PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Protocol for a Prospective Cohort Study of Assessing Postoperative Cognitive Changes After Total Hip and Knee Arthroplasty in the Greater Toronto Area
AUTHORS	Choi, Stephen; Avramescu, Sinziana; Orser, Beverley; Au, Shelly

VERSION 1 – REVIEW

REVIEWER	Nicolai Goettel, MD, DESA, EDIC University Hospital Basel, Switzerland
REVIEW RETURNED	28-May-2018

GENERAL COMMENTS	Thank you for the opportunity to review this work. This report by Choi and coworkers describes the research protocol for a prospective observational cohort study of assessing postoperative delirium (POD) and postoperative cognitive dysfunction (POCD) after major joint arthroplasty. The manuscript deals with an important topic – neurocognitive outcomes of non-neurologic surgery – and is overall well written and pleasant to read. Since this is the protocol for an ongoing study, I would like to request revisions that are generally clarifications for the rationale or details relating to the methods. Please limit the number of outcome definitions to a strict minimum. While the title reads “postoperative cognitive deficits”, the authors also use the terms “postoperative delirium”, “postoperative cognitive decline”, postoperative cognitive dysfunction”, and “neurocognitive disorder (NCD)” in this context throughout the manuscript. These different expressions may sometimes label a common clinical picture. A clear definition of the specific outcome measures is important, especially in postoperative cognitive outcomes research. Certainly, there is an ongoing attempt to simplify and uniform the nomenclature of cognitive changes associated with anesthesia and surgery recommended by an international panel of experts; however, these are still unpublished and controversially debated. Mild and major NCD are definitions based on the standard deviation differences published in the DSM-5; they usually stand for mild cognitive impairment (MCI) (= mild NCD) or dementia (= major NCD). It is still questionable whether POCD is the mild or major form of NCD, or both. The time being, I would suggest sticking to the “old” nomenclature of POD and POCD. In the abstract and further on in the manuscript (introduction), the authors state, “there are no effective treatment strategies for these

	disorders" (meaning POD and POCD). The same is said about the prevention of these disorders. I think that POCD as an entity may be correct here, but POD should prompt a search for treatable factors (e.g. sepsis, drug interactions, etc.). I do not feel it is right to suggest that POD is untreatable, as this would suggest there is nothing that can be amended in the postoperative period when there are factors that can be addressed, even without use of drugs to provide short-term symptom control. Moreover, one study has shown that delirium may be prevented in up to 30% of cases in hospitalized patients, using a non-pharmacological multicomponent intervention strategy. [1] The authors also state: "The incidence of neurocognitive disorders has not been studied rigorously in the total hip and knee arthroplasty (THA/TKA) population." I do not entirely agree with this statement. Both, POD and POCD, have been extensively studied in the hip fracture population. The principal difference is that hip fracture patients are usually emergency/urgent cases, and not elective surgery as in your study. I would highlight this throughout the manuscript. One bigger problem with postoperative cognitive outcomes research is the heterogeneous testing used to detect POCD. More than lack of a new nomenclature, there is a lack of uniform testing and a diagnostic consensus guideline. Different research groups around the world use different test methods at different time point. I understand that you test for POCD at 6 weeks and 4.5 months due to the timing patient visits that are already planned postoperatively in the orthopedics clinic. In past studies, neuropsychological testing was more commonly administered at 1 week, 3 months, or 1 year. Therefore, it may be somewhat difficult to compare the results of study to the existing literature. Please also discuss this limitation. The present study is set to investigate potential risk factors for POD or POCD that were not previously investigated. I do not entirely agree with this statement in the description of strengths. This is probably true in the very specific patient population the authors chose to study (elective THA and TKA); however, most of the predictors have been studied in other populations (namely cardiac surgery). Please avoid describing your sample as the "lower extremity joint population". This would be close to 8 billion potential study participants, counting humans alone… In addition, "lower extremity joint population" is not a procedure. Throughout the manuscript, please change "gender" to "sex". Gender is a social construct that refers to an individual's identity. Sex is the biological construct. In the introduction, you may have confounded the incidences of POCD after mayor non-cardiac surgery found in the ISPOCD study: it is 26% at 1 week and 10% at 3 months. POCD is virtually non-existent at 1 year; in these cases, one would have to look for other causes of cognitive decline than surgery and anesthesia, such as idiopathic dementia.

