  
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3 186 identify the deficit(s) and will apply problem-solving method(s) learnt from the therapist. Feedback and  
4  
5 187 review of performance will be done again in the following therapy session. This session will last for 30  
6  
7 188 minutes and a will be conducted by a trained and certified Occupational Therapist (OT-1) in cognitive  
8  
9 189 therapy and CogniPlus.

### 10 11 190 ***Standard care group***

12  
13 191 This group will receive the best standard care for attention disorders. This is a patient-centred  
14  
15 192 cognitive therapy. It is based on a patient's complaint(s), symptom(s) and therapy aim(s) (self-realization  
16  
17 193 of deficits or guided by therapist). Symptom(s) management may include physical (e.g. imbalance, fatigue,  
18  
19 194 sleep dysregulation), psychological (e.g. mild anxiety or depression) and cognitive (e.g. forgetfulness).  
20  
21 195 Referral to relevant service(s) may be required such as physiotherapy, return to work/drive rehabilitation  
22  
23 196 and counselling, Compensatory strategy includes task specific training (patient-prioritised) e.g. return to  
24  
25 197 drive may involve driving simulation training, visuospatial training and return to drive rehabilitation  
26  
27 198 service. The frequency of sessions will be one hour per week, for 12 weeks. A trained occupational therapist  
28  
29 199 in cognitive therapy (OT-2) who is not involved with the intervention group treatment, will conduct all the  
30  
31 200 sessions (Table 2).

### 32 33 201 ***Control group***

34  
35 202 This will consist of healthy individuals demographically matched for age, gender and education years to  
36  
37 203 the intervention groups (Table 1). The data is collected for comparison purpose.

### 38 39 204 **Randomisation, consent and blinding**

40  
41 205 Participants with mTBI who fulfil the study criteria will be randomized via computer-generated  
42  
43 206 random permuted block assignment, gender-stratified into equally proportioned intervention and control  
44  
45 207 group numbers. The study schedule, procedures and blinding of co-investigators are presented in **Table 2**.

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

Table 2: Study schedule and procedures.

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3 **208 Modification, withdrawal and unblinding within the intervention**  
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5 209 Participants can withdraw their consent from this study at any time and for any reason. Investigators can  
6  
7 210 also withdraw a participant from the study if he/she becomes non-compliant with the treatment protocol.  
8  
9 211 This include poor treatment attendance, poor therapy participation or participant's request for withdrawal  
10  
11 212 from study. We will also provide our participant who requires immediate medical attention or treatment  
12  
13 213 that is otherwise not part of the study intervention throughout the study duration. In the case where  
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15 214 unblinding of a participant is necessary (e.g. medical emergency), an investigator (MM) will be informed of  
16  
17 215 the cause and stage of intervention received by the participant. He/she may continue in the study and  
18  
19 216 follow all study procedures. The participant will only be withdrawn from this study if the immediate  
20  
21 217 treatment violates our study criteria. We will retain all of participant's data (although the participant is no  
22  
23 218 longer blinded) or up to the point of participant's removal from the study.

24  
25 **219 Adherence strategies**  
26

27 220 Adherence to treatment is enabled throughout the intervention for both groups. This will be achieved  
28  
29 221 by providing: 1) participants with clear information on purpose, method and treatment goals during  
30  
31 222 treatment sessions, 2) an appointment card with specific date and time of therapy sessions, and 3) a  
32  
33 223 reminder through phone calls a day before each therapy appointment and a week before DTI scan date.  
34

35 **224 Outcome measures**  
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37 225 All measures will be performed at baseline and at the end of the intervention. The primary outcome  
38  
39 226 measure of this study is the change of attention deficit and other cognitive domains within intervention  
40  
41 227 groups and direct comparison of each intervention group with the healthy control group. This will be  
42  
43 228 measured by Neuropsychological Assessment Battery® (NAB®, PAR, Inc., Florida, USA)[61]. It consists of  
44  
45 229 six modules: Screening Module and five Domain Specific Modules: Attention, Language, Memory, Spatial  
46  
47 230 and Executive Function. This study will only apply the Screening Module (S-NAB) because it measures the  
48  
49 231 same five functional domains similar or identical to the main NAB modules. It consists of 12 individual tests  
50  
51 232 screening all five mentioned cognitive domains for adults aged 18 to 97 years, validated and sensitive for  
52  
53 233 use in healthy and cognitively impaired brain injured population[24,61-64]. S-NAB also provides two  
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55 234 parallel assessment sets (Record Form 1 and Form 2) that will be applied in an alternate fashion to  
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57 235 participants in both groups to avoid practice effect.  
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3 236 S-NAB Domain Attention test items and score are interpreted as a marker of an individual's attentional  
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5 237 capacity, working memory, psychomotor speed, selective attention, divided attention and information  
6  
7 238 processing [61]. S-NAB has also been applied in our previous cohort study [24] with good validation  
8  
9 239 outcome in our Malaysian mTBI population.

10  
11 240 The secondary outcome measures are microstructural WMT parameters and functional GAS scores.  
12  
13 241 The DTI MRI scan is a Siemens Magnetom Prisma 3T MRI (Siemens AG, Muenchen, Germany). This study  
14  
15 242 will analyse Fractional Anisotropy (FA), Mean Diffusivity (MD) and Radial Diffusivity (RD) parameter  
16  
17 243 changes at pre- and post-intervention[24,65-70]. These parameters quantify the direction and degree of  
18  
19 244 tissue water diffusion within the WMT[65,66]. FA which measures the direction of the diffusion is an index  
20  
21 245 expressed in a range from 0-1, with a higher score indicating a higher integrity of white matter consisting  
22  
23 246 of highly parallel fibres[65,66]. MD measures the average magnitude of the diffusion while RD quantifies  
24  
25 247 pathology in the myelin[65,66]. Changes in the index values of the parameters at different injury timeline  
26  
27 248 will indicate the pathological changes of the WMT.

28  
29 249 The tool to measure functional outcome is GAS[77-79]. The difficulty and importance of rehabilitation  
30  
31 250 goals will be individually set according to his/her current levels of functional performance to underline a  
32  
33 251 realistic expectation. The sensitivity of GAS is increased by the quantifiable set goals relevant and specific  
34  
35 252 to the participant. Each goal is rated on a 5-point scale and score is given on the extent to which a patient's  
36  
37 253 individual goals are achieved in the course of the intervention. The overall GAS scores calculation will  
38  
39 254 generate a standardized measure (T score) (mean of 50 Standard Deviation  $\pm$  10). The details of each goal  
40  
41 255 outcome will be recorded in the GAS Record Sheet[77-79] by a cognitive therapist of each study arm (OT-  
42  
43 256 1 and OT-2) trained in GAS application.

44  
45 257 Another important factor to note is participant's psychological status following mTBI. This study will  
46  
47 258 also perform screening of anxiety and depression symptoms by using the Generalised Anxiety Disorder 7-  
48  
49 259 item (GAD7) and Patient Health Questionnaire-9 (PHQ-9) screening tools at each study timeline.  
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51 260 Participant's lifestyle changes will also be reviewed and recorded. Although these parameters will not be  
52  
53 261 part of the study outcome measure, they however remain relevant in influencing treatment adherence and  
54  
55 262 outcome.

### 263 **Sample size and power calculation**

264 In order to fulfil our study objectives we will base the intended sample size calculation on a previous  
265 study that had applied similar treatment approach and with one similar outcome measure to our study[40].  
266 This study applied the non-commercial statistical power analysis program G\*Power Version 3.1.9.2. An  
267 effect size of 0.58, which was the functional cognitive outcome of attention [40], is used to calculate the  
268 statistical power *a priori*. We will apply Analysis of Variance (ANOVA): repeated measures, within-between  
269 interaction, setting an alpha level of 0.05, and approximately 10 participants will provide 89% power to  
270 detect a statistical significance. Recruitment is doubled (n=20) for both arms and inflated to 28 to counter  
271 40% attrition rate.

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

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

### 280 **Ethics considerations**

281 This study was approved by Medical Research Ethics Committee, UMMC (MREC ID NO: 2016928-  
282 4293). We will obtain written consent from adult participants. During consenting, participant will be  
283 provided with Patient Information Sheet detailing the purpose of study, reason for participation, study  
284 investigation and intervention methods, withdrawal from study and contact details of investigators. Once  
285 consent is given the form and all other documents with participant's personal details will be stored  
286 immediately in a locked filing cabinet by the consent taker and is accessible only to several investigators.  
287 Study ID code will be allocated upon consenting and subsequent study documentation will only use the ID  
288 code.

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



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2  
3 292 the event where information sharing is required for medical reasons, the participant will be informed  
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5 293 immediately followed by referral to relevant professional either based at UMMC or a different centre of  
6  
7 294 choice. However, cost of further investigation or treatment that is not part of this study is not funded by  
8  
9 295 the study grants. Treatment compliance is achieved through our adherence strategy. We strictly adhere to  
10  
11 296 the privacy and confidentiality of participant's medical information. Any information sharing with a third  
12  
13 297 party for various reasons will be managed in accordance with UMMC professional and legal code of conduct.

### 14 15 298 **Patient and public involvement**

16  
17 299 We applied the Medical Research Council (MRC) Developing and Evaluating Complex Intervention:  
18  
19 300 New Guidance (2006) and Multiphase Optimization Strategy (MOST) framework to guide the development  
20  
21 301 of this study. The choice of deficit to treat was based on the relevant theoretical evidence whereas  
22  
23 302 treatment approach was evinced through our systematic review, clinical experience and practice setting of  
24  
25 303 interest. We conducted 1) a pilot study and 2) Expert Panel review to evaluate the study design and  
26  
27 304 treatment method that may require further focus.

28  
29 305 Our pilot study was approved by Medical Research Ethics Committee, UMMC, Malaysia (UM/EC Ref:  
30  
31 306 947.15) for the application of cognitive treatment on mTBI patients. They were involved in the testing of  
32  
33 307 treatment method, clinical practicality, fidelity of treatment and treatment compliance. We have identified  
34  
35 308 several components required for optimization of intervention. These findings were also assessed by the  
36  
37 309 Expert Panel reviewers.

38  
39 310 The panel comprised of clinicians who were credentialed in brain injury management and cognitive  
40  
41 311 rehabilitation with minimum of 10 years clinical experience in Malaysia. Panels were made up of seven  
42  
43 312 rehabilitation medicine consultants, one neurosurgeon consultant, one neuroimaging consultant, five  
44  
45 313 cognitive occupational therapists and one clinical psychologist. The focus of discussion was on the  
46  
47 314 feasibility of structured cognitive rehabilitation for mTBI patients in Malaysia, guided by the current  
48  
49 315 evidence, current practise of cognitive rehabilitation in local setting, reviewers clinical experience and our  
50  
51 316 pilot study findings. A summary of the pilot study outcomes and Expert Panel recommendations are best  
52  
53 317 illustrated in Table 3.

54 318 Following the commencement of this study, the input from participants (experience, feedback and  
55  
56 319 outcomes) will be recorded. The data and study materials belong to UMMC, Malaysia. We will inform the  
57  
58 320 result of the study to our participants following its completion even if he/she did not complete the study  
59  
60 321 unless he/she has requested not to be contacted.



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

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

## 322 **Statistical analysis**

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

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

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

338 The secondary analysis will include measurement of structural brain changes following intervention.  
339 This data will be obtained from the DTI MRI scan performed at pre and post intervention, for all groups.  
340 We will identify FA, MD and RD parameters with statistically significant mean values ( $p<0.05$ ) via whole  
341 brain analysis known as Tract-based Spatial Statistics (TBSS)[80] and region of interest (ROI) approach  
342 which is part of the FSL (v5.0.6; University of Oxford, Oxford UK) [81] and AFNI (v2011\_12\_21\_1014;  
343 National Institute of Mental Health, Bethesda, MD) software packages. The DTI parameters of both  
344 intervention groups at three- and six months study timelines will be compared with the healthy control  
345 group by using repeated measure analysis. This is in the assumption that the study fulfils the repeated  
346 measure analysis of normally distributed data sample and homogeneity of variance.

