PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	A randomised controlled clinical trial of a structured cognitive rehabilitation in patients with attention deficit following mild traumatic brain injury: Study protocol
AUTHORS	Hamzah, Norhamizan; Narayanan, Vairavan; Ramli, Norlisah; Mustapha, Nor Atikah; Mohammad Tahir, Nor Adibah; Tan, Li Kuo; Danaee, Mahmoud; Muhamad, Nor Asiah; Drummond, Avril; dasNair, Roshan; Goh, Sing Yau; Mazlan, Mazlina

VERSION 1 - REVIEW

REVIEWER	Dana Wong La Trobe University Australia
REVIEW RETURNED	06-Mar-2019

GENERAL COMMENTS	This paper reports the protocol for a novel trial of a complex cognitive rehabilitation intervention for individuals with persistent attentional difficulties following mild TBI. This has the potential to make an important contribution to the literature. In particular, it is excellent to see this kind of research being conducted in Malaysia, and that the design generally adheres to best practice guidelines. However, the paper could be strengthened in a number of ways prior to publication. One of the inclusion criteria is “abnormal NAB® Attention Domain score at three months after mTBI”. How is abnormal being defined? Is it relative to estimated premorbid functioning? This needs to be specified. On page 7 line 158, it states “However, those with other cognitive domain deficit other than Attention Domain will also receive treatment for that specific domain deficit(s).” The meaning of this is unclear – does this mean that those without a deficit in the Attention Domain will also be enrolled and randomised into the study, or does it mean that they will be treated separately from this study? A central concern with the proposed design is the nature of the “standard care” comparison group. While I understand the many difficulties selecting appropriate control group conditions for complex cognitive interventions, the components of standard care (as they are briefly described) appear to overlap somewhat with the main intervention (e.g., using “compensatory strategies” in

	standard care may overlap with “metacognitive awareness and compensatory strategies”), but not in a clear or clean way. This will make it difficult to determine the effect of the components that are different between the 2 conditions. While it appears it is too late to change the design, these issues with the choice of comparison group should be acknowledged. Also, I am not sure about the characterisation of the main intervention as “individualised structured cognitive rehabilitation”. Arguably, the standard care intervention could also be characterised as “individualised structured cognitive rehabilitation” if it involves management of presenting symptoms with compensatory strategies targeting those individual problems. It may be more accurate to characterise it as “computerised cognitive training + strategy training” versus “strategy training only”. Furthermore, the addition of training in metacognitive awareness in the main intervention condition is significant as this is an evidence-based intervention in and of itself (though the ‘dose’ is unclear in this context). It is possible that this could drive any treatment effect observed. Again, while it may be too late to include a measure of metacognitive awareness as an outcome variable, some discussion of this is warranted. The NAB screening module is a gross multifactorial screening measure and may not pick up subtle changes in attentional function, especially in a mild TBI cohort. Did the authors consider using more sensitive and specific measures of focused/sustained/selective/divided attention, which are the domains targeted by CogniPlus? A clearer rationale for the choice of cognitive outcome measure should be provided. Also, I could not see reporting of the measures given at baseline to characterise the sample. In particular, measures of premorbid intellectual functioning and anxiety would be important to characterise the sample, as these factors are known to influence both attention and response to rehabilitation. Due to the inconsistent use of present and past tense in the “Patient and Public Involvement” section, it wasn’t clear whether the expert panels have already been consulted and their input already incorporated into the study design, or whether this will happen in the future. If it has already happened, it would be helpful to include a summary of the recommendations made by the panels. There are numerous grammatical errors throughout the manuscript. It is recommended that the writing is reviewed and edited by one of the native English speaking authors.

REVIEWER	Gabriela Markovic Institution of Clinical Sciences, Karolinska Institutet Division of Rehabilitation Medicine, Danderyd University Hospital Stockholm, SWEDEN
REVIEW RETURNED	10-Apr-2019

GENERAL COMMENTS	Thank for a thorough study protocol and very interesting research plan. You are targeting a field of research that is important due to the large number of incidents, and complex due to the heterogeneity of the study population. You aim high and have many important issues. I do however have a few concerns in regards to probable confounding factors and how you deal with them, the rationale behind intensity and frequency of intervention, and patient recruitment. Enclosed are my comments, high and low. Enjoy collection, analysis and above all bringing forth the results. Looking forward to this important contribution to clinical research! A randomized controlled trial of a structured cognitive rehabilitation in patients with attention deficit following mild traumatic brain injury: Study protocol REVIEW Following are a few concerns I have regarding the rationale behind certain issues. In the end I will just mention a few minor details. All in all, the study protocol is correct and impressive and as I said, I do look forward to the results – they are a much welcome contribution to this clinical population. 1. Patient recruitment is always tricky – as soon as you decide to study a population, they disappear! Could you please clarify why there will be only RTA's in your study, and back it up with studies done. Would the aftermath (natural history, development/persistence of symptoms) of mTBI be different depending on cause of injury? I haven't come across any studies confirming that. You need 46 patients in each arm (?) and for two years only 15 patients are enrolled. See if you can group your patients according to common data elements and then run analysis on subgroups. Opening up for other causes of injury could speed up the data collection. 2. I was also thinking of the intervention given. How did you decide upon frequency and intensity of treatment? It is an essential question as you are tapping in on neuroplasticity during and after restorative training. You offer 6 hours of repetitive hierarchically organized tasks together with 6 hours of metacognitive training at a frequency rate of 1 hour per week (i was very pleased to see that you add metacognitive training given the importance of it for sustainable behavioral change). Boman et al provided 9 hours of treatment (Attention process training + metacognition) and barely reached results. Cog Med, another computerized restorative attention training provides 25 sessions during a period of 5 weeks (sessions of 30-45 minutes depending on task difficulty). If you are aiming for "Hebbian" plasticity you might need to make the treatment denser. For behavioral change, i e modulation in performance, the intensity might work but only with extra home