	The paragraph on neuropsychological assessment battery used in this study located at the end of the introduction better belongs to the study methodology section. Some of the information given in the introduction also better suits the discussion section. Please tone down the conclusions that you expect to obtain from your study in the last paragraph of the introduction. This goes hand-in-hand with more general considerations for the choice of the neuropsychological assessment battery used to measure POCD in this study. The CogState Brief Battery (CBB) is one of many research tools, but a relatively new commercial product. The CBB tool is appealing because of the computerized, somewhat self-administered, features. However, its place in postoperative cognitive outcomes research is not yet well established. Like many other neuropsychological assessment batteries, CBB was developed to aid the diagnosis of mild and major neurocognitive disorders, not POCD. CBB might not assess all relevant cognitive domains that are relevant in POCD. Moreover, some changes in cognition attributed to POCD are very subtle and may require more in-depth testing. Has CBB been validated in surgical patients? Are there normative data for CBB? If yes, please reference appropiately. In addition, it seems that CBB total scores are demographically adjusted to age and sex, and not education. From the ISPOCD study, we know that little education is an important risk factor for POCD. Education might not be normally distributed across age and sex categories; results of this study should be interpreted in the light of this limitation. In contrast to POCD, previous studies have suggested that anesthetic technique may influence the occurrence of POD after surgery. If you use supplemental sedation during spinal anesthesia in the majority of your patients, you may find a significant effect depending on the depth of sedation monitored by the bi-spectral index. The use of light propofol sedation decreases the prevalence of POD by 50% compared with deep sedation. [2] The Ramsey Sedation Scale correlates with the BIS; however, varying levels of sedation in specific patient subgroups (i.e., the elderly are more susceptible to propofol over-dosing) may introduce confounders in your analysis. Ideally, you would refrain from using supplemental sedation for study purposes. Moreover, if general anesthesia is a rare choice in your patients, you may consider to exclude individuals having the procedure under general anesthesia altogether. The primary outcome measure of this study is the incidence of postoperative major NCD at 4.5 months, defined as a CBB score <80 (points?) in any of the 4 tasks. Please include the reference corresponding to this definition. In addition, if a CBB score of <80 indicates major NCD (2 standard deviations lower than the normative population (in other words: dementia)), I suspect that only few patients will score this low after surgery. You are, therefore, likely to end up with an incidence of lower than 10% in this population. Instead of using cut-off scores for the primary outcome measure, you may want to consider a sliding scale of pre- to postoperative changes in cognition (cognitive trajectory over time). In addition, a

	non-surgical control group would have been ideal to adjust for changes in cognition that are attributable to normal aging. However, you may compensate this by using a neuropsychological assessment battery that is adjusted for demographic variables (like the CBB). May I recommend the review article by Nadelson and colleagues, which suggests some improvements in POCD research? [3] The author base the sample size on the reported incidence of major NCD 3 months after major elective orthopedic surgery (10%). Where is this number reported? I would expect a dropout rate higher that the loss to follow-up due to the overall perioperative patient mortality (1%). Other studies on POCD commonly report higher dropout rates (up to 20%) due to withdrawal of consent, logistic problems, etc. Table 1: Please provide a rationale for excluding patients with pre-existing severe cognitive impairment. These particular patients are at very high risk for POD and POCD. What happens to CBB assessment data of patients with POD (CAM positive) in the first 3 days after surgery? A delirious patient is unlikely to perform appropriately in CBB assessments. In my opinion, CBB data of these patients should be excluded from analysis. Please provide a more extensive discussion of the protocol. In summary, this research protocol has many merits and touches a new population to be studied. Without any doubt, the authors able to root their research in a unique institutional setting and obtain a sample size that is unparalleled in monocentric studies on postoperative cognitive outcomes. I wish the investigators best of luck with the ongoing trial! 1. Inouye, S.K., et al., A multicomponent intervention to prevent delirium in hospitalized older patients. N Engl J Med, 1999. 340(9): p. 669-76. 2. Sieber, F.E., et al., Sedation depth during spinal anesthesia and the development of postoperative delirium in elderly patients undergoing hip fracture repair. Mayo Clin Proc, 2010. 85(1): p. 18-26. 3. Nadelson, M.R., R.D. Sanders, and M.S. Avidan, Perioperative cognitive trajectory in adults. Br J Anaesth, 2014. 112(3): p. 440-51.

