PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Alpha-2-adrenergic receptor agonists for the prevention of delirium and cognitive decline after open heart surgery (ALPHA2PREVENT): protocol for a multicentre randomised controlled trial
AUTHORS	Neerland, Bjørn; Busund, Rolf; Haaverstad, Rune; Helbostad, Jorunn; Landsverk, Svein Aslak; Martinaityte, Ieva; Norum, Hilde Margrethe; Ræder, Johan; Selbaek, Geir; Simpson, Melanie R.; Skaar, Elisabeth; Skjærvold, Nils Kristian; Skovlund, Eva; Slooter, Arjen; Svendsen, Øyvind Sverre; Tønnessen, Theis; Wahba, Alexander; Zetterberg, Henrik; Wyller, Torgeir

VERSION 1 – REVIEW

REVIEWER	Choi, Stephen Sunnybrook Health Sciences Center, Anesthesiology From an academic perspective, my work involves perioperative cognitive changes and secondarily delirium.
REVIEW RETURNED	09-Nov-2021

GENERAL COMMENTS	The authors submit a manuscript detailing a protocol that will examine delirium is a primary outcome after cardiac surgery in participants randomized to standard care versus 2 different alpha agonists. The background is well written and justifies the trial. It would be helpful, however, to acknowledge that delirium is multifactorial and the biological basis as to why alpha 2 agonists may be beneficial. What may also be helpful in the background is acknowledgement that the largest trial (ref 33 Turan at el 800 participants) was negative for DEX, but that even included in the meta analysis (ref 27 Li) DEX still demonstrated benefit for delirium. Of note, ref 35 (Cheng et al Anaesthesia 2019) has been retracted and should not be used. THis chagnes the context of the sentence (page 12 L172 in that there is now no evidence for benefit in cardiac surgery. Deiner et al was in non-cardiac surgery as well as a secondary outcome. Methods: Depending on jurisdiction initiation of DEX or clonidine started prior to CPB with a primary outcome of delirium could be considered off-label use which the authors may wish to consider given various journals requirements with regards to registration of off-label uses of medication. The study methodology is well designed. With regards to secondary outcomes - the authors might wish to consider how they will define changes in cognitive function - will they use the Relative Change Index? Will a decline in any of the cognitive tests they list be considered 'cognitive decline'? Does the decline have to reach a specific threshold? I do realize the authors are

	examining trajectories (pre-op to postop month 1 and 6) but then what change in trajectory qualifies as a significant change? I may have missed it, but if not ICU length of stay, hospital length of stay would also be worthwhile secondary outcomes. With regards to sample size, the study has been powered to a placebo delirium of 30%, clonidine 20% (290 per group) then increased another 290 to account for 3 groups. In effect the authors are expecting a 33% effect size with clonidine, 50% with DEX. These are quite large effect sizes for a condition so multifactorial as delirium but in line with meta-analyses. Discussion: Consider rewording the first sentence. The DECADE trial is quite large (800). As the primary outcome is delirium and the study is not adequately powered for cognitive decline (secondary outcome). There is good explanation of the differences in DEX parameters with the DECADE trial. Despite meta-analysis suggesting a 50% effect size for DEX, it is still quite a large expectaion and the limitations should acknowledge that is the effect size is lower, the study may be underpowered.