	assignments. I am afraid you will not reach the results we all hope for, not because of study design, but because of low intensity of treatment. Please state studies supporting your choices. 3. Confounding factors for study outcome and influential demographic factors for persistent symptoms post mTBI. It is known that cognitive and emotional reserve have an impact on the persistence of symptoms after mTBI, at least in the Western world. How will you get about to collect that information? It is even more important, considering the cultural aspect of your study questions. The reserves mentioned influence advise and training given, thus could possibly have an impact on outcome. Please, state also expected confounding factors for outcome. Minor questions/issues/suggestions: a. When referring to acute or post-acute, please define what you mean (your cut-off). There are not many conclusive studies on nearly attention rehabilitation and TBI, let alone mTBI. May I suggest you include the latest Cicerone reference (2019). b. In study hypothesis and objectives, I suggest you make a list of all your specific research questions/objectives that will be responded to in coming papers. In that way the reader will be able to go back to your study protocol and see what objectives to look forward to. It would help clarify your quest. c. Participants and recruitment process: please describe your unit/center/location with more detail – what is your specialty for example, in what setting will the training be conducted, are there any other therapies involved like for example physical exercise, etc? d. Inclusion criteria: please state a definition of mTBI (LOC, PTA, GCS, or the like). Do you take all concussions, with or without DT/MRI/fMRI? For inclusion and exclusion, provide cut-off levels with a rationale included (this criterion because it measures x with cut-off level y to make sure z). Could be presented in a table. e. Intervention: se comments above. Clarify what rehabilitative processes this part of the intervention is based on (restorative? Compensatory?). Who will be doing the testing (training of assessors, blinding). How will you keep record of interventions given for the standard care group? Provide examples of symptoms of expected attention deficit. Also, are there other services/interventions during this period of 12 weeks? f. Withdrawal etc: Do you provide the option for patients in control group to receive the structured training after concluded intervention period? Love the part about adherence strategies! g. Patient and public involvement. Well written and beautifully arranged! Bravo. h. Statistical analysis. Just a suggestion…you are doing repetitive GAS, at least 12 measures. As goals attained would be the expected outcome of better attention function, you could use GAS for process analysis (look into Statistical Process Control, SPC) thus following improvement patterns both for individuals and the two treatment arms. It would be of interest to identify what variables would prove predictive of rapid or steady improvement, versus no improvement during treatment. i. References are a bit dated and Boman is mentioned twice (44 and 79). Consider adding the updated Cicerone et al (2019). No doubt will you update them when writing the results.

	Details: i. Insert ”clinical” in the title ii. Abstract: (line 5) is it the patients overall cognitive function or specific? Do you expect such generalization of the attention training? (line 24) state number of hours in treatment i e intensity and frequency iii. Background: (line 70) give a perspective on why there is no standard treatment protocol for the group (as a whole), i e due to heterogenous population. There are protocols for specific symptoms. iv. Discussion (line 311): Caucasian ethnic group…there is an ‘n’ missing

REVIEWER	Professor Suzanne Martin School of Health Sciences Faculty of Life and Health Sciences Ulster University - Jordanstown Campus Shore Road Newtownabbey Northern Ireland.
REVIEW RETURNED	19-Apr-2019

GENERAL COMMENTS	Thank you for this submission. An interesting study which i think will make a useful contribution to knowledge. The research question is clear in the title however the aims/objective require a review.The abstract would benefit from a few sentences of preamble introduction to give context to this research. Refer to other examples within the journal as helpful guide. Overall, the main body of the manuscript is fairly well presented. The sections within the introduction section are well aligned to the topic and interesting. The following amendments aim to further development this work. 1) Within the abstract and the main body state a single aim(or primary objective) rather than a hypothesis followed by secondary objectives. 2)Ethical governance. Whilst confirmation of ethical approval is provided, more detail on ethical considerations, risks and challenges should be provided. 3) Patient and public involvement. The content in this section doesn't adequately deal with the aspects of PPI. Have the team involved any patients directly in roles other than participants? Are there any organisations who work to support people with mTBI that might be interested to support and inform this work? 4)Limitations of the study requires further development. 5) Line 193 clarify what is meant by withdrawing participants who become non-compliant. 6) Line 194 requires a review as it requires the reader to move beyond this line to understand the intention. 7) Blinding - more information required to outline how blinding will be maintained. 8) Recruitment. More detailed information is required on the recruitment to assure participants are given enough information by the identifying clinician before going towards the researching therapist.

VERSION 1 – AUTHOR RESPONSE

<table>
<tr><td>Reviewer 1: Dana Wong
Institution and Country: La Trobe University, Australia</td><td>Authors response</td></tr>
<tr><td>This paper reports the protocol for a novel trial of a complex cognitive rehabilitation intervention for individuals with persistent attentional difficulties following mild TBI. This has the potential to make an important contribution to the literature. In particular, it is excellent to see this kind of research being conducted in Malaysia, and that the design generally adheres to best practice guidelines. However, the paper could be strengthened in a number of ways prior to publication.</td><td>Thank you.</td></tr>
<tr><td>One of the inclusion criteria is “abnormal NAB® Attention Domain score at three months after mTBI”. How is abnormal being defined? Is it relative to estimated premorbid functioning? This needs to be specified.</td><td>Abnormal S-NAB Attention Domain score is defined as Standard Score <85 (below average category) determined by the NAB test manual. The standard score was derived from demographically corrected population (age, gender, education year). Grading of severity is further based on:

<table><tr><td>Category</td><td>Score</td></tr><tr><td>Below average</td><td>85-91</td></tr><tr><td>Mildly impaired</td><td>77-84</td></tr><tr><td>Mildly to moderately impaired</td><td>70-76</td></tr><tr><td>Moderately impaired</td><td>62-69</td></tr><tr><td>Moderately to severely impaired</td><td>56-61</td></tr><tr><td>Severely impaired</td><td>45-54</td></tr></table>
All potential participants are screened at 2 weeks post diagnosis for clinical review and undergo S-NAB to establish cognitive baseline following injury.
Good premorbid functioning is assessed and established through clinical reviews and screening (2 weeks, 6 weeks post trauma) prior to recruitment (at 3 months). This include physical symptoms, psychological symptoms, lifestyle changes, return to work/education, return to drive, litigation issues, health cost issues.
Since this paper submission, we have started our recruitment and for your information, several subjects with abnormal S-</td></tr>
</table>

	NAB findings at 2 weeks had attained all domains normalised standard S-NAB scores at 3 months (recovered) post injury recruitment stage. We are also following up this group. Revised manuscript line 141-143; 161-162
On page 7 line 158, it states "However, those with other cognitive domain deficit other than Attention Domain will also receive treatment for that specific domain deficit(s)." The meaning of this is unclear – does this mean that those without a deficit in the Attention Domain will also be enrolled and randomised into the study, or does it mean that they will be treated separately from this study?	Cognitive deficits in traumatic mTBI is rarely singular, and is heterogenous within the population. Due to this complex presentation, subjects with other than Attention deficit are also enrolled for the study to receive treatment (following randomisation). This is on based on the theory that Attention is the basis to all other cognitive domains and therefore despite evidence of other domain deficits, the subject does potentially have Attention deficit component too. The S-NAB is also designed to follow a presumed hierarchical order of neuropsychological functioning, that recognises Attention as a basic function that underlies all cognitive domains, that is if an individual has limited attentional capacity, he/she would most likely have impairment in more complex cognitive domains and functioning. As recruitment is ongoing, we have a small number of subjects that do fall under this category (deficits other than Attention) that do have Attention deficits upon further assessment. This recruitment approach is also to prevent early exclusion of potential participants due to strict study criteria when this group may also benefit from the treatment approach. Revised manuscript line 160-165.
A central concern with the proposed design is the nature of the "standard care" comparison group. While I understand the many difficulties selecting appropriate control group conditions for complex cognitive interventions, the components of standard care (as they are briefly described) appear to overlap somewhat with the main intervention (e.g., using "compensatory strategies" in standard care may overlap with "metacognitive awareness and compensatory strategies"), but not in a clear or clean way. This will make it difficult to determine the effect of the components that are different between the 2 conditions. While it appears it is too late to change the design,	The standard care group receives 'best standard care' component, based on current standard care that we have in Malaysia (following Expert Panel study protocol review) as well as outcomes from our pilot study. Currently, what is commonly practised here is a patient-centred cognitive approach, which means that the goals and treatment is based on what participant requested and perceived as symptoms and problems following/associated with the trauma as well as guided by assessment results. Therefore, the compensatory strategies have a broader non-standardised approach compared to the individualised structured approach. However, we agree that overlap may still occur as both groups are mTBI participants with potentially similar cognitive deficits. We will acknowledge this issue in the report of study outcome. Revised manuscript line 180-188; 192-199.

<table>
<tr><td>these issues with the choice of comparison group should be acknowledged.</td><td></td></tr>
<tr><td>Also, I am not sure about the characterisation of the main intervention as “individualised structured cognitive rehabilitation”. Arguably, the standard care intervention could also be characterised as “individualised structured cognitive rehabilitation” if it involves management of presenting symptoms with compensatory strategies targeting those individual problems. It may be more accurate to characterise it as “computerised cognitive training + strategy training” versus “strategy training only”.</td><td>We came up with the term ‘computer-based cognitive training + strategy training’ versus ‘strategy training only’ at the initial design of the study. The treatment term was changed to ‘individualised structured cognitive rehabilitation’ to emphasize on the structured/scheduled treatment approach. All participants of this group will receive a computer-based Attention training.
The metacognitive awareness includes:
feedback on participant’s computer-based training performance to improve participant’s awareness of the measured impairment (proof/severity of deficits). This process is intended to regulate their learning experience and in turn instil the practise of self-monitoring and self-regulation of learning activities.
Compensatory strategy component involves applying the cognitive awareness in recognizing impairment that is present in daily activities followed by the application of cognitive methods to ameliorate the deficits to maximise daily functioning.
A participant will identify the deficit(s) and apply the taught method (within a week duration) with feedback of performance in the following therapy session.
We believe the combination of computer-based and strategy approach is a very regulated stepwise therapy model with increase complexity.

The standard care group receives ‘best standard care’ as an ideal treatment approach widely practised in Malaysia (but not necessarily achieved in real practice) and is patient-centred. It is based on a patient’s complaint(s), symptom(s) and therapy aim(s) (self-realization of deficits or guided by therapist), which differs from person to person (individualised) hence the treatment methods largely vary.
Symptom management may include management of anxiety, fatigue, sleep dysregulation, forgetfulness etc.
Compensatory strategy may include task specific or work-related (patient-prioritised). For example, an individual, who’s aim is to return to drive, the training may focus on that task alone (e.g. driving simulation training, visuospatial training etc).
Revised manuscript line 180-188; 192-199.</td></tr>
<tr><td>Furthermore, the addition of training in metacognitive awareness in the main intervention condition is significant as this is an evidence-based</td><td><table><tr><td>Treatment arm</td><td>Individualised structured approach</td><td>Standard care approach</td><td></td></tr></table></td></tr>
</table>

