PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Improving Neurodevelopmental Outcomes in Children with Congenital Heart Disease: Protocol for a Randomized Controlled Trial of Working Memory Training
AUTHORS	Calderon, Johanna; Bellinger, David; Hartigan, Catherine; Lord, Alison; Stopp, Christian; Wypij, David; Newburger, Jane

VERSION 1 – REVIEW

REVIEWER	Amy H. Schultz Seattle Children's Hospital Seattle, WA United States of America
REVIEW RETURNED	23-Apr-2018

GENERAL COMMENTS	Calderon and colleagues report a planned study to assess the utility of an established, computer-based intervention in ameliorating deficits in executive function in children with congenital heart disease (CHD) who required surgery in the first year of life. This is an important study to conduct, because while much work has been done to document the prevalence of various neurodevelopmental impairments in children with CHD, and efforts have been made to identify interventions (primarily during the intraoperative period) to prevent such complications, the latter efforts have been largely negative. Clinicians who care for these patients have little that they can offer to patients who struggle with these deficits. As noted by the authors, if effective, this home-based intervention would be accessible to patients without need to miss school or travel to appointments. The paper is overall very well written, clear and easy to follow. Power calculations, statistical analysis and ethical considerations have all been addressed. The study protocol could be easily replicated based on the methods described here. I do have a few questions and concerns that I will list below. #1-3 are related to each other. 1) **The authors use the term "critical congenital heart disease" liberally throughout the paper without ever defining this term explicitly**. This is a problematic term to treat in this fashion, because there is quite a bit of variability in how this term is used in the literature. Depending on the definition, there could be significant differences in the baseline prevalence of executive dysfunction. Specifically, the CDC defines "critical" CHD as lesions requiring cardiac surgery in the first year of life, which thus includes isolated ventricular septal defect as well as much more complex

	lesions. For the purposes of pulse oximetry screening, the HHS Secretary's Advisory Committee on Heritable Disorders in Newborns and Children defined 7 specific CHD lesions to target for "critical CHD" screening. More traditionally, pediatric cardiologists have considered "critical" CHD to encompass lesions that required ductal patency to maintain stability (e.g. "critical" aortic stenosis, "critical" coarctation, and "critical" pulmonary stenosis), which typically require intervention as neonates. 2) **Related to #1 above, I would like to ask the authors to reconsider whether the inclusion criterion of CHD requiring open-heart surgery before <u>one year of age</u> is the most appropriate cutoff, or whether the age at surgery should be younger, for example <4-6 weeks.** Executive function impairments have been well documented in D-transposition of the great arteries and single ventricle lesions and other complex lesions requiring neonatal surgery. However, my impression of the literature on simpler lesions (e.g. isolated ventricular septal defect) is that the groups studied are smaller and the results much more mixed. The authors do provide references that include a range of different types of CHD. The concern here is that if the study ends up enrolling predominantly a group of children who underwent surgery for isolated VSD who have no genetic syndrome, and no severe developmental or intellectual disorder (as per the other inclusion criteria) that the study group might have a low baseline incidence of executive dysfunction and any study effect might not be apparent. The opportunity to identify an important intervention for children with more complex CHD could be missed. 3) **The concern in #2 could be addressed by changing the eligibility criteria. Absent this, I would ask whether the enrollment stratification should be changed.** The current scheme plans to stratify on type of CHD: univentricular versus biventricular. I would ask whether this should be changed to CHD requiring neonatal (<4 weeks of age) surgery versus CHD requiring surgery between 4 weeks and 1 year of age. Another way of posing this question is: Is the baseline incidence of executive dysfunction patients with D-transposition of the great arteries, total anomalous pulmonary venous connection, truncus arteriosus, and interrupted aortic arch/VSD more similar to: a. Hypoplastic left heart syndrome, tricuspid atresia, pulmonary atresia/intact ventricular septum, other single ventricle --OR— b. Isolated VSD, Tetralogy of Fallot (no genetic syndrome) requiring repair at >1 month of age, complete common atrioventricular canal (no genetic syndrome) 4) **In several places, the authors use the term "longer-term" effects of the intervention to describe the 3 month post-intervention assessment.** I do not think that this is an appropriate use of "longer-term". At best, this could be considered intermediate-term follow-up, but I think mostly it qualifies as short-term follow-up. I understand that the authors are trying to describe a point in time that is not immediately post-intervention, but a more conservative