REVIEWER	Arora, RC University of Manitoba, Surgery
REVIEW RETURNED	20-Nov-2021

GENERAL COMMENTS	Study Setting: Multi-Centre Study Design: RCT P: Adult patient undergoing cardiac surgery I: Dexmedetomidine or Clonidine C: Placebo O (Primary Endpoint): Prevelent delirium to POD#7 Strengths: 1. An important study targeting an important perioperative complication that occurs in at least 1-5 patients following cardiac surgery. 2. Comparing an iv (and more expensive) agent to a i.v/p.o. (lower cost) agent as part of the study design. 3. Inclusion of frailty, cognitive and HRQoL assessments as part of the perioperative evaluation. 4. The use of accelerometers to assist in the determination of delirium motoric subtype. Comments/Concerns: The following comments/questions are seeking clarification on a few issues (separated by section) to further strengthen the manuscript. METHODS: The Authors have chosen to limit the study to those over the age of 70. While in agreement that this would be a higher risk patient population, it may be worthwhile to consider inclusion of patient over the age of 60. METHODS: Patient awaiting in hospital may have different rates of postoperative delirium. Have the Authors considered looking this factor as part of their analysis? METHODS: Please clarify the predicted rates of bradycardia and hypotension associated with i.v. dexmedetomine vs. clonidine. In

	addition, can the Authors provide additional details on the peri-operative teams' ability to stop the drug if bradycardiac or hypotension is encountered (or alternatively, what the algorithm of management would be in these circumstances)? METHODS: The Authors have described the use of the CAM-ICU for the ICU, what tool will be used on the post-operative ward? In addition, can the Authors provide additional details on the timing of the delirium assessments (i.e. time of day) and if this will be standardized across sites. METHODS: Please provide additional details on the frailty testing (and timing) to be undertaken postoperatively (if any are to be investigated). METHODS: Can the Authors if they utilize any enhancing recovery after surgery (ERAS) protocols for their cardiac surgery patients at their centres? METHODS: The Authors have indicated "duration of delirium " (ln 399) as a secondary endpoint. Can the Authors provide a definition of how they will determine an episode of delirium to have ended? STATISTICS: Power analysis: have the Authors factored perioperative mortality in their calculations? STATISTICS: Can the Author provide additional details on the planned modeling of examining the interaction of frailty and the occurrence of delirium? Minor Concerns: 1. Suggest to change the title from "open heart" to "cardiac surgery" as open heart refers to valve operations as the more general term cardiac surgery refers to CABG + valvular surgery. 2. Suggest to change the term "elderly" to "older adult" where used in the manuscript

REVIEWER	Bryson, Gregory University of Ottawa, Anesthesiology and Pain Medicine
REVIEW RETURNED	21-Nov-2021

GENERAL COMMENTS	Thank you for the opportunity to review this protocol for a multicentre, randomized controlled trial evaluating the influence of dexmedetomidine, clonidine, and placebo on the incidence of delirium 7-days following cardiac surgery. My review will reference the SPIRIT statement for the reporting of protocols for randomized controlled trials https://doi.org/10.7326/0003-4819-158-3-201302050-00583. SPIRIT 2. This trial is registered with both EUDRA CT and ClinicalTrials.gov. This manuscript is concordant with the registration on both platforms. SPIRIT 6. The selection of parenteral clonidine as a comparator requires a bit more explanation, at least for North Americans for whom it is not readily available. Similarly, a brief discussion of the discordance between the 12-24 h duration of alpha-2 agonist therapy and the 7-day window for the primary outcome would be welcome.