intervention in and of itself (though the 'dose' is unclear in this context). It is possible that this could drive any treatment effect observed. Again, while it may be too late to include a measure of metacognitive awareness as an outcome variable, some discussion of this is warranted.	Treatment frequency	1 hour/12 weeks	1 hour/12 weeks	We have similar frequency and duration for both groups
	Treatment intensity	30 minutes computer training+30 min metacognitive awareness and compensatory strategy	1 hour of symptom management + compensatory strategies	Both are individualised treatment approach but differs in intensity and method. Intervention group has less duration in metacognitive but receive specific and regulated Attention training, whereas standard group has longer duration of symptom management and metacognitive approach.
	Treatment method	CogniPlus + strategy approach (metacognitive awareness and compensatory strategies)	Patient-centred i.e. symptom(s) management (noted by patient and/or therapist) + strategy approach	Similarity in the metacognitive strategies is possible because each arm is an individualised therapy approach based on symptoms and treatment goals. The strategy method that is applied is

	recorded for each patient for comparison purpose whereas patient clinical performance is based on S-NAB and GAS evaluation for functional outcome.

Metacognitive awareness will be measured through GAS evaluation. Patient statements and feedback on performance will be recorded in written format. This include:

- CogniPlus performance outcome
- Participant's self-evaluation and identification of deficits in daily activities
- Method that is taught e.g. external strategy for memory
- Review of participant's performance/feedback in the subsequent session following application of taught methods.

Revised manuscript line 167-169; 180-188; 192-199.

The NAB screening module is a gross multifactorial screening measure and may not pick up subtle changes in attentional function, especially in a mild TBI cohort. Did the authors consider using more sensitive and specific measures of focused/sustained/selective/divided attention, which are the domains targeted by CogniPlus? A clearer rationale for the choice of cognitive outcome measure should be provided.	Some of our authors had published previous cohort studies on mTBI with evidence of multiple persistent cognitive deficits chronically detectable using S-NAB as the NP of choice (please refer references below). We chose similar outcome measures for this study to maintain consistencies with our previous work. We have also performed a validation study of S-NAB in mTBI population in Malaysia (the current manuscript is already accepted by a journal upon review and is awaiting publication). In this study, we performed construct validity and reliability (internal consistency) assessments. Acceptable internal consistency (Cronbach $\alpha \geq .70$) was found for Attention, Language and Memory domains but weak internal consistencies (Cronbach $\alpha < .50$) were found for Spatial and Executive Function domains due to various factors. S-NAB is also designed based on the hierarchical order of neuropsychological function that emphasizes on complexity of cognitive functioning and the interaction of each domain for complete functioning. The next tier of interpretation involves the Total S-NAB Index Score, giving an overall neuropsychological functioning that accounts for all five domains assessed. The Total Screening Score was of

	acceptable value (Cronbach α of 0.83) which is reflective of the overall /summative of the five assessed domains. Ref: 1. Veeramuthu et al, (2015) Diffusion Tensor Imaging Parameters in Mild Traumatic Brain Injury and Its Correlation with Early Neuropsychological Impairment: A Longitudinal Study, J Neurotrauma 2. Veeramuthu et al, (2016), Microstructural Change and Cognitive Alteration in Maxillofacial Trauma and Mild Traumatic Brain Injury: A Diffusion Tensor Imaging Study, J Oral Maxillofac Surg Revised manuscript line 237-240.
Also, I could not see reporting of the measures given at baseline to characterise the sample. In particular, measures of premorbid intellectual functioning and anxiety would be important to characterise the sample, as these factors are known to influence both attention and response to rehabilitation. Due to the inconsistent use of present and past tense in the "Patient and Public Involvement" section, it wasn't clear whether the expert panels have already been consulted and their input already incorporated into the study design, or whether this will happen in the future. If it has already happened, it would be helpful to include a summary of the recommendations made by the panels.	We do not perform IQ test but the number of education years are recorded. Clinical review occurs at 2 weeks (+S-NAB), at 6 weeks screening phases and at 3 months post injury (study recruitment). This includes psychological screening for anxiety (GAD7) and depression (PHQ9). A clinical review and repeat screening will also be done at the end of intervention. We did not include the 6 weeks clinical review in the protocol because it is still a screening phase without S-NAB assessment, which we have included in the revised manuscript – refer Figure 1, Table 2 and participants & recruitment process section. The rationale behind this is to 1) record symptom progress, 2) early detection and urgent treatment intervention if required (in which patient may be withdrawn from recruitment process if it violates our study criteria) 3) part of adherence strategy. The systematic review, pilot study and expert panel review were performed prior to the final design of the study. All the findings and responses were incorporated in the final design of the study. A summary of the recommendations is added in the manuscript Table 3.
There are numerous grammatical errors throughout the manuscript. It is recommended that the writing is reviewed and edited by one of the native English speaking authors.	Proof reading performed and corrections made.