	descriptor is warranted. 5) **Blinding:** it will be impossible to blind parents to the intervention. However, teachers could potentially be blinded if the study protocol coached the parents not to inform the teachers about the assignment. There will be limitations (i.e. the child could go to school and tell the teacher about what he/she is working on), but at least an attempt should be made in this respect. 6) **Limitations:** There is a section on "Strengths and Limitations of the Study" immediately following the abstract. **I note that the authors have not included any limitations of their study, which is an omission.** The two most obvious limitations of this study are (1) lack of parent blinding and use of parent rating scales to assess the effect of the intervention (2) short duration of follow-up. The authors need to acknowledge these and potentially other limitations.

REVIEWER	Lisa Paquette University of Southern California, United States
REVIEW RETURNED	11-May-2018

GENERAL COMMENTS	This is a very interesting, necessary, well-designed study! Thank you! Positive results will provide unique tangible hope for the CHD population to begin mastering significant life-altering developmental differences. Negative results will hopefully inspire your team to continue the experiment for longer!

REVIEWER	Walter Knirsch Walter Knirsch, MD Pediatric Cardiology University Children's Hospital Zurich – Eleonore Foundation Steinwiesstrasse 75 CH-8032 Zurich Switzerland phone +41 44 266 76 17 fax +41 44 266 79 81 walter.knirsch@kispi.uzh.ch www.kispi.uzh.ch
REVIEW RETURNED	26-May-2018

GENERAL COMMENTS	This is a clearly structured, and very well written study protocol for a randomized controlled trial of working memory training in children with congenital heart disease (CHD) aged 7-12 years after open-heart surgery within the first year of life. The authors have to be congratulated for their efforts to improve neurodevelopmental outcome in CHD patients focussing on the importance of executive functions in these children and evaluation by this test tool. The data of the study (start, end, length) are not given, and unfortunately, it is solely planned as a single center study (page 3, line 13). Regarding the defined study design the study is not single-blinded to my understanding (page 3, line 13), because the participants know in which study arm they participate, i.e. COGMED vs. standard care arm, where treatment remains unchanged. This should be clarified. The main question remains whether a computer based test program for 5 weeks with 5 sessions per week lasting for one hour per session is accepted by the participants. I am not familiar with the COGMED test whether it is boring after some sessions? So what is the appreciated compliance with the test. I am astonished about the use of a tablet game after the COGMED test as a kind of reward

	(page 13, line 31). Please give a comment on this.Children aged 7-12 years are fascinated by tablet games and of course they are widely used. Nevertheless, the use of digital media should be taken into account. As a pediatric cardiologist, I am not familiar whether there are any alternatives to COGMED or to the other used tests and parental and teacher questionnaires (page 4, line 12-22). There should be a statement on the use of this methods. The link to ADHD (page 3, line 31) is important, but to my understanding ADHD symptoms in CHD patients may be related to a secondary effect due to impaired EF leading to behavioural compensation mechanisms mimicking ADHD, which should be mentioned. The sustainable long-term effect of COGMED Training program will be evaluated after 3 months. Would it be worthwhile to check this again after 12 months? Other important psycho-social factors are not included in the study protocol, i.e. the type of school the children attend, the specific support (if one?) the get, the family situation, the role / interaction with the siblings, the overall family background, i.e. the socio-economic status. The inclusion criteria should be clarified, whether the children have been operated for more than one time and even after 12 months of age. Within the exclusion criteria (4) (page 11, line 25..) "the placement in a separate class room recieving individual Support" should be more clearly defined. For the interested Reader it would be helpful to give more details on the COGMED test (page 12, line 40). Full intellectual concentration for more than 50 minutes per day for 5 days per week over a period of 5 weeks is a real burden for the participants - the study protocol should include a limitation of number of participants with an early breakup of the COGMED test. So far I understand the study protocol there is a control group of patients with standard care without any intervention, are there any alternatives to COGMED as a third study arm? The role of parents and teachers and their support of the study should be more clearly defined. What about the idea to include cerebal MRI findings in the patients and control group (page 17, line 30).

