PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Minimizing ICU Neurological Dysfunction with Dexmedetomidine-induced Sleep (MINDDS): protocol for a randomized, double blind, parallel-arm, placebo-controlled trial
AUTHORS	Shelton, Kenneth; Qu, Jason; Bilotta, Federico; Brown, Emery; Cudemus, Gaston; D'Alessandro, David; Deng, Hao; DiBiasio, Alan; Gitlin, Jacob; Hahm, Eunice; Hobbs, Lauren; Houle, Timothy T.; Ibala, Reine; Loggia, Marco; Pavone, Kara; Shaefi, Shahzad; Tolis, George; Westover, Brandon; Akeju, Oluwaseun

VERSION 1 – REVIEW

REVIEWER	George Djaiani Toronto General Hospital, Toronto, Canada
REVIEW RETURNED	09-Nov-2017

GENERAL COMMENTS	I feel that the expected delirium rate in suggested patient population is too high (48%). Furthermore, did the authors consider including a third group of patients with a continuous infusion of dexmedetomidine overnight. It is also unclear if the primary objective is to reduce delirium rates or assess the sleep patterns.

REVIEWER	Michael Avidan Washington University School of Medicine, St. Louis, Missouri, USA
REVIEW RETURNED	12-Nov-2017

GENERAL COMMENTS	Overall this is a well-designed protocol for an important clinical trial to determine whether dexmedetomidine administered to promote physiological sleep after cardiac surgery can prevent delirium and improve cognitive and other outcomes. The study design is well conceptualized and conveyed. I have minor comments for the investigators' consideration. 1. The investigators state, "To ensure that the study is appropriately powered for the primary outcome measure, patients will be recruited and randomized into the study until 300 patients receive the study intervention on post-operative day 0." This is a good approach, but it is implied that (some) enrolled patients will not receive the study intervention. 2. To state that delirium is a leading 'cause' of mortality is over-interpreting the current evidence. To date, we do not know for certain whether delirium reflects morbidity, or whether it independently drives poor outcomes. 3. Sleep deprivation precedes the onset of delirium in (some) patients. The word 'some' is missing in the manuscript. 4. The problem with screening patients with the 3D-CAM and

	then diagnosing patients postoperatively with the long CAM is that comparing with baseline performance is an important component in conducting the long CAM (e.g., in judging acute change or new onset inattention). This will be difficult absent a baseline long CAM. 5. Most (or many) extubated patients will stay in the CSICU only for one night, suggesting that many patients will have the intervention only for a single night. 6. The major weakness with this study is the sample size calculation for the following reasons: a. The primary outcome is the incidence of delirium only on POD-1. This is likely to be much lower than 48%. At our institution, the incidence of delirium following cardiac surgery is about 25%. Even if it is higher than this (e.g., 50%) at the MGH, this is a likely to be a cumulative incidence over several days, and not just on POD-1. b. The way this study is designed (patients who are intubated for >12 hours on the ICU are dropped) will predictably exclude patients who are likely to become delirious, and will therefore probably result in a lower than predicted delirium incidence. c. The effect size is ambitious, which increases the likelihood of a 'false negative' finding. d. There is a strong suggestion that studies should be powered for smaller 'p values' (e.g., P<0.005). Therefore, even if this study were to be positive, it might be reasonably interpreted as providing suggestive rather than compelling evidence. (Obviously this would depend on the effect size and precision.) 7. Why is there no sample size calculation for any of the secondary outcomes? 8. The intervention will make blinding difficult. Patients might 'know' if they receive the intervention, and could communicate this to investigators. 9. A major potential confound in this study is pain. It is possible that the intervention will decrease pain or decrease opioid requirement. Either of these (mechanisms) could decrease delirium incidence. It is good that the investigators plan to account for these variables in their regression analyses. 10. One of the mechanisms for discontinuation from the trial is "voluntary discontinuation by the patient." But this is a major potential confounder and problem. What if a patient is approached on POD-1, and they say, "Leave me alone, I do not want to answer any of your questions. I no longer trust your research." How will you know whether they are making an informed decision or if they are delirious with paranoid delusions? This is a challenge and a dilemma when conducting research into delirium. 11. How will the investigators assess delirium when patients are non-compliant with the long CAM (e.g., a patient who says, "Sorry I am in too much pain at the moment to answer your questions.)? 12. The DSMB should only consider early termination for harm from the intervention, not from benefit. 13. There is no methodological elaboration in the protocol regarding EEG dynamics as an outcome. 14. Aims 2 and 3 of the grant (which was provided as an appendix) do not appear to be elaborated in the protocol. They are discussed in the grant application. Minor comments: 1. "patterns the activity patterns" should be re-written more clearly. 2. "The maximum dexmedetomidine dose that will be administered is 80 mcg." I think that the investigators mean on any one occasion.