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

### 350 **Data management**

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

### 358 **Discussion**

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

### 371 **Trial status**

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

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379 Science and Innovation (MOSTI) grant (MOSTI Flagship Project FP0911F001)

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

381 **Protocol Registered date:** 18<sup>th</sup> July 2017

382 **Protocol updated date:** 16<sup>th</sup> August 2017

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

## 384 **Declarations**

385 The authors declare that they have no competing interests.

## 386 **Acknowledgement**

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

## 389 **Authors' contribution**

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

## 398 **Availability of data and material**

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

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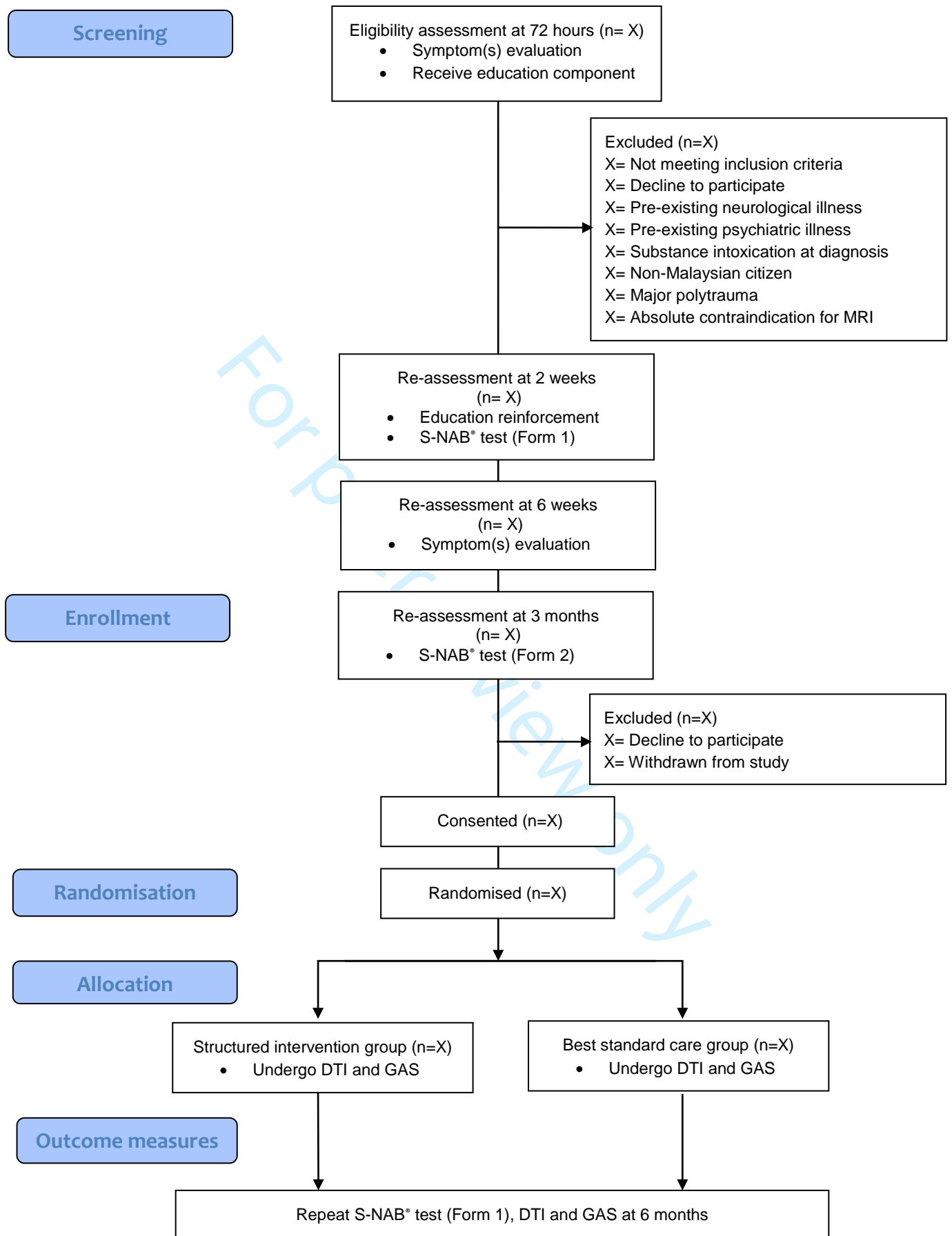
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**Figure 1:** Flowchart showing the stages of recruitment in this study.



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



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

| Section/item                      | Item No | Description  | Addressed on line number |
|-----------------------------------|---------|--|--------------------------|
| <b>Administrative information</b> |         |  |                          |
| 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                       |



|    |   |     |   |                   |
|----|---|-----|---|-------------------|
| 1  | <b>Introduction</b>                                       |     |   |                   |
| 2  |   |     |   |                   |
| 3  | Background and  | 6a  | Description of research question and justification for undertaking the trial, including summary of relevant   | 44-105            |
| 4  | rationale   |     | studies (published and unpublished) examining benefits and harms for each intervention                        |                   |
| 5  |   |     |   |                   |
| 6  |   | 6b  | Explanation for choice of comparators   | 44-105            |
| 7  |   |     |   |                   |
| 8  | Objectives  | 7   | Specific objectives or hypotheses   | 107-117           |
| 9  |   |     |   |                   |
| 10 | Trial design  | 8   | Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), |                   |
| 11 |   |     | allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)                   | 118-132; Figure 1 |
| 12 |   |     |   |                   |
| 13 |   |     |   |                   |
| 14 | <b>Methods: Participants, interventions, and outcomes</b> |     |   |                   |
| 15 |   |     |   |                   |
| 16 | Study setting   | 9   | Description of study settings (eg, community clinic, academic hospital) and list of countries where data will | 122-128           |
| 17 |   |     | be collected. Reference to where list of study sites can be obtained  |                   |
| 18 |   |     |   |                   |
| 19 | Eligibility criteria                                      | 10  | Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and  | 133-150, Table 1  |
| 20 |   |     | individuals who will perform the interventions (eg, surgeons, psychotherapists)                               |                   |
| 21 |   |     |   |                   |
| 22 | Interventions   | 11a | Interventions for each group with sufficient detail to allow replication, including how and when they will be | 151-203; Figure 1 |
| 23 |   |     | administered  |                   |
| 24 |   |     |   |                   |
| 25 |   | 11b | Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose  | 208-218           |
| 26 |   |     | change in response to harms, participant request, or improving/worsening disease)                             |                   |
| 27 |   |     |   |                   |
| 28 |   | 11c | Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence        | 219-223           |
| 29 |   |     | (eg, drug tablet return, laboratory tests)  |                   |
| 30 |   |     |   |                   |
| 31 |   | 11d | Relevant concomitant care and interventions that are permitted or prohibited during the trial                 | NA                |
| 32 |   |     |   |                   |
| 33 | Outcomes  | 12  | Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood       |                   |
| 34 |   |     | pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, | 224-262           |
| 35 |   |     | median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen         |                   |
| 36 |   |     | efficacy and harm outcomes is strongly recommended  |                   |
| 37 |   |     |   |                   |
| 38 | Participant timeline                                      | 13  | Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for   | 204-207; Table 2  |
| 39 |   |     | participants. A schematic diagram is highly recommended (see Figure)  |                   |
| 40 |   |     |   |                   |
| 41 |   |     |   |                   |
| 42 |   |     |   |                   |
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|   |             |    |   |                  |
|---|-------------|----|---|------------------|
| 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 | 263-279          |
| 2 |             |    |   |                  |
| 3 |             |    |   |                  |
| 4 | Recruitment | 15 | Strategies for achieving adequate participant enrolment to reach target sample size   | 219-223; 263-279 |
| 5 |             |    |   |                  |

## 6 **Methods: Assignment of interventions (for controlled trials)**

### 7 Allocation:

|    |                    |     |  |                  |
|----|--------------------|-----|--|------------------|
| 8  |                    |     |  |                  |
| 9  |                    |     |  |                  |
| 10 | Sequence           | 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 |
| 11 | generation         |     |  |                  |
| 12 |                    |     |  |                  |
| 13 |                    |     |  |                  |
| 14 |                    |     |  |                  |
| 15 |                    |     |  |                  |
| 16 | Allocation         | 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 |
| 17 | concealment        |     |  |                  |
| 18 | mechanism          |     |  |                  |
| 19 |                    |     |  |                  |
| 20 | Implementation     | 16c | Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions  | Table 2          |
| 21 |                    |     |  |                  |
| 22 |                    |     |  |                  |
| 23 |                    |     |  |                  |
| 24 | Blinding (masking) | 17a | Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how  | Table 2          |
| 25 |                    |     |  |                  |
| 26 |                    |     |  |                  |
| 27 |                    | 17b | If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial   | 208-218          |
| 28 |                    |     |  |                  |
| 29 |                    |     |  |                  |
| 30 |                    |     |  |                  |

## 31 **Methods: Data collection, management, and analysis**

|    |                 |     |  |  |
|----|-----------------|-----|--|--|
| 32 |                 |     |  |  |
| 33 | Data collection | 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 |
| 34 | methods         |     |  |  |
| 35 |                 |     |  |  |
| 36 |                 |     |  |  |
| 37 |                 |     |  |  |
| 38 |                 | 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  |
| 39 |                 |     |  |  |
| 40 |                 |     |  |  |
| 41 |                 |     |  |  |
| 42 |                 |     |  |  |

|    |                     |     |   |         |
|----|---------------------|-----|---|---------|
| 1  | 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 |
| 2  |                     |     |   |         |
| 3  |                     |     |   |         |
| 4  |                     |     |   |         |
| 5  | 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 |
| 6  |                     |     |   |         |
| 7  |                     |     |   |         |
| 8  |                     | 20b | Methods for any additional analyses (eg, subgroup and adjusted analyses)  | NA      |
| 9  |                     |     |   |         |
| 10 |                     | 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 |
| 11 |                     |     |   |         |
| 12 |                     |     |   |         |
| 13 |                     |     |   |         |

14 **Methods: Monitoring**

|    |                 |     |   |         |
|----|-----------------|-----|---|---------|
| 15 |                 |     |   |         |
| 16 | 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      |
| 17 |                 |     |   |         |
| 18 |                 |     |   |         |
| 19 |                 |     |   |         |
| 20 |                 |     |   |         |
| 21 |                 |     |   |         |
| 22 |                 | 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      |
| 23 |                 |     |   |         |
| 24 |                 |     |   |         |
| 25 | 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 |
| 26 |                 |     |   |         |
| 27 |                 |     |   |         |
| 28 | Auditing        | 23  | Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor   | NA      |
| 29 |                 |     |   |         |
| 30 |                 |     |   |         |
| 31 |                 |     |   |         |

32 **Ethics and dissemination**

|    |                          |    |  |                    |
|----|--------------------------|----|--|--------------------|
| 33 |                          |    |  |                    |
| 34 | Research ethics approval | 24 | Plans for seeking research ethics committee/institutional review board (REC/IRB) approval  | 280-297            |
| 35 |                          |    |  |                    |
| 36 |                          |    |  |                    |
| 37 | 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 |
| 38 |                          |    |  |                    |
| 39 |                          |    |  |                    |
| 40 |                          |    |  |                    |
| 41 |                          |    |  |                    |
| 42 |                          |    |  |                    |

|    |                               |     |   |                 |
|----|-------------------------------|-----|---|-----------------|
| 1  | 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         |
| 2  |                               |     |   |                 |
| 3  |                               |     |   |                 |
| 4  |                               | 26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable   | NA              |
| 5  |                               |     |   |                 |
| 6  |                               |     |   |                 |
| 7  | 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 |
| 8  |                               |     |   |                 |
| 9  |                               |     |   |                 |
| 10 | Declaration of interests      | 28  | Financial and other competing interests for principal investigators for the overall trial and each study site   | 376-385         |
| 11 |                               |     |   |                 |
| 12 |                               |     |   |                 |
| 13 | 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 |
| 14 |                               |     |   |                 |
| 15 |                               |     |   |                 |
| 16 | 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              |
| 17 |                               |     |   |                 |
| 18 |                               |     |   |                 |
| 19 |                               |     |   |                 |
| 20 | 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         |
| 21 |                               |     |   |                 |
| 22 |                               |     |   |                 |
| 23 |                               |     |   |                 |
| 24 |                               | 31b | Authorship eligibility guidelines and any intended use of professional writers  | BMJ guideline   |
| 25 |                               |     |   |                 |
| 26 |                               | 31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code   | NA              |
| 27 |                               |     |   |                 |
| 28 |                               |     |   |                 |
| 29 | <b>Appendices</b>             |     |   |                 |
| 30 |                               |     |   |                 |
| 31 | Informed consent materials    | 32  | Model consent form and other related documentation given to participants and authorised surrogates  | -               |
| 32 |                               |     |   |                 |
| 33 |                               |     |   |                 |
| 34 | 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              |
| 35 |                               |     |   |                 |
| 36 |                               |     |   |                 |

\*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](https://creativecommons.org/licenses/by-nc-nd/3.0/)" 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

|                                 |  |
|---------------------------------|--|
| Journal:                        | <i>BMJ Open</i>  |
| Manuscript ID                   | bmjopen-2018-028711.R2   |
| Article Type:                   | Research   |
| Date Submitted by the Author:   | 17-Jul-2019  |
| Complete List of Authors:       | Hamzah, Norhamizan; University of Malaya, Rehabilitation Medicine<br>Narayanan, Vairavan; University of Malaya, Surgery<br>Ramli, Norlisah; University of Malaya, Biomedical Imaging<br>Mustapha, Nor Atikah ; University of Malaya Medical Centre, Rehabilitation Medicine<br>Mohammad Tahir, Nor Adibah; University of Malaya Medical Centre, Dept of Rehabilitation Medicine<br>Tan, Li Kuo; University of Malaya, Biomedical Imaging<br>Danaee, Mahmoud ; University of Malaya, Department of Social and Preventive Medicine, Faculty of Medicine<br>Muhamad, Nor Asiah; Ministry of Health Malaysia, Institute of Public Health<br>Drummond, Avril; University of Nottingham Faculty of Medicine and Health Sciences<br>dasNair, Roshan; University of Nottingham Faculty of Medicine and Health Sciences<br>Goh , Sing Yau; Universiti Tunku Abdul Rahman, Lee Kong Chian Faculty of Engineering and Science<br>Mazlan, Mazlina; University of Malaya, Rehabilitation Medicine |
| <b>Primary Subject Heading</b>: | Rehabilitation medicine  |
| Secondary Subject Heading:      | Rehabilitation medicine, Research methods, Radiology and imaging   |
| Keywords:                       | mild traumatic brain injury, cognitive rehabilitation, randomised controlled trial, neuropsychology, Diffusion Tensor Imaging  |
|                                 |  |

SCHOLARONE™  
Manuscripts

**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**

1  
2  
3 1 **TITLE: A randomised controlled clinical trial of a structured cognitive rehabilitation in patients**  
4  
5 2 **with attention deficit following mild traumatic brain injury: Study protocol**  
6

7 3 **ABSTRACT**

8 4 **Objectives:** To measure the clinical, structural and functional changes of an individualized structured  
9  
10 5 cognitive rehabilitation in mild traumatic brain injury (mTBI) population.  
11