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Amy H. Schultz
Institution and Country: Seattle Children's Hospital, Seattle, WA, United States of America
Please state any competing interests: none declared
Please leave your comments for the authors below

Very well written, important subject, overall well designed. My major question that I would like addressed has to do with whether age at surgery <1 year is the appropriate enrollment criterion for this study or whether the age cutoff should be younger. Please see the attached file for more detail about my questions. If not changed, I would like to see these questions/concerns more explicitly addressed in your paper. Congratulations on conceiving and designing this study, I look forward to seeing its results at some point in time.

Calderon and colleagues report a planned study to assess the utility of an established, computer-based

intervention in ameliorating deficits in executive function in children with congenital heart disease (CHD)
who required surgery in the first year of life. This is an important study to conduct, because while much
work has been done to document the prevalence of various neurodevelopmental impairments in children with CHD, and efforts have been made to identify interventions (primarily during the intraoperative period) to prevent such complications, the latter efforts have been largely negative. Clinicians who care for these patients have little that they can offer to patients who struggle with these
deficits. As noted by the authors, if effective, this home-based intervention would be accessible to patients without need to miss school or travel to appointments.
The paper is overall very well written, clear and easy to follow. Power calculations, statistical analysis and ethical considerations have all been addressed. The study protocol could be easily replicated based
on the methods described here. I do have a few questions and concerns that I will list below. #1-3 are related to each other.

Responses to Reviewer 1: We thank this reviewer for the detailed and helpful comments on our manuscript. Please see below for a specific response to each comment.

1) The authors use the term “critical congenital heart disease” liberally throughout the paper without ever defining this term explicitly. This is a problematic term to treat in this fashion, because there is quite a bit of variability in how this term is used in the literature. Depending on the definition, there could be significant differences in the baseline prevalence of executive dysfunction. Specifically, the CDC defines “critical” CHD as lesions requiring cardiac surgery in the first year of life, which thus includes isolated ventricular septal defect as well as much more complex lesions. For the purposes of pulse oximetry screening, the HHS Secretary’s Advisory Committee on Heritable Disorders in Newborns and Children defined 7 specific CHD lesions to target for “critical CHD” screening. More traditionally, pediatric cardiologists have considered “critical” CHD to encompass lesions that required ductal patency to maintain stability (e.g. “critical” aortic stenosis, “critical” coarctation, and “critical” pulmonary stenosis), which typically require intervention as neonates.

Response: We agree that the term “critical congenital heart disease” should be defined in our manuscript. In the Regional Infant Cardiac Program, critical congenital heart disease was defined as heart disease leading to surgery, cardiac catheterization, or death in the first year of life. (Fyler, 1980). For our protocol, we chose to study the subset of infants with critical congenital heart disease who were managed with open heart surgery in the first year of life, consistent with the American Heart Association’s scientific statement on management of neurodevelopmental disabilities. In this statement, children with CHD (cyanotic or acyanotic) who underwent open-heart surgery as neonates or infants are considered to be at highest risk for neurodevelopmental disabilities (Class I, Level of Evidence A). This group may include various anatomical and physiological presentations of CHD; although neonatal age at surgery is known to be a risk factor for worse outcomes, infants undergoing open heart surgery beyond the neonatal period but in the first year of life have a higher risk for later developmental issues, including executive function deficits. We added this definition as: “Congenital Heart Defects requiring cardiac surgery in the first year of life”. (Introduction, page 4).