Reviewer 2: Gabriela Markovic Institution and Country: Institution of Clinical Sciences, Karolinska Institutet, Division of Rehabilitation Medicine, Danderyd University Hospital, Stockholm, SWEDEN	Authors response
Patient recruitment is always tricky – as soon as you decide to study a population, they disappear! Could you please clarify why there will be only RTA's in your study, and back it up with studies done. Would the aftermath (natural history, development/persistence of symptoms) of mTBI be different depending on cause of injury? I haven't come across any studies confirming that.	In Malaysia, the main cause of mTBI is by RTA in the young age group (productive age group), based on our National Trauma Database and Clinical Research Centre, Ministry of Health, Malaysia and Malaysian Institute of Road Safety Research (references in manuscript). These reports are also consistent with the projection of Global Status Report on Road Safety, 2015 and 2018, and that RTA will further increase in the developing countries. We however do not have a high number of mTBI caused by sports or blast-related injuries (war veterans) compared to other countries. It is in the national interest to study mTBI caused by RTA in Malaysia. Some of our authors had published previous cohort studies on mTBI caused by RTA, and reported findings of multiple persistent cognitive deficits detectable by using S-NAB as the NP of choice (please refer references below). We chose similar population for this study to maintain the consistencies with our previous work/findings. 1. Veeramuthu et al, (2015) Diffusion Tensor Imaging Parameters in Mild Traumatic Brain Injury and Its Correlation with Early Neuropsychological Impairment: A Longitudinal Study, J Neurotrauma 2. Veeramuthu et al, (2016), Microstructural Change and Cognitive Alteration in Maxillofacial Trauma and Mild Traumatic Brain Injury: A Diffusion Tensor Imaging Study, J Oral Maxillofac Surg
You need 46 patients in each arm (?) and for two years only 15 patients are enrolled. See if you can group your patients according to common data elements and then run analysis on subgroups. Opening up for other causes of injury could speed up the data collection.	Our sample size calculation is based on pre-existing studies that had small sample sizes (this observation is further supported by Bogdanova et al, 2019 findings). We inflated the sample size to account for attrition rate and applied analysis calculation method (effect size calculation) as part of sample size estimation too to increase the number that will achieve statistical significance.

	Due to our strict study criteria, to date we currently have n=50 recruited, randomized and undergoing intervention at various timeline. Thank you for your suggestion on the grouping approach. We will consider it during our data analysis.
I was also thinking of the intervention given. How did you decide upon frequency and intensity of treatment? It is an essential question as you are tapping in on neuroplasticity during and after restorative training. You offer 6 hours of repetitive hierarchically organized tasks together with 6 hours of metacognitive training at a frequency rate of 1 hour per week (i was very pleased to see that you add metacognitive training given the importance of it for sustainable behavioral change). Boman et al provided 9 hours of treatment (Attention process training + metacognition) and barely reached results. Cog Med, another computerized restorative attention training provides 25 sessions during a period of 5 weeks (sessions of 30-45 minutes depending on task difficulty). If you are aiming for "Hebbian" plasticity you might need to make the treatment denser. For behavioral change, i e modulation in performance, the intensity might work but only with extra home assignments. I am afraid you will not reach the results we all hope for, not because of study design, but because of low intensity of treatment. Please state studies supporting your choices	This is a complex clinical trial, and in the development of this study design we adhered to the MRC Developing and Evaluating Complex Intervention: New Guidance (2006) and the Multiphase Optimization Strategy (MOST) framework. We came to the treatment dosing through three stages: 1. Systematic review 2. Expert panel reviews 3. Pilot study 1. We have performed systematic reviews (unpublished manuscript) of cognitive rehabilitation in mTBI. Due to the scarcity of clinical trials/study in this population, we have extended our search to all categories of TBI. Based on our criteria, 17 intervention studies and 11 review papers (2 guideline papers, 1 meta-synthesis, 7 systematic reviews, 1 review) were chosen. *we have not included Bogdanova et al, 2019 and Cicerone et al, 2019 in our systematic review was performed in 2017. Duration of therapy: • The frequency and intensity of training varies (hours, weeks or months). Majority of studies applied individualized treatment approach. The duration of treatment ranged from 6-27 weeks but majority of studies applied treatment between 6-10 weeks. One study only applied 3 weeks duration of treatment but the intervention was emphasized on education and measured the learning outcome amongst TBI patients in relation to function (Niemeier et al., 2005). Four studies applied computer-based or software program as part of the treatment approach (Dirette, 2004; Zickefoose et al., 2013; Johansson & Tornmalm, 2012; Lebowitz et al., 2012).

	The cognitive rehabilitation setting was mostly done as outpatient setting or at home. 2. Pilot study (manuscript currently submitted for publication) • The aims were to assess treatment feasibility for mTBI population in Malaysia. This was a case-controlled study that applied similar treatment approach. However, treatment was applied sub-acutely (2 weeks post RTA) to also compare intervention effect vs natural recovery. Intensity of treatment was higher in the first 3 months and reduced frequency the following 3 months (total treatment 6 months). Treatment- as-usual (TAU) group consisted of patient-focused symptom(s) management and coping strategies throughout six months duration. Healthy individuals were also recruited as healthy control group (n=12). • The computer-based treatment approach was well accepted by participants. • Attrition rate was high (50%) due to high frequency of therapy sessions. Feedback from participants on therapy duration of >1 hour caused them mental fatigue and loss of concentration. Other factors of poor compliance were concomitant injuries of RTA, 'readiness' to receive treatment, long duration of therapy (6 months), treatment costs, logistics cost (transportation to hospital), and work demands (time off work and pay lost). 3. Expert panel review • Consisted of Rehabilitation medicine consultants (n=7), Neurosurgeon (n=1), Neuroimaging consultant (n=1), Cognitive OT (n=5), Clinical psychologist (n=1), credentialed in cognitive rehabilitation practice and brain injury with clinical experience minimum of 10 years in Malaysia. • Evaluation centred on the i) level of evidence on cognitive rehabilitation principles and its application in mTBI ii) level of evidence on current application of cognitive rehabilitation in local setting, iii) the adapted method of cognitive