12  
13 6 **Setting:** A single centre study, Malaysia.  
14

15 7 **Participants:** Adults aged between 18 to 60 years with mTBI as a result of road traffic accident, with no  
16  
17 8 previous history of head trauma, minimum of nine years education and abnormal cognition at three months  
18  
19 9 will be included. The exclusion criteria include pre-existing chronic illness or neurological/psychiatric  
20  
21 10 condition, long-term medication that affects cognitive/psychological status, clinical evidence of substance  
22  
23 11 intoxication at the time of injury and major polytrauma. Based on multiple estimated calculations, the  
24  
25 12 minimum intended sample size is 50 participants (Cohen's *d* effect size 0.35; alpha level of 0.05; 85% power  
26  
27 13 to detect statistical significance; 40% attrition rate).  
28

29 14 **Interventions:** Intervention group will receive individualised structured cognitive rehabilitation. Control  
30  
31 15 group will receive best patient-centred care for attention disorders. Therapy frequency for both groups  
32  
33 16 will be one hour per week for 12 weeks.  
34

35 17 **Outcome measures:** *Primary:* Neuropsychological Assessment Battery-Screening Module (S-NAB) scores.  
36  
37 18 *Secondary:* Diffusion Tensor Imaging (DTI) parameters and Goal Attainment Scaling score (GAS).  
38

39 19 **Results:** Results will include descriptive statistics of population demographics, CogniPlus cognitive  
40  
41 20 program and metacognitive strategies. The effect of intervention will be the effect size of S-NAB scores and  
42  
43 21 mean GAS T scores. DTI parameters will be compared between groups via repeated measure analysis.  
44  
45 22 Correlation analysis of outcome measures will be calculated using Pearson's correlation coefficient.  
46

47 23 **Conclusion:** This is a complex clinical intervention with multiple outcome measures to provide a  
48  
49 24 comprehensive evidence-based treatment model.  
50

51 25 **Trial registration:** This study is registered with ClinicalTrials.gov ID NCT 03237676  
52

53 26 **Ethics and Dissemination:** The study protocol was approved by the Medical Research Ethics Committee,  
54  
55 27 UMMC (MREC ID NO: 2016928-4293). The findings of the trial will be disseminated through peer-reviewed  
56  
57 28 journals and scientific conferences.  
58  
59 29  
60

## 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 approach is 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].



## 59 **Cognitive rehabilitation in mTBI**

60 Currently, there is no standard cognitive rehabilitation treatment for mTBI population[19]. The  
61 heterogeneity of cognitive deficits, varied intervention methodology, different reporting style and variable  
62 treatment outcomes[6,17,27,28,30-57] led to a challenge for professionals to come to an agreement on  
63 mTBI treatment[19]. The early neuropsychological model of attention has already made the assumption  
64 that attention should be the focus of rehabilitation, before more advanced cognitive skills be treated[33].  
65 In the last 20 years, various cognitive treatment approaches have been reported in systematic reviews[34-  
66 37]. These include remediation strategies,[38-49], compensatory strategies[50-57] and patient education  
67 intervention[6,39,53,58]. These approaches are usually applied in combination, to optimise both cognitive  
68 and functional recovery[17,27,28,30,31,33- 38]. In particular, treatment for attention deficits in TBI was  
69 recommended at post-acute (3 months) stage of trauma[28,30,34,44]. Methods of treatment included  
70 multidimensional approach, and tasks with hierarchical difficulty and complexity[30,34,44]. Several  
71 studies also reported improved psychological outcome and coping of symptoms on those who received  
72 patient education and reassurance following mTBI[6,35,36]. However, these conclusions were based on a  
73 limited number of high-quality clinical trials. The consensus was for more robust clinical trials of larger  
74 sample size, well-described complex intervention and standardised reporting method [19,34-37,44,46].

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

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

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

1  
2  
3 88 reliability[41,51,57,61-64], was cost effective and practical to use in a clinical setting[53,62-64] would be  
4  
5 89 ideal.

6  
7 90 The structural injury in mTBI however, is too miniscule for detection through routine computed  
8  
9 91 tomography (CT) and Magnetic Resonance Imaging (MRI)[65-67]. Over the last ten years, Diffusion Tensor  
10  
11 92 Imaging (DTI) has become accepted as a non-invasive tool that is able to quantify microstructural brain  
12  
13 93 changes in mTBI[24,65-70]. Changes in its parameters are indicative of microstructural remodelling at  
14  
15 94 acute and chronic stages of injury, potentially explaining the persistence of symptoms that would otherwise  
16  
17 95 be attributed to other causes [24,65-70]. A longitudinal DTI study may increase our understanding of the  
18  
19 96 brain structural transformation in mTBI.

20  
21 97 The most important outcome following mTBI is the ability for survivors to return to their previous  
22  
23 98 functional state and quality of life. Commonly used scales to measure disability and function are usually  
24  
25 99 sensitive to cognitive deficits but not necessarily specific to the TBI population[39-41,52,53]. Many studies  
26  
27 100 have also reported specific outcome measures for TBI that has good validity, reliability and practical in a  
28  
29 101 clinical setting[71-79], such as Goal Attainment Scaling[71,72,77-79], Extended Glasgow Outcome  
30  
31 102 Scale[73] and Functional Assessment Measure[74].

32  
33 103 This trial evaluates a complex clinical intervention, to provide evidence on the effect of cognitive  
34  
35 104 rehabilitation in mTBI. The outcome measures include anatomical, clinical and functional aspects to  
36  
37 105 provide a comprehensive evidence-based treatment model.

## 38 39 106 **METHODS**

### 40 41 107 **Study hypothesis**

42  
43 108 We hypothesize that structured cognitive rehabilitation for attention deficits following mTBI will  
44  
45 109 improve patients' cognitive function of attention compared to standard care.

### 46 47 110 **Study objectives**

48  
49 111 The objectives are:

- 50  
51  
52 112 • to measure the clinical effect of a 12-week individualized structured cognitive rehabilitation which  
53  
54 113 addresses attention deficit and overall cognitive status
- 55  
56 114 • to analyse the effect of treatment on brain structures and functional changes
- 57  
58 115 • to correlate clinical effects following cognitive rehabilitation with structural brain changes and  
59  
60 116 participants' overall functional outcomes

## 117 **Design**

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

## 120 **Participants and recruitment process**

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

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

## 133 **Inclusion criteria**

134 Mild TBI is defined as physiological disruption of brain function as a result of trauma with symptoms  
135 of loss of consciousness 30 minutes or less, focal neurological deficit that may/may not be transient, altered  
136 mental state with Glasgow Coma Scale of 13-15 and loss of memory with post traumatic amnesia not  
137 greater than 24 hours. The inclusion criteria for this study are mTBI as a result of RTA; adult aged between  
138 18 to 60 years old; Malaysian resident; no previous history of head trauma; minimum of nine years  
139 education; persistently abnormal S-NAB Attention Domain score at three months of mTBI; ability to give  
140 consent and willingness to comply with cognitive rehabilitation program. Persistently abnormal S-NAB  
141 Attention Domain score is defined as Standard Score <85 (below average category) at screening phase and  
142 at enrolment phase as set by the NAB test manual (Table 1).

## 143 **Exclusion criteria**

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

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

| Inclusion criteria  |    |    |    | Exclusion criteria   |    |    |    |
|---|----|----|----|--|----|----|----|
| Criteria  | IG | SG | HG | Criteria   | IG | SG | HG |
| 18-60 years old of age                                    | ✓  | ✓  | ✓  | Pre-existing chronic illness or neurological or psychiatric condition                  | ✓  | ✓  | ✓  |
| No previous history of head trauma                        | ✓  | ✓  | ✓  | On long term medication that can alter or affect cognitive and/or psychological status | ✓  | ✓  | ✓  |
| Minimum of 9 years education                              | ✓  | ✓  | ✓  | Clinical evidence of alcohol intoxication at the time of injury                        | ✓  | ✓  |    |
| Consented   | ✓  | ✓  | ✓  | Major polytrauma (multiple bone fractures, nerve injury)                               | ✓  | ✓  |    |
| mTBI as a result of motor vehicle accidents only          | ✓  | ✓  |    | Absolute contraindication for MRI  | ✓  | ✓  |    |
| Abnormal S-NAB Attention Domain score at 3 months of mTBI | ✓  | ✓  |    |  |    |    |    |
| Willingness to comply with rehabilitation program         |    |    |    |  |    |    |    |

**Table 1:** The study criteria.

Note: IG-individualised structured cognitive rehabilitation group; SG- standard care group, HG- healthy control group

## 149 Intervention

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

1  
2  
3 158 At three months after injury, potential participants will undergo a repeat of clinical review and S-NAB  
4  
5 159 test. Participants with persistently abnormal Attention Domain scores (standard domain score <85) will  
6  
7 160 be enrolled in the study. However, participants with deficits of cognition of more than one domain  
8  
9 161 involvement (standard domain score <85) other than in the Attention domain, will also be included and  
10  
11 162 will receive treatment for attention following randomization. The concomitant domain deficit(s) will also  
12  
13 163 be evaluated upon completion of therapy. The cognitive intervention will be conducted at the  
14  
15 164 Neurorehabilitation Therapy Unit, Department of Rehabilitation Medicine, UMMC in an outpatient setting.  
16  
17 165 Participants will be assigned to different treatment groups via the randomization process. Written records  
18  
19 166 of the intervention will be recorded and kept by the therapist of each treatment arm until treatment  
20  
21 167 completion. This will include the participant's goals, symptom(s), cognitive strategy/method and  
22  
23 168 participant's feedback.

### 24 25 169 ***Individualised structured cognitive rehabilitation group***

26  
27 170 Intervention group participants will receive a two-part 12-week individualized structured cognitive  
28  
29 171 rehabilitation. The first part will be Direct Attention Training (DAT), a deficit-oriented computer-based  
30  
31 172 attention-training program called CogniPlus[45]. Each session last 30 minutes, once a week.

32  
33 173 CogniPlus is a computer-based software program with interactive multimedia approach for multiple  
34  
35 174 attention cognitive training modules. The training programs are ALERT (focused and sustained attention),  
36  
37 175 FOCUS (focused attention), VIG (sustained attention), SELECT (selective attention) and DIVID (divided  
38  
39 176 attention). Each attention-training category is designed based on real-life scenarios. The screen graphics  
40  
41 177 are three-dimensional. This program has an artificial intelligence capacity that can automatically adapt to  
42  
43 178 an individual's performance and alter the training difficulty level (hierarchical difficulty).

44  
45 179 The second part of this intervention will be strategy approach (metacognitive awareness and  
46  
47 180 compensatory strategy) performed after CogniPlus training. Metacognitive awareness includes feedback  
48  
49 181 on the participant's CogniPlus performance to improve their awareness of impairment severity. This  
50  
51 182 process is intended to regulate learning experience and in turn instil the practise of self-monitoring and  
52  
53 183 self-regulation through learning activities. Compensatory strategy component involves instilling cognitive  
54  
55 184 awareness in recognizing impairment that is present in daily activities. This will be followed by the  
56  
57 185 application of cognitive methods to ameliorate the deficit to maximise daily functioning. A participant will  
58  
59 186 identify the deficit(s) and will apply problem-solving method(s) learnt from the therapist. Feedback and  
60

1  
2  
3 187 review of performance will be done again in the following therapy session. This session will last for 30  
4  
5 188 minutes and a will be conducted by a trained and certified Occupational Therapist (OT-1) in cognitive  
6  
7 189 therapy and CogniPlus.

### 9 190 ***Standard care group***

11 191 This group will receive the best standard care for attention disorders. This is a patient-centred  
12  
13 192 cognitive therapy. It is based on a patient's complaint(s), symptom(s) and therapy aim(s) (self-realization  
14  
15 193 of deficits or guided by therapist). Symptom(s) management may include physical (e.g. imbalance, fatigue,  
16  
17 194 sleep dysregulation), psychological (e.g. mild anxiety or depression) and cognitive (e.g. forgetfulness).  
18  
19 195 Referral to relevant service(s) may be required such as physiotherapy, return to work/driving  
20  
21 196 rehabilitation and counselling. Compensatory strategy includes task specific training (patient-prioritised)  
22  
23 197 e.g. return to driving may involve driving simulation training, visuospatial training and return to drive  
24  
25 198 rehabilitation service. The frequency of sessions will be one hour per week, for 12 weeks. A trained  
26  
27 199 occupational therapist in cognitive therapy (OT-2) who is not involved with the intervention group  
28  
29 200 treatment, will conduct all the sessions (Table 2).

### 31 201 ***Control group***

33 202 This will consist of healthy individuals demographically matched for age, gender and education years to  
34  
35 203 the intervention groups (Table 1). They will undergo S-NAB assessment battery, DTI imaging and  
36  
37 204 psychological screening tools which will include the Generalised Anxiety Disorder 7-item (GAD7) and  
38  
39 205 Patient Health Questionnaire-9 (PHQ-9). Their lifestyle aspects will also be reviewed and recorded  
40  
41 206 (spiritual practice, diet, physical exercise, occupation and driving). The data will be collected for  
42  
43 207 comparison purpose.