1. Fyler DC. Report of the New England Regional Infant Cardiac Program. Pediatrics. 1980;65:S375-S461.

2) Related to #1 above, I would like to ask the authors to reconsider whether the inclusion criterion of CHD requiring open-heart surgery before one year of age is the most appropriate

cutoff, or whether the age at surgery should be younger, for example <4-6 weeks. Executive function impairments have been well documented in D-transposition of the great arteries and single ventricle lesions and other complex lesions requiring neonatal surgery. However, my impression of the literature on simpler lesions (e.g. isolated ventricular septal defect) is that the groups studied are smaller and the results much more mixed. The authors do provide references that include a range of different types of CHD. The concern here is that if the study ends up enrolling predominantly a group of children who underwent surgery for isolated VSD who have no genetic syndrome, and no severe developmental or intellectual disorder (as per the other inclusion criteria) that the study group might have a low baseline incidence of executive dysfunction and any study effect might not be apparent. The opportunity to identify an important intervention for children with more complex CHD could be missed.

Response: As a first randomized controlled trial of cognitive interventions in the population with CHD, we designed this study to provide a first proof of concept that a well-structured and cost-effective intervention can improve neurodevelopmental outcomes (executive function, behavior and social skills) in children at high risk for developmental issues. We agree that the literature offers a more fine-grained phenotypic description of executive function impairments in certain types of CHD (i.e., d-TGA, post-Fontan). However, there is evidence to suggest that children with other types of CHD who did not undergo neonatal heart surgery may display a similar pattern of executive challenges. Studies including children who underwent surgery in infancy such as those with Tetralogy of Fallot (Bellinger et al., 2015, Hovels-Gurich et al., 2007), isolated ventricular septal defects or atrial septal defects (Sarrechia et al., 2013; 2015a, b) show high rates of executive functioning difficulties among other impairments. We agree that there may be variations in the degree of severity of executive dysfunction and factors such as timing of surgery and type of CHD may play an important role. We will conduct statistical analyses to identify these potential risk factors and investigate how they might interact with response to treatment. We clarified this in our data analysis plan, page 18. Finally, we stratify by level of executive function deficit (NIH Toolbox Working Memory test score <85 or >85) in order to ensure an equal distribution of children with executive function impairments in both groups (intervention versus standard of care).

1. Bellinger DC, Rivkin MJ, Demaso D, Robertson RL, Stopp C, Dunbar-Masterson C, Wypij D, Newburger JW. Adolescents with tetralogy of Fallot: neuropsychological assessment and structural brain imaging. Cardiol Young. 2015;25:338-47.
2. Hovels-Gurich HH, Konrad K, Skorzenski D, Herpertz-Dahlmann B, Messmer BJ, Seghaye MC. Attentional dysfunction in children after corrective cardiac surgery in infancy. Ann Thorac Surg. 2007;83:1425-30.
3. Sarrechia I, Miatton M, De Wolf D, Francois K, Vingerhoets G. Neurobehavioral functioning in school-aged children with a corrected septal heart defect. Acta Cardiol. 2013;68:23-30.
4. Sarrechia I, Miatton M, Francois K, Gewillig M, Meyns B, Vingerhoets G, De Wolf D. Neurodevelopmenta outcome after surgery for acyanotic congenital heart disease. Res Dev Disabil. 2015;45-46:58-68.
5. Sarrechia I, De Wolf D, Miatton M, Francoi K, Gewillig, Meyns B, Vingerhoets G. Neurodevelopment and behavior after transcatheter versus surgical closure of secundum type atrial septal defect. J Pediatr. 2015;166:31-8.