	3. Can patients receive clonidine on the ICU? 4. This wording does not make the meaning easy to understand, "ICU and hospital delirium/coma-free days assessed twice daily through postoperative day 3, or up until postoperative day 7 or discharge for patients who are delirious beyond postoperative day 5." 5. It is not clear what the following means as an outcome: "Peri-operative EEG dynamics of delirium" 6. It is not clear from the methods how post-hospital discharge mortality will be ascertained. If a patient is dead, who will answer the phone or respond to the survey?

VERSION 1 – AUTHOR RESPONSE

Reviewer 1:
I feel that the expected delirium rate in suggested patient population is too high (48%). Furthermore, did the authors consider including a third group of patients with a continuous infusion of dexmedetomidine overnight. It is also unclear if the primary objective is to reduce delirium rates or assess the sleep patterns.
Response
We thank the reviewer for his comments. We have modified our expected delirium rate on POD 1 to 15%. This number, which is similar to the rate reported by Su et al. (Lancet, 2016), is based on data from our CSICU.
We agree with the reviewer that a third group of patients, with a continuous infusion of dexmedetomidine administered to approximate N2 sleep, would be informative to study. We intend, in future studies, to characterize the putative benefits of continuous vs. single bolus dosing paradigms of dexmedetomidine.
The primary objective of our study is to investigate whether a single nighttime bolus of dexmedetomidine is associated with a reduced incidence of delirium. Our hypothesis is that improved sleep patterns will correlate with decreased incidence of delirium. We have now made this more explicit in our introduction section:
"The primary objective of the MINDDS (Minimizing ICU Neurological Dysfunction with Dexmedetomidine-induced Sleep) trial is to evaluate dexmedetomidine-induced sleep as a pharmacological preventative strategy for delirium, and to characterize the impact of delirium prevention on patient-centered outcomes such as functional recovery."

Reviewer 2:
Overall this is a well-designed protocol for an important clinical trial to determine whether dexmedetomidine administered to promote physiological sleep after cardiac surgery can prevent delirium and improve cognitive and other outcomes. The study design is well conceptualized and conveyed. I have minor comments for the investigators' consideration.

Response
We thank the reviewer for his favorable review of our manuscript.

1. The investigators state, "To ensure that the study is appropriately powered for the primary outcome measure, patients will be recruited and randomized into the study until 300 patients receive the study intervention on post-operative day 0." This is a good approach, but it is implied that (some) enrolled patients will not receive the study intervention.

Response

The reviewer correctly infers that some enrolled patients will not receive the study medication on POD 0 (i.e. prolonged surgical case), and that not accounting for this variable could potentially lead to an underpowered study (primary outcome measure; incidence of delirium on POD 1). We chose this approach because we could not accurately predict the percentage of patients that will not receive the study intervention on POD 0.

2. To state that delirium is a leading 'cause' of mortality is over-interpreting the current evidence. To date, we do not know for certain whether delirium reflects morbidity, or whether it independently drives poor outcomes.

Response
We have revised the manuscript as follows:

"Although previously reported associations between delirium and increased mortality are debatable, delirium remains a leading cause of preventable morbidity in hospitalized elderly patients."

3. Sleep deprivation precedes the onset of delirium in (some) patients. The word 'some' is missing in the manuscript.

Response
We have revised the manuscript.

4. The problem with screening patients with the 3D-CAM and then diagnosing patients postoperatively with the long CAM is that comparing with baseline performance is an important component in conducting the long CAM (e.g., in judging acute change or new onset inattention). This will be difficult absent a baseline long CAM.