	treatment for mTBI applied in this research, iv) the assessment methods/tools applied in this intervention v) current treatment setting in Malaysia and, vi) pilot study findings. The recommendations included: - To increase review frequency (48h, 2 weeks and 6 weeks) prior to recruitment to monitor clinical changes and maintain contact/rapport - Adherence strategies (as stated in manuscript) - Agreement on the individualised treatment method for both groups, but to label the metacognitive approach applied for each individual to assess similarity/differences of treatment arms. - Agreement on the frequency and intensity of treatment. Findings from literature review and pilot study reported that mTBI patients have mild cognitive deficits with relatively good insight. A minimum of at least once a week attention training (ACRM Cog Rehab Manual, 2014) and 1-hour duration (patient's compliance acceptance). The weekly interval will also allow for patient to apply taught cognitive strategy outside of therapy session ('homework' in real life setting situation) as you have mentioned - given the importance of it for sustainable behavioral change- followed by review of performance and feedback upon its application in the following session. - To report on treatment effect to towards quantifiable functional outcomes (GAS application). Revised manuscript under section 'Patient and public involvement' and Table 3.
Confounding factors for study outcome and influential demographic factors for persistent symptoms post mTBI. It is known that cognitive and emotional reserve have an impact on the persistence of symptoms after mTBI, at least in the Western world. How will you get about to	We agree with you on this. Cultural context may likely influence the study outcomes. The multiple clinical reviews (72 hours, 2 weeks, 6 weeks, 3 months, 6 months and weekly therapy sessions) allow us to assess patient's emotional status, perceptions of injury, litigation issues, cost and

collect that information? It is even more important, considering the cultural aspect of your study questions. The reserves mentioned influence advise and training given, thus could possibly have an impact on outcome. Please, state also expected confounding factors for outcome.	insurance status/claims. We also recorded lifestyle changes such as diet change and supplementary, physical exercise, 'brain' game exercise, spiritual input, occupation, return to work, return to drive, insurance claims and litigation status (2 weeks, 6 weeks, 3 months, 6 months). We also quantify anxiety and depressive symptoms by using PHQ9 and GAD7 screening tools. Our demographic data analysis thus far reported minimal change on lifestyle apart from early return to work/education and return to drive (<2 weeks injury). Our mTBI patients are also from the low-income group population, with occupation such as drivers, goods deliveries, uniformed workers, labourers (with more time spent on the road). Litigation issues were also of low rate. The level of anxiety and depression were of mild categories at early stage of injury, with improvement of symptoms over time. Revised manuscript line 258-263.
Minor questions/issues/suggestions: a. When referring to acute or post-acute, please define what you mean (your cut-off). There are not many conclusive studies on nearly attention rehabilitation and TBI, let alone mTBI. May I suggest you include the latest Cicerone reference (2019).	Acute is defined as <2 weeks duration of injury, and post-acute in this study is defined as at 3 months of injury. Chronic injury is defined as >6 months post injury. Revised manuscript line 70. Reference no 44: Cicerone et al, 2019
b. In study hypothesis and objectives, I suggest you make a list of all your specific research questions/objectives that will be responded to in coming papers. In that way the reader will be able to go back to your study protocol and see what objectives to look forward to. It would help clarify your quest	The suggestion has been added in the revised manuscript under section 'Study objectives' line 112-118.
c. Participants and recruitment process: please describe your unit/center/location with more detail – what is your specialty for example, in what setting will the training be conducted, are there any other therapies involved like for example physical exercise, etc?	Description has been added in the revised manuscript under section 'participants and recruitment process' and 'Intervention'.
d. Inclusion criteria: please state a definition of mTBI (LOC, PTA, GCS, or	The mTBI definition has been added in the revised manuscript under section 'inclusion

the like). Do you take all concussions, with or without DT/MRI/fMRI? For inclusion and exclusion, provide cut-off levels with a rationale included (this criterion because it measures x with cut-off level y to make sure z). Could be presented in a table	criteria'. We have also included Table 1: inclusion criteria/exclusion criteria
e. Intervention: se comments above. Clarify what rehabilitative processes this part of the intervention is based on (restorative? Compensatory?). Who will be doing the testing (training of assessors, blinding). How will you keep record of interventions given for the standard care group? Provide examples of symptoms of expected attention deficit. Also, are there other services/interventions during this period of 12 weeks?	e. Revised manuscript line 180-188; 192-199; under section 'Intervention'. The details of assessors, intervention providers, blinding process is illustrated in Table 2. Written records of intervention are made and kept by therapist of each treatment arm until completion of treatment durations. This include: • Participant's goals • Participants symptom(s) • Cognitive strategy/method • Participant's feedback Revised manuscript line 167-169.
f. Withdrawal etc: Do you provide the option for patients in control group to receive the structured training after concluded intervention period? Love the part about adherence strategies!	No for the purpose of this study. We however follow participants up to a year post injury to record clinical status, cognitive symptoms, lifestyle changes, work status and litigation status.
g. Patient and public involvement. Well written and beautifully arranged! Bravo.	Thank you
h. Statistical analysis. Just a suggestion…you are doing repetitive GAS, at least 12 measures. As goals attained would be the expected outcome of better attention function, you could use GAS for process analysis (look into Statistical Process Control, SPC) thus following improvement patterns both for individuals and the two treatment arms. It would be of interest to identify what variables would prove predictive of rapid or steady improvement, versus no improvement during treatment.	Thank you. We will consider your suggestion.
i. References are a bit dated and Boman is mentioned twice (44 and 79). Consider adding the updated Cicerone	References are corrected and updated in the revised manuscript.

et al (2019). No doubt will you update them when writing the results.	
Details: i) Insert ”clinical” in the title ii) Abstract: (line 5) is it the patients overall cognitive function or specific? Do you expect such generalization of the attention training? (line 24) state number of hours in treatment i e intensity and frequency iii) Background: (line 70) give a perspective on why there is no standard treatment protocol for the group (as a whole), i e due to heterogenous population. There are protocols for specific symptoms. iv) Discussion (line 311): Caucasian ethnic group…there is an ‘n’ missing	i) Clinical word inserted in the title ii) The abstract has been rewritten to fulfil the requirements made by the journal. Yes, we do expect generalisation to occur based on our treatment approach. Intensity and frequency have been inserted in the revised manuscript abstract. iii) The addition made in revised manuscript line no 61-64. iv) Correction made in revised manuscript.