### 45 208 **Randomisation, consent and blinding**

47 209 Participants with mTBI who fulfil the study criteria will be randomized via computer-generated  
48  
49 210 random permuted block assignment, gender-stratified into equally proportioned intervention and control  
50  
51 211 group numbers. The study schedule, procedures and blinding of co-investigators are presented in **Table 2**.

| TIMEPOINT**   | STUDY PERIOD                  |   |                                       |  |                            |                      |   |                      |                      |                        |                       |  |
|---|-------------------------------|---|---------------------------------------|--|----------------------------|----------------------|---|----------------------|----------------------|------------------------|-----------------------|--|
|   |                               | Enrolment                                 | Enrolment                             | Enrolment                                | Allocation                 | Post-allocation      |   |                      |                      |                        | End of treatment      |  |
|   |                               | <i>-t<sub>3</sub></i><br>72 hours<br>mTBI | <i>-t<sub>2</sub></i><br>2 weeks mTBI | <i>-t<sub>1</sub></i><br>6 weeks<br>mTBI | 0<br>3 months mTBI         | <i>t<sub>1</sub></i> | <i>t<sub>2</sub></i>                        | <i>t<sub>3</sub></i> | <i>t<sub>4</sub></i> | <i>t<sub>5</sub></i>   | <i>t<sub>12</sub></i> | <i>f<sub>1</sub></i><br>6 months<br>mTBI |
|   | Co-investigator<br>(initials) | Pre-study<br>screening                    | Pre-study<br>screening                | Pre-study<br>screening                   | Baseline/<br>Randomisation | Study<br>Visit 1     | Study visit<br><i>t<sub>2</sub></i> onwards |                      |                      | Last<br>study<br>visit | Outcome<br>measures   |  |
| <b>ENROLMENT:</b>                                     |                               |   |                                       |  |                            |                      |   |                      |                      |                        |                       |  |
| 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) &<br>NAMT (OT-2)   |   |                                       |  |                            | X                    | X   | X                    | X                    | X                      | X                     | X  |
| <b>INTERVENTIONS:</b>                                 |                               |   |                                       |  |                            |                      |   |                      |                      |                        |                       |  |
| Education component/<br>symptom(s) evaluation         | ED team/RP-1                  | X<br>(ED team)                            | X<br>(RP-1)                           | X<br>(RP-1)                              |                            |                      |   |                      |                      |                        |                       |  |
| Individualized structured<br>cognitive rehabilitation | NAM (OT-1)                    |   |                                       |  |                            | X                    | X   | X                    | X                    | X                      | X                     |  |
| Best standard care                                    | NAMT (OT-2)                   |   |                                       |  |                            | X                    | X   | X                    | X                    | X                      | X                     |  |
| <b>OUTCOME MEASURES:</b>                              |                               |   |                                       |  |                            |                      |   |                      |                      |                        |                       |  |
| S-NAB Test  | NH                            |   |                                       |  | X                          |                      |   |                      |                      |                        |                       | X  |
| DTI   | VN/NR                         |   |                                       |  | X                          |                      |   |                      |                      |                        |                       | X  |
| GAS   | NAM/NAMT<br>(OT-1/OT-2)       |   |                                       |  |                            | X                    | X   | X                    | X                    | X                      | X                     | X  |

Table 2: Study schedule and procedures.



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

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

## 223 **Adherence strategies**

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

## 228 **Outcome measures**

229 All measures will be performed at baseline and at 12 weeks of intervention after randomisation. The  
230 primary outcome measure for this study is the change in attention deficit and other cognitive domains  
231 within intervention groups and direct comparison of each intervention group with the healthy control  
232 group. This will be measured by Neuropsychological Assessment Battery® (NAB®, PAR, Inc., Florida,  
233 USA)[61]. It consists of six modules: Screening Module and five Domain Specific Modules: Attention,  
234 Language, Memory, Spatial and Executive Function. This study will only apply the Screening Module (S-  
235 NAB) because it measures the same five functional domains similar or identical to the main NAB modules.  
236 It consists of 12 individual tests screening all five mentioned cognitive domains for adults aged 18 to 97  
237 years, validated and sensitive for use in healthy and cognitively impaired brain injured population[24,61-  
238 64]. S-NAB also provides two parallel assessment sets (Record Form 1 and Form 2) that will be applied in  
239 an alternate fashion to participants in both groups to avoid practice effect.



1  
2  
3 240 S-NAB Domain Attention test items and score are interpreted as a marker of an individual's attentional  
4  
5 241 capacity, working memory, psychomotor speed, selective attention, divided attention and information  
6  
7 242 processing [61]. S-NAB has also been applied in our previous cohort study [24] with good validation  
8  
9 243 outcome in our Malaysian mTBI population.

10  
11 244 The secondary outcome measures are microstructural WMT parameters and GAS scores. The DTI MRI  
12  
13 245 scan is a Siemens Magnetom Prisma 3T MRI (Siemens AG, Muenchen, Germany). This study will analyse  
14  
15 246 Fractional Anisotropy (FA), Mean Diffusivity (MD) and Radial Diffusivity (RD) parameter changes at pre-  
16  
17 247 and post-intervention[24,65-70]. These parameters quantify the direction and degree of tissue water  
18  
19 248 diffusion within the WMT[65,66]. FA which measures the direction of the diffusion is an index expressed  
20  
21 249 in a range from 0-1, with a higher score indicating a higher integrity of white matter consisting of highly  
22  
23 250 parallel fibres[65,66]. MD measures the average magnitude of the diffusion while RD quantifies pathology  
24  
25 251 in the myelin[65,66]. Changes in the index values of the parameters at different injury timeline will indicate  
26  
27 252 the pathological changes of the WMT.

28  
29 253 The tool to measure functional goal outcome will be the GAS[77-79]. The difficulty and importance of  
30  
31 254 rehabilitation goals will be individually set according to his/her current levels of functional performance  
32  
33 255 to reinforce realistic expectations. The sensitivity of GAS is increased by the quantifiable set goals relevant  
34  
35 256 and specific to the participant. Each goal is rated on a 5-point scale and score is given on the extent to which  
36  
37 257 a patient's individual goals are achieved in the course of the intervention. The overall GAS scores calculation  
38  
39 258 will generate a standardized measure (T score) (mean of 50 Standard Deviation  $\pm$  10). The details of each  
40  
41 259 goal outcome will be recorded in the GAS Record Sheet[77-79] by a cognitive therapist of each study arm  
42  
43 260 (OT-1 and OT-2) trained in GAS application.

44  
45 261 Another important factor to note is the participant's psychological status following mTBI. This study  
46  
47 262 will also perform a screening of anxiety and depression symptoms by using GAD7 and PHQ-9 screening  
48  
49 263 tools at each study timeline. Participant's lifestyle changes/modifications such as spiritual practice, diet  
50  
51 264 change, physical exercise, return to work/education, return to driving, litigation issues and insurance  
52  
53 265 claims will also be reviewed and recorded. Although these parameters will not be part of the study outcome  
54  
55 266 measure, they however remain relevant in influencing treatment adherence and outcome.

### 267 **Sample size and power calculation**

268 In order to fulfil our study objectives we will base the intended sample size calculation on a previous  
269 study that had applied a similar treatment approach and which had a similar outcome measure to our  
270 study[40]. This study applied the non-commercial statistical power analysis program G\*Power Version  
271 3.1.9.2. An effect size of 0.58, which was the functional cognitive outcome of attention [40], is used to  
272 calculate the statistical power *a priori*. We will apply Analysis of Variance (ANOVA): repeated measures,  
273 within-between interaction, setting an alpha level of 0.05, and approximately 10 participants will provide  
274 89% power to detect a statistical significance. Recruitment is doubled (n=20) for both arms and inflated  
275 to 28 to counter 40% attrition rate.

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

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

### 284 **Ethics considerations**

285 This study was approved by Medical Research Ethics Committee, UMMC (MREC ID NO: 2016928-  
286 4293). We will obtain written consent from participants. During consenting, participant will be provided  
287 with Patient Information Sheet detailing the purpose of study, reason for participation, study investigation  
288 and intervention methods, withdrawal from study and contact details of investigators. Once consent is  
289 given the form and all other documents with the participant's personal details will be stored immediately  
290 in a locked filing cabinet by the consent taker. This will be accessible only to a small number of  
291 investigators. Study ID codes will be allocated after consent is obtained and subsequent study  
292 documentation will only use the ID code.

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

1  
2  
3 296 the event of information sharing being required for medical reasons, the participant will be informed  
4  
5 297 immediately followed by referral to the relevant professional either based at UMMC or a different centre of  
6  
7 298 choice. However, costs of further investigation or treatment that is not part of this study will not be funded  
8  
9 299 from the study grants. Treatment compliance will be achieved through our adherence strategy. We strictly  
10  
11 300 adhere to the privacy and confidentiality of participant's medical information. Any information sharing  
12  
13 301 with a third party for various reasons will be managed in accordance with UMMC professional and legal  
14  
15 302 code of conduct.

### 17 303 **Patient and public involvement**

18  
19 304 We applied the Medical Research Council's (MRC) Developing and Evaluating Complex Intervention:  
20  
21 305 New Guidance (2006) and Multiphase Optimization Strategy (MOST) framework to guide the development  
22  
23 306 and design of this study. The treatment approach was based on the relevant theoretical evidence whereas  
24  
25 307 treatment approach was evinced through our systematic review, clinical experience and practice setting of  
26  
27 308 interest. We conducted 1) a pilot study and 2) Expert Panel review to evaluate the study design and  
28  
29 309 treatment method that may require further focus.

30  
31 310 Our pilot study was approved by Medical Research Ethics Committee, UMMC, Malaysia (UM/EC Ref:  
32  
33 311 947.15) for the application of cognitive treatment on mTBI patients. They were involved in the testing of  
34  
35 312 treatment method, clinical practicality, fidelity of treatment and treatment compliance. We have identified  
36  
37 313 several components required for optimization of intervention. These findings were also assessed by the  
38  
39 314 Expert Panel reviewers.

40  
41 315 The panel comprised of clinicians who were credentialed in brain injury management and cognitive  
42  
43 316 rehabilitation with minimum of ten years clinical experience working in Malaysia. Panels were made up of  
44  
45 317 seven rehabilitation medicine consultants, one neurosurgeon consultant, one neuroimaging consultant,  
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47 318 five cognitive occupational therapists and one clinical psychologist. The focus of discussion was on the  
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49 319 feasibility of structured cognitive rehabilitation for mTBI patients in Malaysia, guided by the current  
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51 320 evidence, current practise of cognitive rehabilitation in local setting, reviewers clinical experience and our  
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53 321 pilot study findings. A summary of the pilot study outcomes and Expert Panel recommendations are best  
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55 322 illustrated in Table 3.

56 323 Following the commencement of this study, the input from participants (experience, feedback and  
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58 324 outcomes) will be recorded. The data and study materials will belong to UMMC, Malaysia. We will inform  
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325 our participants of the result of the study to following completion even if he/she did not complete the study  
326 unless he/she has requested no contact.

For peer review only

| Pilot study   | Expert panel review   |
|---|---|
| <p>Design: a case-controlled study</p> <p>Study components:</p> <p><b>Non-randomisation</b> –to identify participant’s willingness to attend therapy as a measure of good compliance.</p> <p><b>Treatment application</b> - treatment was given at early stage of injury (2 weeks post injury) to measure the treatment effect versus spontaneous’ recovery.</p> <p><b>Treatment accessibility</b> – outpatient hospital-based treatment is feasible.</p> <p><b>Treatment compliance</b>–high attrition rate (50%) which compromised the treatment fidelity. Reasons for poor treatment compliance were:</p> <ul style="list-style-type: none"> <li>• treatment frequency and intensity (&gt;1 hour/weekly for the first 3 months followed by monthly session the following 3 months)</li> <li>• mental fatigue</li> <li>• ‘unreadiness’ to receive treatment</li> <li>• treatment and transportation costs</li> <li>• work demand (limited time off work and income lost)</li> </ul> <p><b>Treatment method</b>- clinical application of treatment was acceptable to participants.</p> <p><b>Treatment effect</b> - the application of effect size measurement is consistent with MOST recommendation.</p> <p><b>Outcome measure application</b> –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: Randomization was recommended in clinical trial design</p> <p>Review components:</p> <p><b>Fidelity of treatment</b></p> <ol style="list-style-type: none"> <li>1) clear information on purpose, method and treatment goals during treatment sessions</li> <li>2) an appointment card with specific date and time of therapy sessions</li> <li>3) a reminder through phone calls a week and a day before each therapy</li> <li>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.</li> </ol> <p><b>Treatment method</b></p> <ol style="list-style-type: none"> <li>1) as outpatient setting, with frequency 1hour/week for 12 weeks duration.</li> <li>2) individualised treatment approach with standardization through direct attention training and metacognitive strategy</li> <li>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</li> </ol> <p><b>Outcome measure</b></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> |

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

## 327 **Statistical analysis**

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

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

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

344 The secondary analysis will include measurement of structural brain changes following intervention.  
345 This data will be obtained from the DTI MRI scan performed at pre and post intervention, for all groups.  
346 We will identify FA, MD and RD parameters with statistically significant mean values ( $p<0.05$ ) via whole  
347 brain analysis known as Tract-based Spatial Statistics (TBSS)[80] and region of interest (ROI) approach  
348 which is part of the FSL (v5.0.6; University of Oxford, Oxford UK) [81] and AFNI (v2011\_12\_21\_1014;  
349 National Institute of Mental Health, Bethesda, MD) software packages. The DTI parameters of both  
350 intervention groups at three- and six months study timelines will be compared with the healthy control  
351 group by using repeated measure analysis. This is in the assumption that the study fulfils the repeated  
352 measure analysis of normally distributed data sample and homogeneity of variance.

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

## 356 **Data management**

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

## 364 **Discussion**

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

## 378 **Trial status**

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

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384

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388 Science and Innovation (MOSTI) grant (MOSTI Flagship Project FP0911F001)

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

390 **Protocol Registered date:** 18<sup>th</sup> July 2017

391 **Protocol updated date:** 16<sup>th</sup> August 2017

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

393 **Competing interest:** none declared

## 394 **Acknowledgement**

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

## 397 **Authors' contribution**

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

## 406 **Availability of data and material**

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

## 409 **Ethics and Dissemination**

410 The study protocol was approved by the Medical Research Ethics Committee, UMMC (MREC ID NO:  
411 2016928-4293). The findings of the trial will be disseminated through peer-reviewed journals and  
412 scientific conferences.