Response
The reviewer raises a very important point and practical challenge (i.e. obtaining appropriate baseline data to enable a principled comparison). During the MINDDS baseline study visit, we obtain both the 3D-CAM and T-MoCA (abbreviated MoCA) in each study patient. Although the long-CAM is not conducted during this visit, both the 3D-CAM and abbreviated MoCA capture all the cognitive domains that are tested by the long-CAM. We us 3D-CAM/abbreviated MoCA to long-CAM conversion. We now make this fact more explicit in our study protocol:
"A combination of the 3D-CAM and the abbreviated Montreal cognitive assessment conducted at baseline includes all the cognitive domains that are captured by the long-CAM. Thus, long-CAM results will be benchmarked against these baseline data for delirium scoring (i.e. change from baseline)."

5. Most (or many) extubated patients will stay in the CSICU only for one night, suggesting that many patients will have the intervention only for a single night.

Response
The reviewer correctly infers that many enrolled patients will receive study intervention for a single night. This is why we have powered our study for a POD 1 primary outcome. We note that a single intervention may result in a clinically meaningful reduction in the incidence of delirium up until POD 7 as reported by Su et al. (Lancet, 2016). Thus, we intend to also study the effect of our intervention up until POD 3. Although the mechanism for this prolonged effect of dexmedetomidine is not clear, it is conceivable that dexmedetomidine helps to regularize post-surgical circadian cycle disruption and/or reduce the impact of acute nociceptive pain on developing delirium.

6. The major weakness with this study is the sample size calculation for the following reasons:

a. The primary outcome is the incidence of delirium only on POD-1. This is likely to be much lower than 48%. At our institution, the incidence of delirium following cardiac surgery is about 25%. Even if it is higher than this (e.g., 50%) at the MGH, this is a likely to be a cumulative incidence over several days, and not just on POD-1.
b. The way this study is designed (patients who are intubated for >12 hours on the ICU are dropped) will predictably exclude patients who are likely to become delirious, and will therefore probably result in a lower than predicted delirium incidence.
c. The effect size is ambitious, which increases the likelihood of a 'false negative' finding.
d. There is a strong suggestion that studies should be powered for smaller 'p values' (e.g., P<0.005). Therefore, even if this study were to be positive, it might be reasonably interpreted as providing suggestive rather than compelling evidence. (Obviously this would depend on the effect size and precision.)

Response
We have modified our expected delirium rate on POD 1, based on institutional data in our CSICU, to 15%. We note that this rate is similar to the POD1 delirium rate reported by Su et al (Lancet, 2016). Similarly, based on data reported by Su et al (Lancet, 2016), we have reduced our expected effect size of 15% to an estimated effect size of 10%, and increased our power from 80% to 90%. The combination of a: 1) a reduced incidence of delirium; 2) a reduced effect size; and, 3) an increased power results in an estimated sample size of 370 patients. We have updated our IRB and clinicaltrials.gov registration to reflect these changes.
We agree with the reviewer that reproducibility and validity of research findings may be improved by smaller P values. Rather than powering the present study for a smaller P value, we intend to explicitly state the false-positive risks that are associated with P values emanating from our data analyses (Five ways to fix statistics, Nature 2017).
7. Why is there no sample size calculation for any of the secondary outcomes?
Response
We intend for our secondary endpoints to be hypothesis generating, such that effects or trends observed with respect to secondary outcomes would be confirmed through a properly designed clinical trial. Following the notion that discussion of power have a place in reports of study results (Medical Uses of Statistics; John C Bailar III and David C Hoaglin), we will report the power associated with our secondary outcomes to facilitate proper weighing of negative results.

8. The intervention will make blinding difficult. Patients might 'know' if they receive the intervention, and could communicate this to investigators.
Response
We recognize the potential for unblinding and bias i.e. patients reporting that they slept well due to subjective assessment of sleep quality. However, the subjective nature of our delirium assessments (and secondary outcome measures) coupled with detailed long-CAM assessment notes that will be assessed by our data adjudication committee, are expected to significantly reduce the effect of bias in our study.

9. A major potential confound in this study is pain. It is possible that the intervention will decrease pain or decrease opioid requirement. Either of these (mechanisms) could decrease delirium incidence. It is good that the investigators plan to account for these variables in their regression analyses.
Response
We agree with the reviewer.