REVIEWER	George Djaiani Toronto General Hospital, University of Toronto, Toronto, Canada
REVIEW RETURNED	18-Jul-2018

GENERAL COMMENTS	I would strongly suggest the authors to include baseline and postop assessment of depression. This confounder should be adjusted for in the final analysis. In addition, I would advise to use 'AGE' as a continuous variable in addition to your suggested age-groupings. Finally, I would advise for a multicenter trial to add more generalizability and potentially increase the sample size.

REVIEWER	Lei Zhang M.D. PH.D. The third affiliated hospital of Wenzhou Medical University, China.
REVIEW RETURNED	23-Jul-2018

GENERAL COMMENTS	The manuscript aimed to the investigate the risk factors for postoperative cognitive deficits after hip and knee arthroplasty. The topic is valuable and the methodology is valid. However, several issues should be modified before acceptance: 1.More exclusion criteria are required to convince the readers to get precise results. ie: patients with delirium before surgery should be excluded, one-staged bilateral hip or knee arthroplasty should be excluded. 2.The authors used 3D-CAM and CCB to assess PD and NCD. Why did not use DSM-5. What is the Interobserver and intraobserver Reliability of these tools. Who performed the assessments of PD and NCD? 3.The hematological variables might be the risk factors for PD such as PaO2, hemoglobin. The protocol did not involve those variables, please state the reason.

VERSION 1 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

Reviewer: 1

1. Please limit the number of outcome definitions to a strict minimum. While the title…
The title has been amended to post-operative cognitive changes to encompass POD and POCD. Mild/major NCD have been reverted to MCI and POCD respectively. The introduction does maintain reference to the recently published (BJA November issue) recommendations on nomenclature.

2. In the abstract and further on in the manuscript (introduction), the authors state …
This item has been addressed. We now refer to non-pharmacologic strategies to reduce the incidence of PD. Indeed, these interventions are actually part of our institutional standard of care for post-operative patients.

3. The authors also state: "The incidence of neurocognitive disorders has not been…
Acknowledged. The manuscript has been amended (P5) to highlight the PD/POCD literature in hip fracture/arthroplasty and that there are several deficiencies (eg. utilizing MMSE, assessing 1 week post op, new references 14-18) that indicate the need for further study.

4. One bigger problem with postoperative cognitive outcomes …
This item has been addressed (P11).

5. The present study is set to investigate potential risk factors for POD or POCD …
The strength and limitations section has been modified.

6. Please avoid describing your sample as the "lower extremity joint population" …
This term has been changed to total hip and knee arthroplasty (THA/TKA) throughout the manuscript.

7. Throughout the manuscript, please change "gender" to "sex". Gender is a social construct that refers to an individual's identity. Sex is the biological construct.
The appropriate changes have been made.

8. In the introduction, you may have confounded the incidences of POCD after mayor non-cardiac surgery found in the ISPOCD study: it is 26% at 1 week and 10% at 3 months. POCD is virtually non-existent at 1 year; in these cases, one would have to look for other causes of cognitive decline than surgery and anesthesia, such as idiopathic dementia.
Thank you for the comment. The specific sentence in question on P4 involves merger of data from 3 separate studies creating some confusion. The data has been clarified. The ISPOCD group (Moller 1998, Rasmussen 2003) and Monk (2008) demonstrated POCD in ~10% of individual at the end of the 3-month study period. Ballard, Abildstrom, and McDonagh demonstrated an incidence of 11.2, 10.4, and 46.1% respectively. We agree that the longer the duration after surgery, the influence of other causes of normal cognitive decline increases and complicates assessments.

9. The paragraph on neuropsychological assessment battery used in this study located at the end of the introduction better belongs to the study methodology section. Some of the information given in the introduction also better suits the discussion section.
This item has been addressed.