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23 690 analysis and implementation as FSL. *NeuroImage*, 2004; 23(S1):208-219.  
24  
25 691

26 692 **Figure 1:** Flowchart showing the stages of recruitment in this study.  
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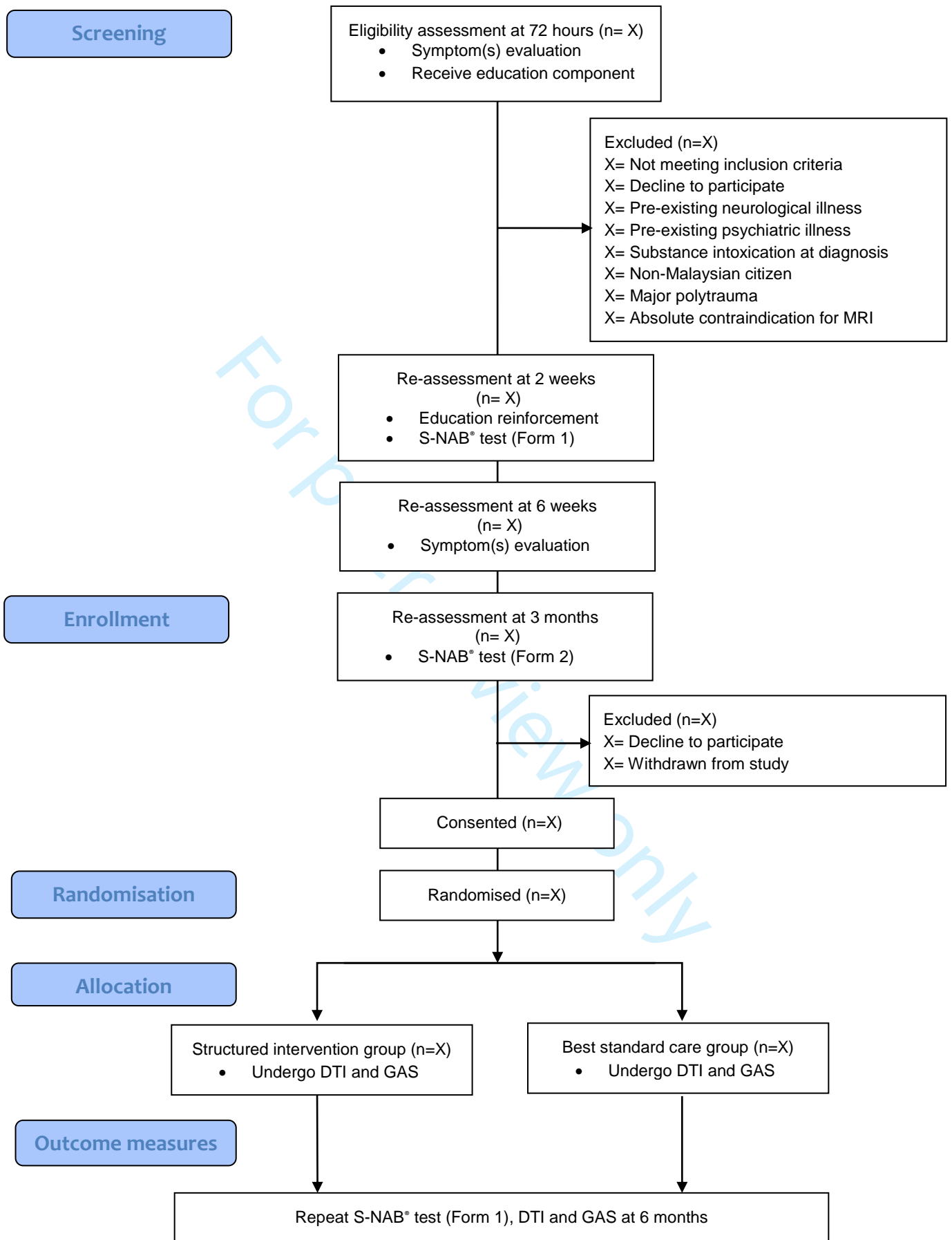


Figure 1: Flowchart showing the stages of recruitment in this study.



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

| Section/item                      | Item No | Description  | Addressed on line number |
|-----------------------------------|---------|--|--------------------------|
| <b>Administrative information</b> |         |  |                          |
| 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                       |

1 **Introduction**

2

3 Background and 6a Description of research question and justification for undertaking the trial, including summary of relevant 44-105  
 4 rationale studies (published and unpublished) examining benefits and harms for each intervention  
 5

6 6b Explanation for choice of comparators 44-105  
 7

8 Objectives 7 Specific objectives or hypotheses 107-117  
 9

10 Trial design 8 Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group),  
 11 allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) 118-132; Figure 1  
 12  
 13

14 **Methods: Participants, interventions, and outcomes**

15

16 Study setting 9 Description of study settings (eg, community clinic, academic hospital) and list of countries where data will 122-128  
 17 be collected. Reference to where list of study sites can be obtained  
 18

19 Eligibility criteria 10 Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and 133-150, Table 1  
 20 individuals who will perform the interventions (eg, surgeons, psychotherapists)  
 21

22 Interventions 11a Interventions for each group with sufficient detail to allow replication, including how and when they will be 151-203; Figure 1  
 23 administered  
 24

25 11b Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose 208-218  
 26 change in response to harms, participant request, or improving/worsening disease)  
 27

28 11c Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence 219-223  
 29 (eg, drug tablet return, laboratory tests)  
 30

31 11d Relevant concomitant care and interventions that are permitted or prohibited during the trial NA  
 32  
 33

34 Outcomes 12 Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood 224-262  
 35 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  
 36 efficacy and harm outcomes is strongly recommended  
 37

38 Participant timeline 13 Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for 204-207; Table 2  
 39 participants. A schematic diagram is highly recommended (see Figure)  
 40  
 41  
 42

|   |             |    |   |                  |
|---|-------------|----|---|------------------|
| 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 | 263-279          |
| 2 |             |    |   |                  |
| 3 |             |    |   |                  |
| 4 | Recruitment | 15 | Strategies for achieving adequate participant enrolment to reach target sample size   | 219-223; 263-279 |
| 5 |             |    |   |                  |

6 **Methods: Assignment of interventions (for controlled trials)**

7 Allocation:

|    |                                  |     |  |                  |
|----|----------------------------------|-----|--|------------------|
| 8  |                                  |     |  |                  |
| 9  |                                  |     |  |                  |
| 10 | 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 |
| 11 |                                  |     |  |                  |
| 12 |                                  |     |  |                  |
| 13 |                                  |     |  |                  |
| 14 |                                  |     |  |                  |
| 15 |                                  |     |  |                  |
| 16 | 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 |
| 17 |                                  |     |  |                  |
| 18 |                                  |     |  |                  |
| 19 |                                  |     |  |                  |
| 20 | Implementation                   | 16c | Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions  | Table 2          |
| 21 |                                  |     |  |                  |
| 22 |                                  |     |  |                  |
| 23 |                                  |     |  |                  |
| 24 | Blinding (masking)               | 17a | Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how  | Table 2          |
| 25 |                                  |     |  |                  |
| 26 |                                  |     |  |                  |
| 27 |                                  | 17b | If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial   | 208-218          |
| 28 |                                  |     |  |                  |
| 29 |                                  |     |  |                  |
| 30 |                                  |     |  |                  |

31 **Methods: Data collection, management, and analysis**

|    |                         |     |  |  |
|----|-------------------------|-----|--|--|
| 32 |                         |     |  |  |
| 33 | 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 |
| 34 |                         |     |  |  |
| 35 |                         |     |  |  |
| 36 |                         |     |  |  |
| 37 |                         |     |  |  |
| 38 |                         |     |  |  |
| 39 |                         | 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  |
| 40 |                         |     |  |  |
| 41 |                         |     |  |  |
| 42 |                         |     |  |  |

|    |                                 |     |   |                    |
|----|---------------------------------|-----|---|--------------------|
| 1  | 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            |
| 2  |                                 |     |   |                    |
| 3  |                                 |     |   |                    |
| 4  |                                 |     |   |                    |
| 5  | 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            |
| 6  |                                 |     |   |                    |
| 7  |                                 |     |   |                    |
| 8  |                                 | 20b | Methods for any additional analyses (eg, subgroup and adjusted analyses)  | NA                 |
| 9  |                                 |     |   |                    |
| 10 |                                 | 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            |
| 11 |                                 |     |   |                    |
| 12 |                                 |     |   |                    |
| 13 |                                 |     |   |                    |
| 14 | <b>Methods: Monitoring</b>      |     |   |                    |
| 15 |                                 |     |   |                    |
| 16 | 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                 |
| 17 |                                 |     |   |                    |
| 18 |                                 |     |   |                    |
| 19 |                                 |     |   |                    |
| 20 |                                 |     |   |                    |
| 21 |                                 |     |   |                    |
| 22 |                                 | 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                 |
| 23 |                                 |     |   |                    |
| 24 |                                 |     |   |                    |
| 25 | 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            |
| 26 |                                 |     |   |                    |
| 27 |                                 |     |   |                    |
| 28 | Auditing                        | 23  | Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor   | NA                 |
| 29 |                                 |     |   |                    |
| 30 |                                 |     |   |                    |
| 31 |                                 |     |   |                    |
| 32 | <b>Ethics and dissemination</b> |     |   |                    |
| 33 |                                 |     |   |                    |
| 34 | Research ethics approval        | 24  | Plans for seeking research ethics committee/institutional review board (REC/IRB) approval   | 280-297            |
| 35 |                                 |     |   |                    |
| 36 |                                 |     |   |                    |
| 37 | 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 |
| 38 |                                 |     |   |                    |
| 39 |                                 |     |   |                    |
| 40 |                                 |     |   |                    |
| 41 |                                 |     |   |                    |
| 42 |                                 |     |   |                    |
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|    |                               |     |   |                 |
|----|-------------------------------|-----|---|-----------------|
| 1  | 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         |
| 2  |                               |     |   |                 |
| 3  |                               |     |   |                 |
| 4  |                               | 26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable   | NA              |
| 5  |                               |     |   |                 |
| 6  |                               |     |   |                 |
| 7  | 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 |
| 8  |                               |     |   |                 |
| 9  |                               |     |   |                 |
| 10 | Declaration of interests      | 28  | Financial and other competing interests for principal investigators for the overall trial and each study site   | 376-385         |
| 11 |                               |     |   |                 |
| 12 |                               |     |   |                 |
| 13 | 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 |
| 14 |                               |     |   |                 |
| 15 |                               |     |   |                 |
| 16 | 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              |
| 17 |                               |     |   |                 |
| 18 |                               |     |   |                 |
| 19 |                               |     |   |                 |
| 20 | 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         |
| 21 |                               |     |   |                 |
| 22 |                               |     |   |                 |
| 23 |                               |     |   |                 |
| 24 |                               | 31b | Authorship eligibility guidelines and any intended use of professional writers  | BMJ guideline   |
| 25 |                               |     |   |                 |
| 26 |                               | 31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code   | NA              |
| 27 |                               |     |   |                 |
| 28 |                               |     |   |                 |
| 29 | <b>Appendices</b>             |     |   |                 |
| 30 |                               |     |   |                 |
| 31 | Informed consent materials    | 32  | Model consent form and other related documentation given to participants and authorised surrogates  | -               |
| 32 |                               |     |   |                 |
| 33 |                               |     |   |                 |
| 34 | 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              |
| 35 |                               |     |   |                 |
| 36 |                               |     |   |                 |

37 \*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items.  
 38 Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons  
 39 "[Attribution-NonCommercial-NoDerivs 3.0 Unported](#)" license.  
 40



# BMJ Open

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

|                                 |  |
|---------------------------------|--|
| Journal:                        | <i>BMJ Open</i>  |
| Manuscript ID                   | bmjopen-2018-028711.R3   |
| Article Type:                   | Protocol   |
| Date Submitted by the Author:   | 19-Aug-2019  |
| Complete List of Authors:       | Hamzah, Norhamizan; University of Malaya, Rehabilitation Medicine<br>Narayanan, Vairavan; University of Malaya, Surgery<br>Ramli, Norlisah; University of Malaya, Biomedical Imaging<br>Mustapha, Nor Atikah ; University of Malaya Medical Centre, Rehabilitation Medicine<br>Mohammad Tahir, Nor Adibah; University of Malaya Medical Centre, Dept of Rehabilitation Medicine<br>Tan, Li Kuo; University of Malaya, Biomedical Imaging<br>Danaee, Mahmoud ; University of Malaya, Department of Social and Preventive Medicine, Faculty of Medicine<br>Muhamad, Nor Asiah; Ministry of Health Malaysia, Institute of Public Health<br>Drummond, Avril; University of Nottingham Faculty of Medicine and Health Sciences<br>dasNair, Roshan; University of Nottingham Faculty of Medicine and Health Sciences<br>Goh , Sing Yau; Universiti Tunku Abdul Rahman, Lee Kong Chian Faculty of Engineering and Science<br>Mazlan, Mazlina; University of Malaya, Rehabilitation Medicine |
| <b>Primary Subject Heading</b>: | Rehabilitation medicine  |
| Secondary Subject Heading:      | Rehabilitation medicine, Research methods, Radiology and imaging   |
| Keywords:                       | mild traumatic brain injury, cognitive rehabilitation, randomised controlled trial, neuropsychology, Diffusion Tensor Imaging  |
|                                 |  |