10. One of the mechanisms for discontinuation from the trial is "voluntary discontinuation by the patient." But this is a major potential confounder and problem. What if a patient is approached on POD-1, and they say, "Leave me alone, I do not want to answer any of your questions. I no longer trust your research." How will you know whether they are making an informed decision or if they are

delirious with paranoid delusions? This is a challenge and a dilemma when conducting research into delirium.

Response

The reviewer raises a very important concern that may significantly confound study results. We hope to mitigate this concern by re-approaching patients within 8 - 24 hours after withdrawal to confirm that they would like to be discontinued from the study. Because delirium is an acute, fluctuating condition, this follow-up measure increases the likelihood that the patient is being approached in a non-delirious state and is making an informed decision to be discontinued from the study. We have now made this detail explicit in our revision.

"Patients who elect to withdraw from the study during their hospital stay will be re-approached by the study team within 8-24 hours of study withdrawal. The study team member will elicit the reason for study discontinuation and confirm the withdrawal decision. This visit serves to ensure that the withdrawal decision was made during an informed and non-delirious cognitive state."

11. How will the investigators assess delirium when patients are non-compliant with the long CAM (e.g., a patient who says, "Sorry I am in too much pain at the moment to answer your questions."?

Response

When patients struggle to complete an assessment due to pain or discomfort, delirium assessors will complete only the long-CAM elements necessary to dispel the presence of delirium (i.e. memory, pain and sleep will not be completed; attention – days of the week backwards will be prioritized; disorganized thinking – to be assessed from patient interview observation; altered level of consciousness – to be assessed from patient interview observation; acute onset – to be gauged from symptom interview). Patients who cannot complete an assessment (i.e. pain, clinical intervention) will be re-approached several hours later when they are feeling better. Data points that are completely missing data will be coded as delirium in sensitivity analyses. We have now made this detail explicit in our revision.

"In the event that a patient finds it difficult to complete an assessment (i.e. pain, clinical intervention), only the long-CAM domains necessary to dispel the presence of delirium will be assessed (i.e. acute onset, inattention, disorganized thinking and altered level of consciousness). Patients who cannot complete this shortened assessment will be re-approached several hours later."

12. The DSMB should only consider early termination for harm from the intervention, not from benefit.

Response

We thank the reviewer. We have made this detail explicit in our DSMB charter and protocol.

"The DSMB is comprised of independent, multidisciplinary experts who will make recommendations regarding the continuation, modification, or termination of the trial for harm from intervention."

13. There is no methodological elaboration in the protocol regarding EEG dynamics as an outcome.

Response

We apologize. We have revised the protocol to clearly state that the EEG analyses will be performed in separate sub-studies.

"In separate sub-studies, risk factors and pathophysiological mechanisms of delirium will be explored using: 1) unbiased serum metabolic, proteomic, and extracellular vesicular profiling; 2) power spectral analyses of intraoperative and CSICU electroencephalogram dynamics; and, 3) integrated positron emission tomography/magnetic resonance imaging of [11C] PBR28."

14. Aims 2 and 3 of the grant (which was provided as an appendix) do not appear to be elaborated in the protocol. They are discussed in the grant application.

Response

We apologize. We have revised the protocol to clearly describe the separate sub-studies that are nested within the MINNDS study.

"In separate sub-studies, risk factors and pathophysiological mechanisms of delirium will be explored using: 1) unbiased serum metabolic, proteomic, and extracellular vesicular profiling; 2) power spectral

analyses of intraoperative and CSICU electroencephalogram dynamics; and, 3) integrated positron emission tomography/magnetic resonance imaging of [11C] PBR28."

Minor comments:

1. "patterns the activity patterns" should be re-written more clearly.

Response

We have removed the second instance of patterns.

2. "The maximum dexmedetomidine dose that will be administered is 80 mcg." I think that the investigators mean on any one occasion.

Response

We have made this important clarification.