3) The concern in #2 could be addressed by changing the eligibility criteria. Absent this, I would ask whether the enrollment stratification should be changed. The current scheme plans to stratify on type of CHD: univentricular versus biventricular. I would ask whether this should be changed to CHD requiring neonatal (<4 weeks of age) surgery versus CHD requiring surgery between 4 weeks and 1 year of age. Another way of posing this question is: Is the baseline incidence of executive dysfunction patients with D-transposition of the great arteries, total anomalous pulmonary venous connection, truncus arteriosus, and interrupted aortic arch/VSD

more similar to:
a. Hypoplastic left heart syndrome, tricuspid atresia, pulmonary atresia/intact ventricular septum, other single ventricle --OR—
b. Isolated VSD, Tetralogy of Fallot (no genetic syndrome) requiring repair at >1 month of age, complete common atrioventricular canal (no genetic syndrome)

Response: Our study randomization scheme involves two stratification factors: type of CHD (univentricular versus biventricular) and degree of executive dysfunction (working memory test score < or =85 versus ≥85). We understand that some surgical or anatomical factors such as neonatal surgery or specific type of CHD might have an impact on the baseline executive score. However, this concern is already addressed by our stratification based on the presence of executive function deficits. Our Specific Aim 3 will explore the associations between patient factors including timing of surgery (neonatal versus non-neonatal) and response to intervention (from baseline to post-treatment and from baseline to 3-month follow-up). We added a clarification noting that this specific factor will be analyzed in our results (Data analysis plan, page 20).

4) In several places, the authors use the term “longer-term” effects of the intervention to describe the 3-month post-intervention assessment. I do not think that this is an appropriate use of “longer-term”. At best, this could be considered intermediate-term follow-up, but I think mostly it qualifies as short-term follow-up. I understand that the authors are trying to describe a point in time that is not immediately post-intervention, but a more conservative descriptor is warranted.

Response: We reviewed the use of this term and now refer to this assessment as “3-month follow-up”.

5) Blinding: it will be impossible to blind parents to the intervention. However, teachers could potentially be blinded if the study protocol coached the parents not to inform the teachers about the assignment. There will be limitations (i.e. the child could go to school and tell the teacher about what he/she is working on), but at least an attempt should be made in this respect.

Response: In our study, we advise parents that it is best not to inform the teacher who will be completing the questionnaires whether their child is receiving the Cogmed intervention. However, we cannot be certain that this is the case for all participants, thus we cannot accurately call this “blinded teacher assessment”. We added some limitations including the lack of participant blinding (page 3, strenghs and limitation of this study).

6) Limitations: There is a section on “Strengths and Limitations of the Study” immediately following the abstract. I note that the authors have not included any limitations of their study, which is an omission. The two most obvious limitations of this study are (1) lack of parent blinding and use of parent rating scales to assess the effect of the intervention (2) short duration of follow-up. The authors need to acknowledge these and potentially other limitations.

Response: We added these limitations to our manuscript (Strengths and limitations, page 3).

Reviewer: 2
Reviewer Name: Lisa Paquette
Institution and Country: University of Southern California, United States
Please state any competing interests: None declared

Please leave your comments for the authors below

This is a very interesting, necessary, well-designed study! Thank you! Positive results will provide unique tangible hope for the CHD population to begin mastering significant life-altering developmental differences. Negative results will hopefully inspire your team to continue the experiment for longer!

Response to Reviewer 2: Thank you for your comment on our manuscript. We hope that this trial will provide important information on how to best address executive function issues in children with CHD. We are very motivated to move this field forward.