SCHOLARONE™  
Manuscripts

**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: 4788**

1  
2  
3 1 **TITLE: A randomised controlled clinical trial of a structured cognitive rehabilitation in patients**  
4  
5 2 **with attention deficit following mild traumatic brain injury: Study protocol**  
6

7 3 **ABSTRACT**

8 4 **Objectives:** To measure the clinical, structural and functional changes of an individualized structured  
9  
10 5 cognitive rehabilitation in mild traumatic brain injury (mTBI) population.  
11

12  
13 6 **Setting:** A single centre study, Malaysia.  
14

15 7 **Participants:** Adults aged between 18 to 60 years with mTBI as a result of road traffic accident, with no  
16  
17 8 previous history of head trauma, minimum of nine years education and abnormal cognition at three  
18  
19 9 months will be included. The exclusion criteria include pre-existing chronic illness or  
20  
21 10 neurological/psychiatric condition, long-term medication that affects cognitive/psychological status,  
22  
23 11 clinical evidence of substance intoxication at the time of injury and major polytrauma. Based on multiple  
24  
25 12 estimated calculations, the minimum intended sample size is 50 participants (Cohen's *d* effect size 0.35;  
26  
27 13 alpha level of 0.05; 85% power to detect statistical significance; 40% attrition rate).  
28

29 14 **Interventions:** Intervention group will receive individualised structured cognitive rehabilitation. Control  
30  
31 15 group will receive best patient-centred care for attention disorders. Therapy frequency for both groups  
32  
33 16 will be one hour per week for 12 weeks.  
34

35 17 **Outcome measures:** *Primary:* Neuropsychological Assessment Battery-Screening Module (S-NAB)  
36  
37 18 scores. *Secondary:* Diffusion Tensor Imaging (DTI) parameters and Goal Attainment Scaling score (GAS).  
38

39 19 **Results:** Results will include descriptive statistics of population demographics, CogniPlus cognitive  
40  
41 20 program and metacognitive strategies. The effect of intervention will be the effect size of S-NAB scores  
42  
43 21 and mean GAS T scores. DTI parameters will be compared between groups via repeated measure analysis.  
44  
45 22 Correlation analysis of outcome measures will be calculated using Pearson's correlation coefficient.  
46

47 23 **Conclusion:** This is a complex clinical intervention with multiple outcome measures to provide a  
48  
49 24 comprehensive evidence-based treatment model.  
50

51 25 **Trial registration:** This study is registered with ClinicalTrials.gov ID NCT 03237676  
52

53 26 **Ethics and Dissemination:** The study protocol was approved by the Medical Research Ethics Committee  
54  
55 27 UMMC (MREC ID NO: 2016928-4293). The findings of the trial will be disseminated through peer-  
56  
57 28 reviewed journals and scientific conferences.  
58  
59 29  
60

## 30 **ARTICLE SUMMARY:**

### 31 **Strengths and limitations of this study:**

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

## 43 **BACKGROUND**

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

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

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3 58 months and may, indeed continue to have neurocognitive functional deficits beyond one year of injury  
4  
5 59 [5,12,25-29].  
6

### 7 60 **Cognitive rehabilitation in mTBI**

9 61 Currently, there is no standard cognitive rehabilitation treatment for mTBI population [19]. The  
10  
11 62 heterogeneity of cognitive deficits, varied intervention methodology, different reporting style and  
12  
13 63 variable treatment outcomes [6,17,27,28,30-57] lead to a challenge for professionals in agreeing mTBI  
14  
15 64 treatment[19]. The early neuropsychological model of attention has already made the assumption that  
16  
17 65 attention should be the focus of rehabilitation, even before more advanced cognitive skills are  
18  
19 66 treated[33]. In the last 20 years, various cognitive treatment approaches have been reported in  
20  
21 67 systematic reviews [34-37]. These include remediation strategies,[38-49], compensatory strategies[50-  
22  
23 68 57] and patient education intervention[6,39,53,58]. These approaches are usually applied in combination,  
24  
25 69 in order to optimise both cognitive and functional recovery [17,27,28,30,31,33-38]. In particular,  
26  
27 70 treatment for attention deficits in TBI has been recommended at post-acute (3 months) stage of trauma  
28  
29 71 [28,30,34,44]. Methods of treatment included multidimensional approach, and tasks with hierarchical  
30  
31 72 difficulty and complexity [30,34,44]. Several studies also reported improved psychological outcome and  
32  
33 73 coping of symptoms on those who received patient education and reassurance following mTBI [6,35,36].  
34  
35 74 However, these conclusions were based on a limited number of high-quality clinical trials. The consensus  
36  
37 75 was for more robust clinical trials with larger sample sizes, with well-described complex intervention and  
38  
39 76 standardised reporting methods [19,34-37,44,46].

40  
41 77 Delivery of cognitive rehabilitation emphasizes six principles: 1) intervention that is theory-driven  
42  
43 78 and meaningful, 2) intervention is task-specific with increasing complexity relevant to individual needs,  
44  
45 79 3) the need to regularly practice skills acquired, 4) progress monitoring to tailor to individual's needs, 5)  
46  
47 80 generalisation of learnt strategies to apply in real-life skills, and 6) real-world adaptation to ensure  
48  
49 81 success [17,49,59]. A practical, widely accepted treatment approach with the application of evidence-  
50  
51 82 based treatment principles may represent a comprehensive treatment model in treating mTBI patients  
52  
53 83 with cognitive deficits. A large randomised trial is required to support this hypothesis.

### 54 84 **Clinical, imaging and functional outcome measures in mTBI**

55  
56  
57 85 A combination of these three outcome measures is a comprehensive approach to analyse cognitive  
58  
59 86 intervention that can make an impact in clinical practice. Scientific reviews and guidelines have  
60

1  
2  
3 87 recommended the use of neuropsychological assessment as an appropriate clinical outcome measure  
4  
5 88 [17,27,28,30,31,33,34,36,37]. In adult mTBI, a test that is sensitive across various cognitive domains  
6  
7 89 [21,24,41,43,53,57,60], specific to population study [24,40,43], has good validity and reliability  
8  
9 90 [41,51,57,61-64], is cost effective and practical to use in a clinical setting[53,62-64] would be ideal.

10  
11 91 The structural injury in mTBI however, is too miniscule for detection through routine computed  
12  
13 92 tomography (CT) and Magnetic Resonance Imaging (MRI)[65-67]. Over the last ten years, Diffusion  
14  
15 93 Tensor Imaging (DTI) has become accepted as a non-invasive tool that is able to quantify microstructural  
16  
17 94 brain changes in mTBI [24,65-70]. Changes in its parameters are indicative of microstructural  
18  
19 95 remodelling at acute and chronic stages of injury, potentially explaining the persistence of symptoms that  
20  
21 96 would otherwise be attributed to other causes [24,65-70]. A longitudinal DTI study may increase our  
22  
23 97 understanding of the brain structural transformation in mTBI.

24  
25 98 The most important outcome following mTBI is the ability for survivors to return to their previous  
26  
27 99 functional state and quality of life. Commonly used scales to measure disability and function are usually  
28  
29 100 sensitive to cognitive deficits but not necessarily specific to the TBI population [39-41,52,53]. Many  
30  
31 101 studies have also reported specific outcome measures for TBI that has good validity, reliability and  
32  
33 102 practical in a clinical setting [71-79], such as Goal Attainment Scaling [71,72,77-79], Extended Glasgow  
34  
35 103 Outcome Scale [73] and Functional Assessment Measure[74].

36  
37 104 This trial evaluates a complex clinical intervention which will provide evidence on the effect of  
38  
39 105 cognitive rehabilitation in mTBI. The outcome measures include anatomical, clinical and functional  
40  
41 106 aspects to provide a comprehensive evidence-based treatment model.

## 42 43 107 **METHODS**

### 44 45 108 **Study hypothesis**

46  
47 109 We hypothesize that structured cognitive rehabilitation for attention deficits following mTBI will  
48  
49 110 improve patients' cognitive function of attention compared to standard care.

### 50 51 111 **Study objectives**

52  
53 112 The objectives are:

- 54  
55 113 • to measure the clinical effect of a 12-week individualized structured cognitive rehabilitation  
56  
57 114 which addresses attention deficit and overall cognitive status
- 58  
59 115 • to analyse the effect of treatment on brain structures and functional changes

- 1  
2  
3 116 • to correlate clinical effects following cognitive rehabilitation with structural brain changes and  
4  
5 117 participants' overall functional outcomes  
6

7 118 **Design**  
8

9 119 This will be a prospective double blind, randomized controlled trial with two parallel groups. The  
10  
11 120 study design is summarized in **Figure 1**.  
12

13 121 **Participants and recruitment process**  
14

15 122 This trial will be conducted at a single centre, University Malaya Medical Centre (UMMC), Malaysia.  
16  
17 123 UMMC is a government funded academic medical institution situated in the urban area of the nation's  
18  
19 124 capital city Kuala Lumpur with a population of 1.76 million. Apart from providing acute medical services,  
20  
21 125 this hospital is also a tertiary referral and training centre in Malaysia. UMMC also houses Department of  
22  
23 126 Rehabilitation Medicine that provides the facility for this study. This department includes the main  
24  
25 127 rehabilitation services (neuro-, spinal cord-, prosthetic and orthotic-, paediatric- and cardiac  
26  
27 128 rehabilitation) for both inpatient and outpatient setting. Other services also include return to  
28  
29 129 work/driving rehabilitation.  
30

31 130 We will recruit participants through the Emergency Medicine Department (ED), UMMC from 1<sup>st</sup>  
32  
33 131 August 2017. ED physicians, radiologists and neurosurgeons will refer mTBI cases to a research assistant  
34  
35 132 for recruitment. Potential cases will also be screened through the UMMC digital medical record system.  
36  
37 133 Screening stages will be performed at 72 hours, two and six weeks following mTBI.  
38

39 134 **Inclusion criteria**  
40

41 135 Mild TBI is defined as physiological disruption of brain function as a result of trauma with symptoms  
42  
43 136 of loss of consciousness 30 minutes or less, focal neurological deficit that may/may not be transient,  
44  
45 137 altered mental state with Glasgow Coma Scale of 13-15 and loss of memory with post traumatic amnesia  
46  
47 138 not greater than 24 hours. The inclusion criteria for this study are mTBI as a result of RTA; adult aged  
48  
49 139 between 18 to 60 years old; Malaysian resident; no previous history of head trauma; minimum of nine  
50  
51 140 years education; persistently abnormal S-NAB Attention Domain score at three months of mTBI; ability to  
52  
53 141 give consent and willingness to comply with cognitive rehabilitation program. Persistently abnormal S-  
54  
55 142 NAB Attention Domain score is defined as Standard Score <85 (below average category) at screening  
56  
57 143 phase and at enrolment phase as set by the NAB test manual (Table 1).  
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59 144  
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3 **145 Exclusion criteria**

4  
5 **146** The exclusion criteria include pre-existing chronic illness that causes neurological symptoms or  
6  
7 **147** complications; severe comorbid neurological or psychiatric disorder; on long-term medication that alters  
8  
9 **148** or affects cognitive and psychological status; clinical evidence of substance intoxication at the time of  
10  
11 **149** injury; major polytrauma and absolute contraindications for MRI (metal or implant not compatible for  
12  
13 **150** MRI, claustrophobia) (Table 1).  
14  
15  
16  
17

| Inclusion criteria  |    |    |    | Exclusion criteria   |    |    |    |
|---|----|----|----|--|----|----|----|
| Criteria  | IG | SG | HG | Criteria   | IG | SG | HG |
| 18-60 years old of age                                    | ✓  | ✓  | ✓  | Pre-existing chronic illness or neurological or psychiatric condition                  | ✓  | ✓  | ✓  |
| No previous history of head trauma                        | ✓  | ✓  | ✓  |  |    |    |    |
| Minimum of 9 years education                              | ✓  | ✓  | ✓  | On long term medication that can alter or affect cognitive and/or psychological status | ✓  | ✓  | ✓  |
| Consented   | ✓  | ✓  | ✓  |  |    |    |    |
| mTBI as a result of motor vehicle accidents only          | ✓  | ✓  |    | Clinical evidence of alcohol intoxication at the time of injury                        | ✓  | ✓  |    |
| Abnormal S-NAB Attention Domain score at 3 months of mTBI | ✓  | ✓  |    |  |    |    |    |
| Willingness to comply with rehabilitation program         |    |    |    | Absolute contraindication for MRI  | ✓  | ✓  |    |

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**Table 1:** The study criteria.