3. Can patients receive clonidine on the ICU?

Response:

Medications such as clonidine and dexmedetomidine may increase our study drop-in rates. Similarly, dexmetomidine induced hypotension may increase our dropout rates. Therefore, pain, agitation, and hypotension treatment in MINDDS study patients follows a well defined protocol (the treatment protocol which follows normal hospital practices is also affixed to the entrance to each MINDDS study patient room and was shared via info sessions with CSICU clinical staff):

MINDDS Study Patient
Please check with attending before giving Precedex.
For agitation:
Please alert ICU attending. Please alert ICU attending. Administer 1 – 4mg of intravenous Haldol for symptomatic relief. May repeat twice for a maximum dose of 10 mg. If agitation continues, 20mg of intravenous propofol may be administered for sedation, followed by a propofol infusion at 50mcg/kg/min, titrate to effect.
For hypotension:
Mild to moderate (SBP 90-100mmHg) hypotension: Please alert ICU attending. Start intravenous norepinephrine at 2mcg/min (via central line) and titrate to meet blood pressure goals. If norepinephrine is already being administered, uptitrate incrementally (i.e. 2 mcg/min – 4 mcg/min) until targeted blood pressure goals are met.
Severe(SBP<80): Please alert ICU attending. Administer 500 ml bolus dose of normal saline (0.9%), and 1.6 mcg norepinephrine or 80 mcg phenylephrine. Phenylephrine may be administered via peripheral or central line. Start intravenous norepinephrine at 2mcg/min (via central line) and titrate to meet blood pressure goals. If norepinephrine is already being administered, uptitrate incrementally (i.e. 2 mcg/min – 4 mcg/min) until targeted blood pressure goals are met.
For mild pain:
Please administer 650 mg Tylenol (oral or rectal; ICU and floor) as needed every 6 hours. For moderate pain, please administer 5-10 mg oral oxycodone (ICU and floor) as needed every 4 hours, or 0.25 mg of intravenous dilaudid (ICU) as needed every hour for a maximum of 3 doses. For severe pain, please administer 50-100 mcg intravenous fentanyl (ICU) for a maximum of 5 doses. Please alert ICU/floor attending for non-responsiveness to appropriate pain therapy. Please alert attending in the event intravenous pain medications are warranted post ICU discharge.

4. This wording does not make the meaning easy to understand, "ICU and hospital delirium/coma-free days assessed twice daily through postoperative day 3, or up until postoperative day 7 or discharge for patients who are delirious beyond postoperative day 5."

Response

We have made this change:

“ICU and hospital delirium/coma-free days assessed twice daily until postoperative day 3. Delirious patients will be assessed until postoperative day 5. In the event that delirium does not resolve by postoperative day 5, assessments will continue until postoperative day 7 or hospital discharge.”

5. It is not clear what the following means as an outcome: “Peri-operative EEG dynamics of delirium”

Response
We apologize. We have revised the protocol to more clearly state that the EEG analyses will be performed in separate sub-studies as mentioned in our response to item 13 above.

6. It is not clear from the methods how post-hospital discharge mortality will be ascertained. If a patient is dead, who will answer the phone or respond to the survey?
Response
We apologize. We have added the following:
“Mortality assessed by chart review, and/or elicited from family member during follow-up calls."

Editorial Requests:

1. Please make it clear in the title that this is a study protocol. We suggest: "Minimizing ICU Neurological Dysfunction with Dexmedetomidine-induced Sleep (MINDDS): protocol for a randomized, double blind, parallel-arm, placebo-controlled trial."

Response
We have made this change.

2. Please revise the first two bullet points of the 'Strengths and Limitations' section on page 18 of the pdf. This section should not be a summary of your study. It should contain up to five short bullet points, no longer than one sentence each, that relate specifically to the methods/ design of the study reported (see: http://bmjopen.bmj.com/site/about/guidelines.xhtml#articletypes).

Response
We have made this change.

3. Please remove the 'conclusion' section on page 33 of the pdf. It isn't necessary to include this section.

Response
We have made this change.

4. Along with your revised manuscript, please provide a completed copy of the SPIRIT checklist (http://www.spirit-statement.org/). Please remember to include the relevant page number(s) from the manuscript next to each reporting item or state 'n/a' next to items that are not applicable to your study. For help and guidance completing the checklist see: http://www.bmj.com/content/346/bmj.e7586
Response:
A completed copy of the SPIRIT checklist has been included in this re-submission.