Reviewer: 3
Reviewer Name: Walter Knirsch
Institution and Country: Walter Knirsch, MD, Pediatric Cardiology, University Children's Hospital Zurich – Eleonore Foundation, Steinwiesstrasse 75, CH-8032 Zurich, Switzerland, phone +41 44 266 76 17, fax +41 44 266 79 81, walter.knirsch@kispi.uzh.ch, www.kispi.uzh.ch
Please state any competing interests: None declared

Please leave your comments for the authors below

This is a clearly structured, and very well written study protocol for a randomized controlled trial of working memory training in children with congenital heart disease (CHD) aged 7-12 years after open-heart surgery within the first year of life.
The authors have to be congratulated for their efforts to improve neurodevelopmental outcome in CHD patients focussing on the importance of executive functions in these children and evaluation by this test tool.
The data of the study (start, end, length) are not given, and unfortunately, it is solely planned as a single center study (page 3, line 13). Regarding the defined study design the study is not single-blinded to my understanding (page 3, line 13), because the participants know in which study arm they participate, i.e. COGMED vs. standard care arm, where treatment remains unchanged. This should be clarified.

Response: We thank this reviewer for his helpful comments and questions. We designed our trial as a single-center study because it is a phase II randomized controlled trial to provide proof of concept that an evidenced-based cognitive intervention can improve outcomes in children with CHD. If our trial yields positive results, we intend to design a multi-center and potentially international intervention study that will further investigate how this and other similar interventions may be effective. Our study design is single-blinded because the neuropsychologists doing all evaluations are blinded to children's cardiac and intervention status.

The main question remains whether a computer based test program for 5 weeks with 5 sessions per week lasting for one hour per session is accepted by the participants. I am not familiar with the COGMED test whether it is boring after some sessions? So what is the appreciated compliance with the test.

I am astonished about the use of a tablet game after the COGMED test as a kind of reward (page 13, line 31). Please give a comment on this. Children aged 7-12 years are fascinated by tablet games and of course they are widely used. Nevertheless, the use of digital media should be taken into account.

Response: We agree that the Cogmed intervention can be very intense and requires a great commitment from children and their parents. We will assess the feasibility of this intervention and carefully track patients' compliance. The program ensures a continuing level of motivation by varying

the activities during the training sessions. Importantly, the difficulty is automatically adjusted to each child's own executive function performance so that it remains challenging without being too easy or too hard. From previous studies, this intervention has good compliance rates. We will evaluate this in our study. Cogmed Program has an integrated reward short video-game that can be offered after completing a day of training. The content of this 3-5 minute video-game is predetermined and timed. This does not significantly extend the time children are handling digital media.

As a pediatric cardiologist, I am not familiar whether there are any alternatives to COGMED or to the other used tests and parental and teacher questionnaires (page 4, line 12-22). There should be a statement on the use of this methods.

Response: There are other experimental laboratory interventions or clinically-based interventions to improve neurodevelopmental and executive function outcomes in children. We chose to test the efficacy of Cogmed because evidenced-based studies support its implementation in children with specific executive function issues. As a home-based intervention, it also requires fewer hospital visits. Thus, although we acknowledge the existence of other interventions (page 6), we chose to focus on presenting data on the results of this intervention. Many of our assessment tools (NIH Toolbox and parent/teacher questionnaires and WISC-V) are gold standards in the evaluation of neurodevelopment in children. The NIH Toolbox (our primary outcome measure) allows for longitudinal assessment in repeated measures design and has strong validity and reliability as indicated in our manuscript.

The link to ADHD (page 3, line 31) is important, but to my understanding ADHD symptoms in CHD patients may be related to a secondary effect due to impaired EF leading to behavioural compensation mechanisms mimicking ADHD, which should be mentioned.

Response: We thank this reviewer for this interesting comment. The scope of our study is to evaluate the efficacy of the Cogmed intervention on a wide variety of outcomes including ADHD symptomatology. We do not seek to evaluate whether children with CHD present with a well-defined disorder but rather to address their "ADHD-like" symptoms and their potential decrease following the intervention. We indicate this by using the terminology "ADHD symptoms" and not ADHD diagnosis.