Note: IG-individualised structured cognitive rehabilitation group; SG- standard care group, HG- healthy control group

**151 Intervention**

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



1  
2  
3 158 symptom evaluation. Early treatment or referral to other medical speciality will be made if indicated  
4  
5 159 during these reviews.  
6

7 160 At three months after injury, potential participants will undergo a repeat of clinical review and S-  
8  
9 161 NAB test. Eligibility criteria will include i) an abnormal S-NAB Attention Domain score at 3 months post-  
10  
11 162 mTBI, or ii) deficits in more than one S-NAB domain, not including the attention domain. The concomitant  
12  
13 163 domain deficit(s) will also be evaluated upon completion of therapy. The cognitive intervention will be  
14  
15 164 conducted at the Neurorehabilitation Therapy Unit, Department of Rehabilitation Medicine, UMMC in an  
16  
17 165 outpatient setting. Participants will be assigned to different treatment groups via the randomization  
18  
19 166 process. Written records of the intervention will be recorded and kept by the therapist of each treatment  
20  
21 167 arm until treatment completion. This will include the participant's goals, symptom(s), cognitive  
22  
23 168 strategy/method and participant's feedback.  
24

#### 25 169 ***Individualised structured cognitive rehabilitation group***

26  
27 170 Intervention group participants will receive a two-part 12-week individualized structured cognitive  
28  
29 171 rehabilitation. The first part will be Direct Attention Training (DAT), a deficit-oriented computer-based  
30  
31 172 attention-training program called CogniPlus [45]. Each session last 30 minutes, once a week.  
32

33 173 CogniPlus is a computer-based software program with interactive multimedia approach for multiple  
34  
35 174 attention cognitive training modules. The training programs are ALERT (focused and sustained  
36  
37 175 attention), FOCUS (focused attention), VIG (sustained attention), SELECT (selective attention) and DIVID  
38  
39 176 (divided attention). Each attention-training category is designed based on real-life scenarios. The screen  
40  
41 177 graphics are three-dimensional. This program has an artificial intelligence capacity that can automatically  
42  
43 178 adapt to an individual's performance and alter the training difficulty level (hierarchical difficulty).  
44

45 179 The second part of this intervention will be strategy approach (metacognitive awareness and  
46  
47 180 compensatory strategy) performed after CogniPlus training. Metacognitive awareness includes feedback  
48  
49 181 on the participant's CogniPlus performance to improve their awareness of impairment severity. This  
50  
51 182 process is intended to regulate learning experience and in turn instil the practise of self-monitoring and  
52  
53 183 self-regulation through learning activities. Compensatory strategy component involves instilling cognitive  
54  
55 184 awareness in recognizing impairment that is present in daily activities. This will be followed by the  
56  
57 185 application of cognitive methods to ameliorate the deficit to maximise daily functioning. A participant will  
58  
59 186 identify the deficit(s) and will apply problem-solving method(s) learnt from the therapist. Feedback and  
60

1  
2  
3 187 review of performance will be repeated in the next following therapy session. The metacognitive  
4  
5 188 strategies applied will also be recorded in writing during the participant's feedback sessions. This session  
6  
7 189 will last for 30 minutes and a will be conducted by a trained and certified Occupational Therapist (OT-1)  
8  
9 190 in cognitive therapy and CogniPlus.

### 11 191 ***Standard care group***

13 192 This group will receive the best standard care for attention disorders. This is a patient-centred  
14  
15 193 cognitive therapy. It is based on a patient's complaint(s), symptom(s) and therapy aim(s) (self-realization  
16  
17 194 of deficits or guided by therapist). Symptom(s) management may include physical (e.g. imbalance, fatigue,  
18  
19 195 sleep dysregulation), psychological (e.g. mild anxiety or depression) and cognitive (e.g. forgetfulness).  
20  
21 196 Referral to relevant service(s) may be required such as physiotherapy, return to work/driving  
22  
23 197 rehabilitation and counselling. Compensatory strategy includes task specific training (patient-prioritised)  
24  
25 198 e.g. return to driving may involve driving simulation training, visuospatial training and return to drive  
26  
27 199 rehabilitation service. The frequency of sessions will be one hour per week, for 12 weeks. A trained  
28  
29 200 occupational therapist in cognitive therapy (OT-2) who is not involved with the intervention group  
30  
31 201 treatment, will conduct all the sessions (Table 2).

### 33 202 ***Control group***

35 203 This will consist of healthy individuals demographically matched for age, gender and education years to  
36  
37 204 the intervention groups (Table 1). They will undergo S-NAB assessment battery, DTI imaging and  
38  
39 205 psychological screening tools, which will include the Generalised Anxiety Disorder 7-item (GAD7) and  
40  
41 206 Patient Health Questionnaire-9 (PHQ-9). Their lifestyle aspects will also be reviewed and recorded  
42  
43 207 (spiritual practice, diet, physical exercise, occupation and driving). The data will be collected for  
44  
45 208 comparison purpose.

### 47 209 **Randomisation, consent and blinding**

49 210 Participants with mTBI who fulfil the study criteria will be randomized via computer-generated  
50  
51 211 random permuted block assignment, gender-stratified into equally proportioned intervention and control  
52  
53 212 group numbers. The study schedule, procedures and blinding of co-investigators are presented in **Table**  
54  
55 213 **2.**

|   |                               | STUDY PERIOD                              |                                       |  |                            |                      |   |                      |                      |                      |                       |  |
|---|-------------------------------|---|---------------------------------------|--|----------------------------|----------------------|---|----------------------|----------------------|----------------------|-----------------------|--|
|   |                               | Enrolment                                 | Enrolment                             | Enrolment                                | Allocation                 | Post-allocation      |   |                      |                      |                      | End of treatment      |  |
| TIMEPOINT**   |                               | <i>-t<sub>3</sub></i><br>72 hours<br>mTBI | <i>-t<sub>2</sub></i><br>2 weeks mTBI | <i>-t<sub>1</sub></i><br>6 weeks<br>mTBI | 0<br>3 months mTBI         | <i>t<sub>1</sub></i> | <i>t<sub>2</sub></i>                        | <i>t<sub>3</sub></i> | <i>t<sub>4</sub></i> | <i>t<sub>5</sub></i> | <i>t<sub>12</sub></i> | <i>f<sub>1</sub></i><br>6 months<br>mTBI |
|   | Co-investigator<br>(initials) | Pre-study<br>screening                    | Pre-study<br>screening                | Pre-study<br>screening                   | Baseline/<br>Randomisation | Study<br>Visit 1     | Study visit<br><i>t<sub>2</sub></i> onwards |                      |                      | Last study<br>visit  | Outcome<br>measures   |  |
| <b>ENROLMENT:</b>                                     |                               |   |                                       |  |                            |                      |   |                      |                      |                      |                       |  |
| 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) &<br>NAMT (OT-2)   |   |                                       |  |                            | X                    | X   | X                    | X                    | X                    | X                     | X  |
| <b>INTERVENTIONS:</b>                                 |                               |   |                                       |  |                            |                      |   |                      |                      |                      |                       |  |
| Education component/<br>symptom(s) evaluation         | ED team/RP-1                  | X<br>(ED team)                            | X<br>(RP-1)                           | X<br>(RP-1)                              |                            |                      |   |                      |                      |                      |                       |  |
| Individualized structured<br>cognitive rehabilitation | NAM (OT-1)                    |   |                                       |  |                            | X                    | X   | X                    | X                    | X                    | X                     |  |
| Best standard care                                    | NAMT (OT-2)                   |   |                                       |  |                            | X                    | X   | X                    | X                    | X                    | X                     |  |
| <b>OUTCOME MEASURES:</b>                              |                               |   |                                       |  |                            |                      |   |                      |                      |                      |                       |  |
| S-NAB Test  | NH                            |   |                                       |  | X                          |                      |   |                      |                      |                      |                       | X  |
| DTI   | VN/NR                         |   |                                       |  | X                          |                      |   |                      |                      |                      |                       | X  |
| GAS   | NAM/NAMT<br>(OT-1/OT-2)       |   |                                       |  |                            | X                    | X   | X                    | X                    | X                    | X                     | X  |

Table 2: Study schedule and procedures.

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

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

### 225 **Adherence strategies**

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

### 230 **Outcome measures**

231 All measures will be performed at baseline and at 12 weeks of intervention after randomisation. The  
232 primary outcome measure for this study is the change in attention deficit and other cognitive domains  
233 within intervention groups and direct comparison of each intervention group with the healthy control  
234 group. This will be measured by Neuropsychological Assessment Battery® (NAB®, PAR, Inc., Florida,  
235 USA)[61]. It consists of six modules: Screening Module and five Domain Specific Modules: Attention,  
236 Language, Memory, Spatial and Executive Function. This study will only apply the Screening Module (S-  
237 NAB) because it measures the same five functional domains similar or identical to the main NAB modules.  
238 It consists of 12 individual tests screening all five mentioned cognitive domains for adults aged 18 to 97  
239 years, validated and sensitive for use in healthy and cognitively impaired brain injured population [24,61-  
240 64]. S-NAB also provides two parallel assessment sets (Record Form 1 and Form 2) that will be applied in  
241 an alternate fashion to participants in both groups to avoid practice effect.

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3 242 S-NAB Domain Attention test items and score are interpreted as a marker of an individual's  
4  
5 243 attentional capacity, working memory, psychomotor speed, selective attention, divided attention and  
6  
7 244 information processing [61]. S-NAB has also been applied in our previous cohort study [24] with good  
8  
9 245 validation outcome in our Malaysian mTBI population.

10  
11 246 The secondary outcome measures are microstructural WMT parameters and GAS scores. The DTI  
12  
13 247 MRI scan is a Siemens Magnetom Prisma 3T MRI (Siemens AG, Muenchen, Germany). This study will  
14  
15 248 analyse Fractional Anisotropy (FA), Mean Diffusivity (MD) and Radial Diffusivity (RD) parameter changes  
16  
17 249 at pre- and post-intervention [24,65-70]. These parameters quantify the direction and degree of tissue  
18  
19 250 water diffusion within the WMT [65,66]. FA which measures the direction of the diffusion is an index  
20  
21 251 expressed in a range from 0-1, with a higher score indicating a higher integrity of white matter consisting  
22  
23 252 of highly parallel fibres [65,66]. MD measures the average magnitude of the diffusion while RD quantifies  
24  
25 253 pathology in the myelin [65,66]. Changes in the index values of the parameters at different injury timeline  
26  
27 254 will indicate the pathological changes of the WMT.

28  
29 255 The tool to measure functional goal outcome will be the GAS [77-79]. The difficulty and importance  
30  
31 256 of rehabilitation goals will be individually set according to his/her current levels of functional  
32  
33 257 performance to reinforce realistic expectations. The sensitivity of GAS is increased by the quantifiable set  
34  
35 258 goals relevant and specific to the participant. Each goal is rated on a 5-point scale and score is given on  
36  
37 259 the extent to which a patient's individual goals are achieved in the course of the intervention. The overall  
38  
39 260 GAS scores calculation will generate a standardized measure (T score) (mean of 50 Standard Deviation  $\pm$   
40  
41 261 10). The details of each goal outcome will be recorded in the GAS Record Sheet [77-79] by a cognitive  
42  
43 262 therapist from each study arm (OT-1 and OT-2) trained in GAS application.

44  
45 263 Another important factor to note is the participant's psychological status following mTBI. This study  
46  
47 264 will also perform a screening of anxiety and depression symptoms by using GAD7 and PHQ-9 screening  
48  
49 265 tools at each study timeline. Participant's lifestyle changes/modifications such as spiritual practice, diet  
50  
51 266 change, physical exercise, return to work/education, return to driving, litigation issues and insurance  
52  
53 267 claims will also be reviewed and recorded. Although these parameters will not be part of the study  
54  
55 268 outcome measure, they however remain relevant in influencing treatment adherence and outcome.

### 269 **Sample size and power calculation**

270 In order to fulfil our study objectives we will base the intended sample size calculation on a previous  
271 study that had applied a similar treatment approach and which had a similar outcome measure to our  
272 study[40]. This study applied the non-commercial statistical power analysis program G\*Power Version  
273 3.1.9.2. An effect size of 0.58, which was the functional cognitive outcome of attention [40], is used to  
274 calculate the statistical power *a priori*. We will apply Analysis of Variance (ANOVA): repeated measures,  
275 within-between interaction, setting an alpha level of 0.05, and approximately 10 participants will provide  
276 89% power to detect a statistical significance. Recruitment is doubled (n=20) for both arms and inflated  
277 to 28 to counter 40% attrition rate.

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

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

### 286 **Ethics considerations**

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

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

1  
2  
3 298 issues. In the event of information sharing being required for medical reasons, the participant will be  
4  
5 299 informed immediately followed by referral to the relevant professional either based at UMMC or a  
6  
7 300 different centre of choice. However, costs of further investigation or treatment that is not part of this  
8  
9 301 study will not be funded from the study grants. Treatment compliance will be achieved through our  
10  
11 302 adherence strategy. We strictly adhere to the privacy and confidentiality of participant's medical  
12  
13 303 information. Any information sharing with a third party for various reasons will be managed in  
14  
15 304 accordance with UMMC professional and legal code of conduct.

### 17 305 **Patient and public involvement**

18  
19 306 We applied the Medical Research Council's (MRC) Developing and Evaluating Complex  
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21 307 Intervention: New Guidance (2006) and Multiphase Optimization Strategy (MOST) framework to guide  
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23 308 the development and design of this study. The treatment approach was based on the relevant theoretical  
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25 309 evidence whereas treatment approach was evinced through our systematic review, clinical experience  
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27 310 and practice setting of interest. We conducted 1) a pilot study and 2) Expert Panel review to evaluate the  
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29 311 study design and treatment method that may require further focus.

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31 312 Our pilot study was approved by Medical Research Ethics Committee, UMMC, Malaysia (UM/EC  
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33 313 Ref: 947.15) for the application of cognitive treatment on mTBI patients. They were recruited in the  
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35 314 testing of the treatment method, clinical practicality, fidelity of treatment and treatment compliance. We  
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37 315 have additionally identified several components required for the optimization of the intervention. These  
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39 316 findings were also assessed by the Expert Panel reviewers.

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41 317 The panel comprised of clinicians who were credentialed in brain injury management and  
42  
43 318 cognitive rehabilitation with minimum of ten years clinical experience working in Malaysia. Panels were  
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45 319 made up of seven rehabilitation medicine consultants, one neurosurgeon consultant, one neuroimaging  
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47 320 consultant, five cognitive occupational therapists and one clinical psychologist. The focus of discussion  
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49 321 was on the feasibility of structured cognitive rehabilitation for mTBI patients in Malaysia, guided by the  
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51 322 current evidence, current practise of cognitive rehabilitation in local setting, reviewers' clinical  
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53 323 experience and our pilot study findings. A summary of the pilot study outcomes and Expert Panel  
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55 324 recommendations are best illustrated in Table 3.