VERSION 2 – REVIEW

REVIEWER	Michael S. Avidan Washington University School of Medicine

	United States
REVIEW RETURNED	12-Dec-2017

GENERAL COMMENTS	Any power or sample size calculation necessitates educated assumptions. The investigators have stated that this study will have 90% power to detect a 10% absolute reduction in delirium incidence (66% relative reduction) with a p value of 0.05. They might consider presenting a power table with various scenarios to help the readers and to aid interpretation of the study. For example the MCID might be much less than 10% ARR. Even a 2% ARR might be clinically important. The investigators could present a table with different effect sizes and perhaps even different p values. They could show how much 'power' the study would have under each assumption.

REVIEWER	George Djaiani Toronto General Hospital, Toronto, Canada
REVIEW RETURNED	12-Dec-2017

GENERAL COMMENTS	I feel that the authors adequately addressed my primary comments and suggestions.

VERSION 2 – AUTHOR RESPONSE

Response to Review #2

Manuscript ID: bmjopen-2017-020316

Manuscript Title: Minimizing ICU Neurological Dysfunction with Dexmedetomidine-induced Sleep (MINDDS): protocol for a randomized, double blind, parallel-arm, placebo-controlled trial

Reviewer 2:

Any power or sample size calculation necessitates educated assumptions. The investigators have stated that this study will have 90% power to detect a 10% absolute reduction in delirium incidence (66% relative reduction) with a p value of 0.05. They might consider presenting a power table with various scenarios to help the readers and to aid interpretation of the study. For example the MCID might be much less than 10% ARR. Even a 2% ARR might be clinically important. The investigators could present a table with different effect sizes and perhaps even different p values. They could show how much 'power' the study would have under each assumption.

Response

Thank you for your thoughtful suggestion. We now report a power tables with different effect sizes (0.14, 0.13, 0.10, 0.05, 0.04, 0.03, 0.02 and 0.01) and different P-value levels (0.8, 0.9). A corresponding comparative plot is presented for more information.

Primary Outcome (proportion experiencing delirium)

Tests for Two Proportions

Numeric Results for Testing Two Proportions using the Z-Test with Unpooled Variance
H0: P1 - P2 = 0. H1: P1 - P2 = D1 ≠ 0.

Target Power	Actual Power*	N1	N2	N	P1	P2	Diff D1	Alpha
0.80	0.80687	56	56	112	0.0100	0.1500	-0.1400	0.0500

0.90	0.90131	74	74	148	0.0100	0.1500	-0.1400	0.0500
0.80	0.80388	69	69	138	0.0200	0.1500	-0.1300	0.0500
0.90	0.90167	92	92	184	0.0200	0.1500	-0.1300	0.0500
0.80	0.80183	138	138	276	0.0500	0.1500	-0.1000	0.0500
0.90	0.90019	184	184	368	0.0500	0.1500	-0.1000	0.0500
0.80	0.80009	683	683	1366	0.1000	0.1500	-0.0500	0.0500
0.90	0.90027	915	915	1830	0.1000	0.1500	-0.0500	0.0500
0.80	0.80010	1106	1106	2212	0.1100	0.1500	-0.0400	0.0500
0.90	0.90015	1481	1481	2962	0.1100	0.1500	-0.0400	0.0500
0.80	0.80003	2033	2033	4066	0.1200	0.1500	-0.0300	0.0500
0.90	0.90006	2722	2722	5444	0.1200	0.1500	-0.0300	0.0500
0.80	0.80008	4722	4722	9444	0.1300	0.1500	-0.0200	0.0500
0.90	0.90004	6321	6321	12642	0.1300	0.1500	-0.0200	0.0500
0.80	0.80001	19458	19458	38916	0.1400	0.1500	-0.0100	0.0500
0.90	0.90000	26048	26048	52096	0.1400	0.1500	-0.0100	0.0500

* Power was computed using the normal approximation method.

Response to Review #2

Manuscript ID: bmjopen-2017-020316

Manuscript Title: Minimizing ICU Neurological Dysfunction with Dexmedetomidine-induced Sleep (MINDDS): protocol for a randomized, double blind, parallel-arm, placebo-controlled trial