Reviewer	Authors response
Reviewer: 3 Reviewer Name: Professor Suzanne Martin Institution and Country: School of Health Sciences, Faculty of Life and Health Sciences, Ulster University - Jordanstown Campus, Shore Road, Newtownabbey, Northern Ireland. Thank you for this submission. An interesting study which i think will make a useful contribution to knowledge. The research question is clear in the title however the aims/objective require a review. The abstract would benefit from a few sentences of preamble introduction to give context to this research. Refer to other examples within the journal as helpful guide. Overall, the main body of the manuscript is fairly well presented. The sections within the introduction section are well aligned to the topic and interesting. The following amendments aim to further development this work. 1) Within the abstract and the main body state a single aim (or primary objective) rather than a hypothesis followed by secondary objectives. 2)Ethical governance. Whilst confirmation of	The abstract has been rewritten to fulfil the requirements made by the journal. 1) Correction made on the abstract outline and content. 2) Further elaboration on the ethical section was added in the revised manuscript under section ‘ethical consideration’ line 281-298. 3) At this stage we have not involved the patient other than being the participant of the study. We recently established a Brain Injury- Special Interest Group (BI-SIG) (2018) which is a part of Malaysian Association of Rehabilitation Physicians (2011). BI-SIG consist of Malaysian rehabilitation medicine physicians only currently. Apart from journal publications, we plan to disseminate the findings of this study to the members of BI-SIG/MARP and to include organizing training workshops for cognitive practitioners (training of trainers) nationwide.

ethical approval is provided, more detail on ethical considerations, risks and challenges should be provided. 3) Patient and public involvement. The content in this section doesn't adequately deal with the aspects of PPI. Have the team involved any patients directly in roles other than participants? Are there any organisations who work to support people with mTBI that might be interested to support and inform this work? 4)Limitations of the study requires further development. 5) Line 193 clarify what is meant by withdrawing participants who become non-compliant. 6) Line 194 requires a review as it requires the reader to move beyond this line to understand the intention. 7) Blinding - more information required to outline how blinding will be maintained. 8) Recruitment. More detailed information is required on the recruitment to assure participants are given enough information by the identifying clinician before going towards the researching therapist.	4) We have not included section 'limitation of study' for this manuscript, as we are still data collecting/data analysing. 5) Manuscript edited under section 'Modification, withdrawal and unblinding within the intervention line 211-214. 6) Clarification made in the revised manuscript line 211-214. 7) This is illustrated in Table 2 8) This is provided during multiple screening reviews at 2 weeks, 6 weeks and 3 months post injury. Revised manuscript line 133; 152-169.

VERSION 2 – REVIEW

REVIEWER	Dana Wong La Trobe University
REVIEW RETURNED	20-Jun-2019

GENERAL COMMENTS	This revised version is improved (in particular the addition of Table 3 is helpful) and has adequately addressed the reviewer comments for some issues but not for others. Remaining issues include the following: The new objectives on page 4 should not refer to specific measures. The method for addressing the objectives belongs in the Method section. In the authors' response, they appear to misunderstand the meaning of "estimated premorbid functioning". They state "Good premorbid functioning is assessed and established through clinical reviews and screening (2 weeks, 6 weeks post trauma) prior to recruitment (at 3 months). This include physical symptoms, psychological symptoms, lifestyle changes, return to work/education, return to drive, litigation issues, health cost issues.". However "premorbid functioning" was intended to mean "premorbid intellectual functioning", i.e. estimated level of intellectual functioning prior to the mild TBI. This is a very

	important construct in neuropsychological assessment and rehabilitation which does not appear to be formally measured in the current study (other than through years of education which is a very rough measure). This needs to be acknowledged. The sentence “However, those with other cognitive domain deficit(s) (standard domain score <85) other than Attention Domain will also be included in the study and will receive treatment for attention following randomization” is still unclear. Does it mean that participants may have non-attentional cognitive deficits IN ADDITION to the requisite attention impairments, or that they can have non-attentional deficits INSTEAD of attentional deficits and still be eligible for the study? Please ensure the wording is clear. The authors’ response suggests that they mean INSTEAD of. If that’s the case, the inclusion criterion “Abnormal S-NAB Attention Domain score at 3 months of mTBI” is inaccurate and misleading, and should be changed to “Abnormal score on any S-NAB cognitive domain at 3 months post-mTBI”. The authors state that metacognitive awareness will be measured “…through GAS evaluation. Patient statements and feedback on performance will be recorded in written format.” This is not a validated method for measuring metacognitive awareness (see the work of Tamara Ownsworth). The lack of such a measure should be acknowledged. Numerous grammatical errors remain in the manuscript, particularly the incorrect use of singular vs plural nouns, and absence of “a” and “the” in many places.

REVIEWER	Gabriela Markovic Departement of Clinical Sciences, Karolinska Institutet, Stockholm, Sweden
REVIEW RETURNED	07-Jun-2019

GENERAL COMMENTS	Looking forward to the results and good luck with data collection!