In general, ADHD is a neuropsychiatric disorder for which core symptoms involve executive dysfunctions. There are different expressions of ADHD as well as different degrees of severity along the spectrum. Whether the mechanisms are the same in CHD is a very interesting question that remains unknown.

The sustainable long-term effect of COGMED Training program will be evaluated after 3 months. Would it be worthwhile to check this again after 12 months?
Other important psycho-social factors are not included in the study protocol, i.e. the type of school the children attend, the specific support (if one?) the get, the family situation, the role / interaction with the siblings, the overall family background, i.e. the socio-economic status.

Response: The present study is designed with a 3-month follow-up and we agree that it would be interesting to see longer-term effects, i.e., 6 or 12 months after the intervention. We chose then three-month endpoint for ethical and practical reasons. If this intervention is effective at three months, we did not wish to delay its administration to children in our control group. We also require that children enrolled in our study do not initiate other forms of executive function training; this limitation for periods longer than 3 months in our at-risk population could be detrimental to children and their families. From a practical viewpoint, if the Cogmed intervention is not effective at 3 months, further investment of

resources would be undesirable. We agree that, if the intervention is effective at 3 months, further studies to evaluate its longer-term effects would be important.

With respect to the reviewer's question about psychosocial factors, Aim 3 of the study explores the effect of socio-demographic factors including history or current use of remedial services, family socioeconomic status and maternal educational level.

The inclusion criteria should be clarified, whether the children have been operated for more than one time and even after 12 months of age. Within the exclusion criteria (4) (page 11, line 25..) "the placement in a separate class room recieving individual Support" should be more clearly defined.

Response: We thank this reviewer for this useful feedback. We clarified our eligibility criteria in the "Participants and Recruitment" section. Children are eligible if they undergo at least one open-heart surgery before the age of 1 and regardless of the number of surgeries they undergo. Placement in a separate classroom and receiving individual support typically indicate greater neurodevelopmental barriers to benefit from this intervention and constitutes an exclusion criterion. We added a clarification in the same section of our manuscript (page 10).

For the interested Reader it would be helpful to give more details on the COGMED test (page 12, line 40). Full intellectual concentration for more than 50 minutes per day for 5 days per week over a period of 5 weeks is a real burden for the participants - the study protocol should include a limitation of number of participants with an early breakup of the COGMED test.

Response: We agree that the Cogmed standard version as delivered in our study is time-consuming and an intense intervention for children and their parents. The average duration of each session is approximately 45 minutes daily for a total of 25 sessions. We are recording compliance and define it as successful completion of at least 20 sessions. Early drop-outs are possible and we took into account 20% attrition rates in our power calculations. We also offer some flexibility to families who struggle to complete the sessions in the timeframe indicated. We provide constant support and feedback to ensure that the training remains a positive experience and not a time burden for participating children and families. Finally, the trial is overseen by a Data Monitoring and Safety Board, which is authorized to stop the study if the number of dropouts impedes study inferences on efficacy of the intervention.

So far I understand the study protocol there is a control group of patients with standard care without any intervention, are there any alternatives to COGMED as a third study arm?
The role of parents and teachers and their support of the study should be more clearly defined.
What about the idea to include cerebal MRI findings in the patients and control group (page 17, line 30).

Response: We plan on continuing our investigation of this and other alternative interventions to improve executive function outcomes in CHD. Our present Phase II RCT will provide the foundation for the design of a Phase III RCT that will include active control conditions as well as a third study arm to compare the efficacy of this intervention to an alternative one. At that stage, we would also explore the potential neurological imaging biomarkers associated with improved outcomes following the intervention.

VERSION 2 – REVIEW

REVIEWER	Amy H Schultz, MD Seattle Children's Hospital Seattle, WA, USA
REVIEW RETURNED	25-Aug-2018

GENERAL COMMENTS	The authors have thoughtfully addressed my previous comments and I believe this manuscript should be accepted. Thank you for the opportunity to review this paper. I look forward to publication of the results.