10. Please tone down the conclusions that you expect to obtain from your study in the last paragraph of the …
Thank you. The conclusions have been modified. The status of CBB has been clarified with appropriate changes to the manuscript. The paragraph describing CBB (moved from Introduction to Methods – page 8) has been clarified and now indicated, with references, that the CBB is validated against commonly used neuropsychological tests in multiple non-operative scenarios (ref 24 and 25) and in the perioperative period (ref 26 and 27). The CBB does test the same cognitive domains tested by the ISPOCD group and Monk – psychomotor function, attention, learning/memory, and working memory. References 24 to 27 demonstrate that CBB has good intraclass correlation compared to traditional tests and that it was possibly more sensitive in the perioperative period identifying several individuals that traditional tests deemed normal. We have included in the discussion that CBB is one of several computer based cognitive tests, but that this study is utilizing one with perioperative validity.

11. In addition, it seems that CBB total scores are demographically adjusted to age and sex, and not education. From the ISPOCD …
Thank you for the comment. Our logistic regression model already includes participants' highest education status as an ordinal variable.

12. In contrast to POCD, previous studies have suggested that anesthetic …
The reviewer brings up several valid points and these were when the study was designed. The literature regarding the influence of anesthetic technique is somewhat conflicting. Ballard et al (ref 6) demonstrated that anesthetic depth (BIS) during GA affected POCD even at 1 year. However, Evered et al (BJA 2011) determined that the type of anesthetic did not influence the incidence of POCD. Our thoughts are that anesthetic modality may be an influence – specifically the significantly reduced doses associated with sedation in the context of regional anesthesia compared to that required for general anesthesia may be protective. However, the work by Evered et al is robust and therefore we elected to examine any association including the use of GA (approximately 20 individuals at this time).

Ideally, we would have preferred to refrain from supplemental sedation; however, the vast majority of our patients under neuraxial anesthesia specifically request sedation. While perhaps accentuating any possible differences between GA and RA, to significantly deviate from standard practice, would however make our results less reflective of typical anesthetic practice and less externally valid. Additionally, it would risk significantly reducing the number of consenting participants. Our typical propofol infusion rates are 25-50 ug/kg/min, still significantly less than that required for general anesthesia in the absence of neuraxial block.

13. The primary outcome measure of this study is the incidence of postoperative major NCD at 4.5 months, defined as a CBB score <80 (points?) in any of the 4 tasks. Please include the reference corresponding to this definition. In addition, if a CBB score of <80 indicates major NCD (2 standard deviations lower than the normative population (in other words: dementia)), I suspect that only few patients will score this low after surgery. You are, therefore, likely to end up with an incidence of lower than 10% in this population.

Thank you. The 2 SD cutoff corresponds to the cutoffs suggested by Evered et al (ref 2) as well as those used in ISPOCD and by Monk (although here, either a 2SD drop in an individual test or summative 2SD drop across the 7 tests was used). The literature indicates the sensitivity of the CBB is at least equivalent if not better than traditional neuropsychological tests.[1-3] We are currently unaware of any studies where one test at 2SD below diagnoses or equates with dementia although if they do exist then we would have to re-evaluate our cutoffs.

As such there is no specific reference where 1 test at 2SD below specifically means POCD, however Ingraham et al provides evidence that as the number of tests increase, the probability of making a type I error also increases.[4] Utilizing 1 test at 2SD indicates that Type I error would be at approximately 5%. We chose this as a reasonably conservative estimate of sensitivity. With the incidence of POCD in the literature ranging from a little 10% to as high as 46% (from 3 months to 1 year) in studies using the 2SD criteria we hope that 10% is a reasonable, educated, conservative estimate of the incidence for our study. However, we do acknowledge that if we are too conservative with cutoffs for POCD the incidence may be lower. Nonetheless, as we are specifically collecting information on individuals who are normal, mildly reduced, and significantly reduced post-operatively. Thus, we will generate valuable data from which definitions can be further refined.

14. Instead of using cut-off scores for the primary outcome measure…

Thank you for the comment. We completely agree that Nadelson et al is essential reading for POCD research and indeed it is this very manuscript in its draft form and from personal conversations with Dr. Avidan that informed several of the specific choices made in the design of this protocol.

Nadelson et al discuss six major limitations of POCD research. The effects of aging, critical illness after surgery, underlying comorbidities, lack of a consensus definition of POCD, potential inappropriate (ie. excess) adjustment for learning effects from repeated cognitive testing, and lack of knowledge surrounding pre-operative cognitive trajectories.