VERSION 2 – AUTHOR RESPONSE

Review	Author’s response
Reviewer: 2 Reviewer Name: Gabriela Markovic Institution and Country: Departement of Clinical Sciences, Karolinska Institutet, Stockholm, Sweden Please state any competing interests or state ‘None declared’: None declared	We have added the competing interest: ‘none declared’ in the manuscript

Review	Author's response
Reviewer 1 Reviewer Name: Dana Wong Institution and Country: La Trobe University Please state any competing interests or state 'None declared': None declared	We have added the competing interest: 'none declared' in the manuscript
The new objectives on page 4 should not refer to specific measures. The method for addressing the objectives belongs in the Method section.	Corrections made as requested to manuscript line no: 111-116
In the authors' response, they appear to misunderstand the meaning of "estimated premorbid functioning". They state "Good premorbid functioning is assessed and established through clinical reviews and screening (2 weeks, 6 weeks post trauma) prior to recruitment (at 3 months). This include physical symptoms, psychological symptoms, lifestyle changes, return to work/education, return to drive, litigation issues, health cost issues.". However "premorbid functioning" was intended to mean "premorbid intellectual functioning", i.e. estimated level of intellectual functioning prior to the mild TBI. This is a very important construct in neuropsychological assessment and rehabilitation which does not appear to be formally measured in the current study (other than through years of education which is a very rough measure). This needs to be acknowledged.	We agree that premorbid IQ and other variables could affect outcomes, but we did not include a test due to several factors: 1) to reduce participant burden. Majority of participants from our previous pilot study declined multiple assessments. It affected our participatory rate too. 2) majority if not all of the IQ assessments (e.g. NART/WTAR) are not validated for Malaysian population 3) through randomisation, this will address any imbalance at baseline. We however included the healthy group to represent the normal values in some parameters i.e. cognitive, physical, psychological and functional. The results (assessed using the same outcome measures) will also be aged-, gender and education matched with mTBI individuals for comparison purposes. Please refer manuscript line 201-206; 261-265
The sentence "However, those with other cognitive domain deficit(s) (standard domain score <85) other than Attention Domain will also be included in the study and will receive treatment for attention following randomization" is still unclear. Does it mean that participants may have non-attentional cognitive deficits IN ADDITION to the requisite attention impairments, or that they can have non-attentional deficits INSTEAD of attentional deficits and still be eligible for the study? Please ensure the wording is clear. The authors' response suggests that they mean INSTEAD of. If that's the case, the inclusion criterion "Abnormal S-NAB Attention Domain score at 3 months of mTBI" is inaccurate and misleading, and should be changed to "Abnormal score on	We will include those with: 1. S-NAB Attention score deficit of <85 at 3 momths 2. presence of >1 domain deficit despite normal S-NAB Attention score >85 S-NAB was designed to follow a presumed hierarchical order of neuropsychological functioning that recognised Attention as a basic function that underlies all other domains of neuropsychological functioning. The hierarchical order is as follows: Attention, Language, Memory, Spatial and Executive Function. Multiple domain deficits may be reflective of a person's limited functioning in higher order areas

any S-NAB cognitive domain at 3 months post-mTBI".	due to attention impairment, despite domain score of >85. Our previous work (Veeramuthu et al, 2015; pilot study, validation study) have not found mTBI patient in Malaysian population to present with a single cognitive domain deficit measured with S-NAB at different timeline of injury (<24h, 2 weeks, 3 months). The pilot study analysis also reported those who received Attention-targeted therapy, despite multiple other domain deficits present, showed improvement in all domain scores post treatment. Therefore, our corrected statement is: "Abnormal S-NAB Attention Domain score at 3 months of mTBI. However, deficits of cognition of more than one domain involvement, other than Attention domain, will also be recruited in this study'. Correction made in manuscript line 159-162.
The authors state that metacognitive awareness will be measured "…through GAS evaluation. Patient statements and feedback on performance will be recorded in written format." This is not a validated method for measuring metacognitive awareness (see the work of Tamara Ownsworth). The lack of such a measure should be acknowledged.	Apologies, we recognise that this was not clear in our manuscript. We will not measure metacognitive awareness using GAS. We apply GAS to measure treatment progress. However, goals set with participants will be focused around obtaining cognitive functional gains. The change will be measured via effect size of GAS T-score. We have also checked our previous review response on this matter but could not find the statement mentioned. However, the application of metacognitive strategies is best explained in manuscript under section 'individualised structured cognitive rehabilitation group, page 7, line 179-186. We have also added a new statement 'The metacognitive strategies applied will be obtained and recorded in writing during participant's feedback sessions.' Line 342-343. In the application of GAS and weekly performance review, the written record of goals and methods will also include the patient's statement and feedback of performance in their daily life aspects – to record the patient's own words of their metacognitive awareness and strategies that they apply, either learnt from therapist or formulated/'figured out' by themselves.

	This is to minimise the loss of qualitative data in measuring the functional outcome.
Numerous grammatical errors remain in the manuscript, particularly the incorrect use of singular vs plural nouns, and absence of “a” and “the” in many places.	Corrections have been made in the revised manuscript.

VERSION 3 - REVIEW

REVIEWER	Dana Wong La Trobe University
REVIEW RETURNED	05-Aug-2019

GENERAL COMMENTS	The authors have generally addressed the remaining comments adequately. The wording of the inclusion criteria remains a little convoluted and could be made even clearer, eg "Eligibility criteria included i) an abnormal S-NAB Attention Domain score at 3 months post-mTBI. or ii) deficits in more than one S-NAB domain, not including the attention domain." Also, the new line "The metacognitive strategies applied will be obtained and recorded in writing during participant’s feedback sessions" belongs in the method/procedure section, not the statistical analysis section. The writing also still requires further editing and improvement. Otherwise, the paper appears ready for publication.

VERSION 3 – AUTHOR RESPONSE

Reviewer’s comment	Author’s response
The wording of the inclusion criteria remains a little convoluted and could be made even clearer, eg "Eligibility criteria included i) an abnormal S-NAB Attention Domain score at 3 months post-mTBI. or ii) deficits in more than one S-NAB domain, not including the attention domain."	Correction made in the manuscript line 161-162
Also, the new line "The metacognitive strategies applied will be obtained and recorded in writing during participant’s feedback sessions" belongs in the method/procedure section,	Correction made in the manuscript line 187-188.

not the statistical analysis section.	
The writing also still requires further editing and improvement. Otherwise, the paper appears ready for publication.	We have also made some changes and further corrections to the paper as requested
-	Corrections were also made to several references under Reference section highlighted in blue