56 325 Following the commencement of this study, the input from participants (experience, feedback and  
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58 326 outcomes) will be recorded. The data and study materials will belong to UMMC, Malaysia. We will inform  
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327 our participants of the result of the study to following completion even if he/she did not complete the  
328 study unless he/she has requested no contact.

For peer review only



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

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

## 329 **Statistical analysis**

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

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

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

346 The secondary analysis will include measurement of structural brain changes following intervention.  
347 This data will be obtained from the DTI MRI scan performed at pre and post intervention, for all groups.  
348 We will identify FA, MD and RD parameters with statistically significant mean values ( $p<0.05$ ) via whole  
349 brain analysis known as Tract-based Spatial Statistics (TBSS)[80] and region of interest (ROI) approach  
350 which is part of the FSL (v5.0.6; University of Oxford, Oxford UK) [81] and AFNI (v2011\_12\_21\_1014;  
351 National Institute of Mental Health, Bethesda, MD) software packages. The DTI parameters of both  
352 intervention groups at three- and six months study timelines will be compared with the healthy control  
353 group by using repeated measure analysis. This is in the assumption that the study fulfils the repeated  
354 measure analysis of normally distributed data sample and homogeneity of variance.

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

## 358 **Data management**

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

## 367 **Discussion**

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

## 381 **Trial status**

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

386

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390 of Science and Innovation (MOSTI) grant (MOSTI Flagship Project FP0911F001)

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

392 **Protocol Registered date:** 18<sup>th</sup> July 2017

393 **Protocol updated date:** 16<sup>th</sup> August 2017

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

395 **Competing interest:** none declared

## 396 **Acknowledgement**

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

## 399 **Authors' contribution**

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

## 408 **Availability of data and material**

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

## 411 **Ethics and Dissemination**

412 The study protocol is approved by the Medical Research Ethics Committee UMMC (MREC ID NO:  
413 2016928-4293). The findings of the trial will be disseminated through peer-reviewed journals and  
414 scientific conferences.

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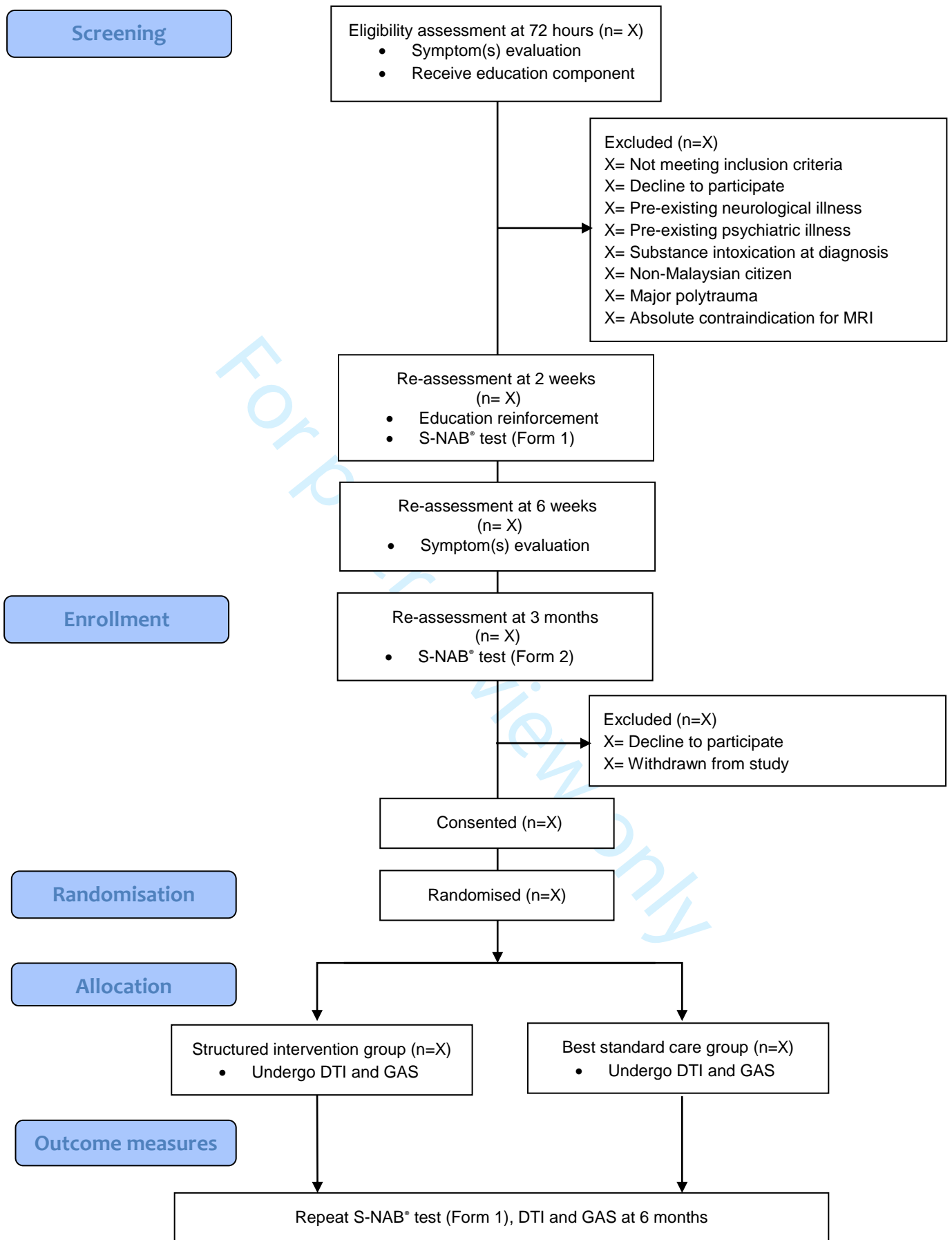
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37 698 analysis and implementation as FSL. *NeuroImage*, 2004; 23(S1):208-219.  
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40 700 **Figure 1:** Flowchart showing the stages of recruitment in this study.  
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**Figure 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 |
|-----------------------------------|---------|--|--------------------------|
| <b>Administrative information</b> |         |  |                          |
| 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                       |



1 **Introduction**

2

3 Background and 6a Description of research question and justification for undertaking the trial, including summary of relevant 44-105  
 4 rationale studies (published and unpublished) examining benefits and harms for each intervention  
 5

6 6b Explanation for choice of comparators 44-105  
 7

8 Objectives 7 Specific objectives or hypotheses 107-117  
 9

10 Trial design 8 Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group),  
 11 allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) 118-132; Figure 1  
 12  
 13

14 **Methods: Participants, interventions, and outcomes**

15

16 Study setting 9 Description of study settings (eg, community clinic, academic hospital) and list of countries where data will 122-128  
 17 be collected. Reference to where list of study sites can be obtained  
 18

19 Eligibility criteria 10 Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and 133-150, Table 1  
 20 individuals who will perform the interventions (eg, surgeons, psychotherapists)  
 21

22 Interventions 11a Interventions for each group with sufficient detail to allow replication, including how and when they will be 151-203; Figure 1  
 23 administered  
 24

25 11b Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose 208-218  
 26 change in response to harms, participant request, or improving/worsening disease)  
 27

28 11c Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence 219-223  
 29 (eg, drug tablet return, laboratory tests)  
 30

31 11d Relevant concomitant care and interventions that are permitted or prohibited during the trial NA  
 32  
 33

34 Outcomes 12 Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood  
 35 pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, 224-262  
 36 median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen  
 37 efficacy and harm outcomes is strongly recommended  
 38  
 39

40 Participant timeline 13 Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for 204-207; Table 2  
 41 participants. A schematic diagram is highly recommended (see Figure)  
 42  
 43  
 44  
 45  
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|   |             |    |   |                  |
|---|-------------|----|---|------------------|
| 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 | 263-279          |
| 2 |             |    |   |                  |
| 3 |             |    |   |                  |
| 4 | Recruitment | 15 | Strategies for achieving adequate participant enrolment to reach target sample size   | 219-223; 263-279 |
| 5 |             |    |   |                  |

6 **Methods: Assignment of interventions (for controlled trials)**

7 Allocation:

|    |                                  |     |  |                  |
|----|----------------------------------|-----|--|------------------|
| 8  |                                  |     |  |                  |
| 9  |                                  |     |  |                  |
| 10 | 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 |
| 11 |                                  |     |  |                  |
| 12 |                                  |     |  |                  |
| 13 |                                  |     |  |                  |
| 14 |                                  |     |  |                  |
| 15 |                                  |     |  |                  |
| 16 | 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 |
| 17 |                                  |     |  |                  |
| 18 |                                  |     |  |                  |
| 19 |                                  |     |  |                  |
| 20 | Implementation                   | 16c | Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions  | Table 2          |
| 21 |                                  |     |  |                  |
| 22 |                                  |     |  |                  |
| 23 |                                  |     |  |                  |
| 24 | Blinding (masking)               | 17a | Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how  | Table 2          |
| 25 |                                  |     |  |                  |
| 26 |                                  |     |  |                  |
| 27 |                                  | 17b | If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial   | 208-218          |
| 28 |                                  |     |  |                  |
| 29 |                                  |     |  |                  |
| 30 |                                  |     |  |                  |

31 **Methods: Data collection, management, and analysis**

|    |                         |     |  |  |
|----|-------------------------|-----|--|--|
| 32 |                         |     |  |  |
| 33 | 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 |
| 34 |                         |     |  |  |
| 35 |                         |     |  |  |
| 36 |                         |     |  |  |
| 37 |                         |     |  |  |
| 38 |                         |     |  |  |
| 39 |                         | 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  |
| 40 |                         |     |  |  |
| 41 |                         |     |  |  |
| 42 |                         |     |  |  |

|    |                                 |     |   |                    |
|----|---------------------------------|-----|---|--------------------|
| 1  | 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            |
| 2  |                                 |     |   |                    |
| 3  |                                 |     |   |                    |
| 4  |                                 |     |   |                    |
| 5  | 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            |
| 6  |                                 |     |   |                    |
| 7  |                                 |     |   |                    |
| 8  |                                 | 20b | Methods for any additional analyses (eg, subgroup and adjusted analyses)  | NA                 |
| 9  |                                 |     |   |                    |
| 10 |                                 | 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            |
| 11 |                                 |     |   |                    |
| 12 |                                 |     |   |                    |
| 13 |                                 |     |   |                    |
| 14 | <b>Methods: Monitoring</b>      |     |   |                    |
| 15 |                                 |     |   |                    |
| 16 | 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                 |
| 17 |                                 |     |   |                    |
| 18 |                                 |     |   |                    |
| 19 |                                 |     |   |                    |
| 20 |                                 |     |   |                    |
| 21 |                                 |     |   |                    |
| 22 |                                 | 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                 |
| 23 |                                 |     |   |                    |
| 24 |                                 |     |   |                    |
| 25 | 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            |
| 26 |                                 |     |   |                    |
| 27 |                                 |     |   |                    |
| 28 | Auditing                        | 23  | Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor   | NA                 |
| 29 |                                 |     |   |                    |
| 30 |                                 |     |   |                    |
| 31 |                                 |     |   |                    |
| 32 | <b>Ethics and dissemination</b> |     |   |                    |
| 33 |                                 |     |   |                    |
| 34 | Research ethics approval        | 24  | Plans for seeking research ethics committee/institutional review board (REC/IRB) approval   | 280-297            |
| 35 |                                 |     |   |                    |
| 36 |                                 |     |   |                    |
| 37 | 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 |
| 38 |                                 |     |   |                    |
| 39 |                                 |     |   |                    |
| 40 |                                 |     |   |                    |
| 41 |                                 |     |   |                    |
| 42 |                                 |     |   |                    |
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|    |                               |     |   |                 |
|----|-------------------------------|-----|---|-----------------|
| 1  | 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         |
| 2  |                               |     |   |                 |
| 3  |                               |     |   |                 |
| 4  |                               | 26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable   | NA              |
| 5  |                               |     |   |                 |
| 6  |                               |     |   |                 |
| 7  | 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 |
| 8  |                               |     |   |                 |
| 9  |                               |     |   |                 |
| 10 | Declaration of interests      | 28  | Financial and other competing interests for principal investigators for the overall trial and each study site   | 376-385         |
| 11 |                               |     |   |                 |
| 12 |                               |     |   |                 |
| 13 | 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 |
| 14 |                               |     |   |                 |
| 15 |                               |     |   |                 |
| 16 | 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              |
| 17 |                               |     |   |                 |
| 18 |                               |     |   |                 |
| 19 |                               |     |   |                 |
| 20 | 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         |
| 21 |                               |     |   |                 |
| 22 |                               |     |   |                 |
| 23 |                               |     |   |                 |
| 24 |                               | 31b | Authorship eligibility guidelines and any intended use of professional writers  | BMJ guideline   |
| 25 |                               |     |   |                 |
| 26 |                               | 31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code   | NA              |
| 27 |                               |     |   |                 |
| 28 |                               |     |   |                 |
| 29 | <b>Appendices</b>             |     |   |                 |
| 30 |                               |     |   |                 |
| 31 | Informed consent materials    | 32  | Model consent form and other related documentation given to participants and authorised surrogates  | -               |
| 32 |                               |     |   |                 |
| 33 |                               |     |   |                 |
| 34 | 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              |
| 35 |                               |     |   |                 |
| 36 |                               |     |   |                 |

37 \*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items.  
 38 Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons  
 39 "[Attribution-NonCommercial-NoDerivs 3.0 Unported](#)" license.  
 40