The study design or use of CBB addresses five of these factors. Specifically, the CBB normalizes to a large sample population of non-surgical age/sex matched (up to month and year of birth) controls. This control population is growing progressively as increasing numbers of individuals perform assessments. This addresses the effects of aging and removes the need for adjustment secondary to 'learning effects'. The study design incorporates into the analysis comorbidities that influence cognition and post-operative complications. The definition of POCD and MCI, 2SD and between 1-2SD below controls respectively, adheres to the recently published recommendations for nomenclature by Evered et al corresponding to mild and major NCD. Acknowledged is that widespread uptake of these newly published definitions is just beginning. The nature of recruiting patients into the study 2-4 weeks before surgery in preoperative clinic does not allow for establishing pre-operative trajectories.

Initial plans for this study involved an analysis of CBB data both as a binary outcome (ie. POCD yes or no) and continuous/sliding scale outcome. However, discussion with CogState on the specific results produced by the CBB indicated that interpreting test results as a continuous outcome were not feasible. Specifically, the results are only intended to provide an ordinal classification (dysfunction, mild impairment, within normal range). A score going from 125 to 100 could not be interpreted as a 20% drop in function, only that both were in the normal range (>90).

15. The authors base the sample size on the reported incidence of major NCD 3 months after major elective orthopedic surgery (10%). Where is this number reported?

The sentence has been amended to '10% after major elective surgery'. Moller, Rasmussen, Monk report an incidence of approximately 10% (at 3 months) after major elective surgery while Ballard reported an incidence of 11.2% at 1 year after major elective orthopedic surgery. Because the reported estimates of POCD incidence at 1 year are highly variable, the sample size was based on the more conservative 3-month incidence.

16. I would expect a dropout rate higher that the loss to follow-up due to the overall perioperative patient mortality (1%). Other studies on POCD commonly report higher dropout rates (up to 20%) due to withdrawal of consent, logistic problems, etc.
Thank you. We did not mean to suggest that we only expected loss of follow-up of 1% due to perioperative mortality. Rather that 1% is the expected rate that we would not specifically be able to even attempt to follow-up because of perioperative mortality. Indeed, while preparing this manuscript, our pilot study undertaken over 3 months suggested we would have a loss to follow-up rate just under 20%. As we have progressed (273 participants completing the 4.5-month follow-up) with 188 competed surgery and in the progress of completing follow-up, our 4.5-month success is at 82%. Our intention is to have 600 individuals complete the primary outcome of 4.5-month cognitive test. We anticipate that greater than 600 will need to be recruited as we currently have slightly more than 80% of patients achieving the 4.5-month follow-up.

17. Table 1: Please provide a rationale for excluding patients with pre-existing severe cognitive impairment. These particular patients are at very high risk for POD and POCD.
Thank you for the comment. Our primary purpose is to assess the incidence and risk factors for POCD with it defined as at least 1 domain scoring in the severe impairment range (ie. > 2SD). We are excluding those patients who have this pre-operatively (to date none among 544 consented) because they already would be classified as already having the primary outcome of interest. By including them, we would not be able to properly assess risk factors for *developing* POCD. Similarly, while it does predict PD, the purpose is not to examine risk factors for PD, but to determine if PD is predictive of POCD.

18. What happens to CBB assessment data of patients with POD (CAM positive) in the first 3 days after surgery? A delirious patient is unlikely to perform appropriately in CBB assessments. In my opinion, CBB data of these patients should be excluded from analysis.
The in-hospital CBB data of those also 3D-CAM positive are not included in the analysis per se. We agree that CBB data of participants that are acutely delirious are suspect.

19. Please provide a more extensive discussion of the protocol.
This item has been addressed.

Reviewer: 2
1. I would strongly suggest the authors to include baseline and postop assessment of depression. This confounder should be adjusted for in the final analysis.
Thank you for the comment. We completely agree that depression can be a confounder are excluding individuals who have been with diagnosed depression (Table 2). Unfortunately, we have not included assessments for depression post-operatively. Currently, we have had 273 individuals complete the primary 4.5 month CBB and entire study protocol with another 183 in progress compared to approximately 100 complete at the time of initial submission in 05/2018. Currently, it is not feasible to obtain mood data from a logistic standpoint and this will be acknowledged in the discussion. However, going forward our future studies all include pre- and post-operative mood assessments.

1. In addition, I would advise to use 'AGE' as a continuous variable in addition to your suggested age-groupings.
Age is being coded as deciles only for presentation of demographics. For the purpose of analysis, we agree age would be best utilized as a continuous variable. We have not specifically included age in

the analysis because one of the advantages of the CBB is that subjects are normalized to age and sex matched controls in the general population. The results of the CBB therefore have age taken into account allowing us to utilize it as a variable in the analysis, but assess other associations.

2. **Finally, I would advise for a multicenter trial to add more generalizability and potentially increase the sample size.**

Thank you for the comment. We agree and we will explore options to add partners at other institutions.

Reviewer: 3

1. More exclusion criteria are required to convince the readers to get precise results. ie: patients with delirium before surgery should be excluded, one-staged bilateral hip or knee arthroplasty should be excluded.

Thank you for the comment. Participants with pre-operative delirium are excluded. This was an error on our part in mistakenly not listing it and it is now listed in Table 1. With regards to staged bilateral procedures, our institutional practice is to separate bilateral procedures by at least 6 months therefore there is no planned elective surgical intervention during the study assessment period.

2. The authors used 3D-CAM and CCB to assess PD and NCD. Why did not use DSM-5. What is the Interobserver and intraobserver Reliability of these tools. Who performed the assessments of PD and NCD?

Thank you for the comment.

a. PD – all 3D-CAM assessments are conducted by 2 trained research assistants. These research assistants were trained by the first 2 authors (SC and SA) who were trained in small group sessions including multiple scored practice assessments with feedback by Dr. S.K. Inouye. The identical modules that SC and SA were trained on were utilized for the research assistants.
b. NCD (POCD) – the CBB is a computer based program which study participants complete in the presence of the research assistant. The research assistant loads the program for the participant. The participant then completes a short practice program to that is delivered by the software prior to conducting the actual assessment. As such, the inter/intra-observer reliability is essentially 1.0 as the software program is the 'observer'.

3.The hematological variables might be the risk factors for PD such as PaO2, hemoglobin. The protocol did not involve those variables, please state the reason.

Thank you. We agree that these factors may contribute to PD. The primary outcome of our study is POCD and not to explore risk factors for PD. PD is being collected to 1 – establish the incidence in the THA/TKA population; 2 – then use this in the model as a predictor for POCD.

1. Darby DG, Pietrzak RH, Fredrickson J, et al. Intraindividual cognitive decline using a brief computerized cognitive screening test. *Alzheimers Dement* 2012;8(2):95-104. doi: 10.1016/j.jalz.2010.12.009.
2. Maruff P, Lim YY, Darby D, et al. Clinical utility of the cogstate brief battery in identifying cognitive impairment in mild cognitive impairment and Alzheimer's disease. *BMC psychology* 2013;1(1):30. doi: 10.1186/2050-7283-1-30 [published Online First: 2013/01/01]
3. Silbert BS, Maruff P, Evered LA, et al. Detection of cognitive decline after coronary surgery: a comparison of computerized and conventional tests. *Br J Anaesth* 2004;92(6):814-20. Epub 2004 Apr 2.
4. Ingraham LJ, Aiken CB. An Empiral Approach to Determeining Criteria for Abnormality in Test Batteries with Multiple Measures. *Neuropsychology* 1996;10(1):120-24.

VERSION 2 – REVIEW

REVIEWER	Nicolai Goettel, MD, DESA, EDIC Department of Anesthesia, Surgical Intensive Care, Prehospital Emergency Medicine and Pain Therapy, University Hospital Basel, University of Basel, Switzerland
REVIEW RETURNED	21-Dec-2018

GENERAL COMMENTS	All comments have been appropriately addressed in this revision of the manuscript. I wish the authors best of luck with the ongoing trial, and I am looking forward to the results.

REVIEWER	Lei Zhang The third affiliated hospital of WenZhou Medical University, China
REVIEW RETURNED	22-Dec-2018

GENERAL COMMENTS	I think that the manuscript is acceptable for publication after revision.