	SPIRIT 7. I suggest that the hypothesis (hypotheses) be stated as distinct PICO questions and aligned with the analysis plan. SPIRIT 11a. The reader would benefit from a discussion (and reference) attesting to the equipotency of clonidine and dexmedetomidine. While potency regarding delirium prevention is unknown, data attesting to their relative sedative and anti-hypertensive effects. Perhaps some of the Discussion (P23L51 to P24L18) could be moved to Introduction. While the doses of clonidine and dexmedetomidine are similar, in the absence of drug concentration it is unclear how the infusions will be adjusted to ensure masking (particularly for the placebo group). SPIRIT 11b. A more detailed description of the criteria clinicians will use to “decrease, pause or stop administration of study medication” would be welcome. Information in Safety and Adverse Events Management (P20L26) is vague. SPIRIT 12. While the association of frailty and delirium plays a key role in this protocol, it’s the 3rd aim of the study (P6L33), there is little information regarding the measurement of frailty. Rather than drive your reader to the electronic supplement of reference 57, I suggest this be discussed more directly in the protocol. Note that the approach used in reference 57 is idiosyncratic and will be less familiar to the perioperative frailty research community. SPIRIT 14. The sample size estimate quoted on P21L30 suggests the study has been powered to detect an absolute difference in delirium of 10% between placebo (CER 30%) and clonidine (TER 20%). The 300 participant estimate in this two group comparison (I’ve confirmed it assuming a chi-square test) is cloned for the dexmedetomidine group yielding the final sample size of 900. However, the statistical analysis as described on P22L10 “We will thus estimate cumulative incidence by the Kaplan Meier estimator with time to first delirium as the dependent variable and compare time to event curves between treatments by the logrank test” suggests a time to event function and a three group comparison. A dexmedetomidine vs clonidine comparison would appear to be underpowered and no alpha-preserving function has been described. Please clarify and align hypothesis, estimate, and analysis plan. SPIRIT 16. I’m sure it will wash out in a 900-patient trial, but it is curious that “random permuted block sizes of 2 or 4, and stratified according to study centre” have been chosen. One wonders why the block sizes are not multiples of the number of study groups. SPIRIT 18. Operationalizing the DSM-5 criteria is a key feature of this study’s methods. Rather than drive your reader to the protocol for the LUCID study, I suggest you recreate Table 4 from that document in the present manuscript. SPIRIT 20a. The second objective of this study is to determine “the possible effects of dexmedetomidine and clonidine on long-term cognitive trajectories. P10L31” This manuscript should describe how the battery of cognitive tests will be summarized into a single

	assessment of postoperative neurocognitive disorder. Note that training effects and population norms must be accounted for, see https://doi.org/10.1034/j.1399-6576.2001.045003275.x. SPIRIT 21b. Interim analysis, stopping rules, futility analyses, etc are not described. Overall, this is a solid report of the protocol of the ALPHA2PREVENT trial. The clinical question, delirium following cardiac surgery, is of significant importance to both patients and clinicians. The involvement of patient partners in the design of this trial (P25L19) is to be commended. I encourage the investigators to make the data of this trial freely available rather than await a "reasonable request." I practice open peer review, Gregory L Bryson, MD, FRCPC, MSc Associate Professor and Vice Chair Research Department of Anesthesiology and Pain Medicine University of Ottawa

REVIEWER	Yeung, J. University of Birmingham
REVIEW RETURNED	24-Nov-2021

GENERAL COMMENTS	Thank you for opportunity to review this manuscript. My comments below: 1. Please can the authors comment on why the age of included patients are set at 70 and above - seemed overly restrictive? 2. The use of alpha 2 receptor agonists in cardiac patients may run into problems with hypotension and bradycardia. There is mention of adverse events management in the protocol - How will the investigators handle managing potential side effects without the need to unblind every patient who may have bradycardia/hypotension due to surgery rather than trial intervention? 3. Drop out rate is estimated at 5% by investigators and appear a little conservative in a relatively older population having major cardiac surgery. The authors should consider increasing sample size for to account for loss to follow up or drop out to study. 4. The authors should consider including a flow diagram to explain delirium assessment that may explain the stepwise approach more succinctly.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1 Dr. Stephen Choi, Sunnybrook Health Sciences Center Comments to the Author:
The authors submit a manuscript detailing a protocol that will examine delirium is a primary outcome after cardiac surgery in participants randomized to standard care versus 2 different alpha agonists. The background is well written and justifies the trial. It would be helpful, however, to acknowledge that delirium is multifactorial and the biological basis as to why alpha 2 agonists may be beneficial.

We have added in the background, line 163:

"Delirium is multifactorial and relates to both predisposing and to precipitating factors."

Further, we have added, line 171-173:

"It has been hypothesised that dexmedetomidine may reduce postoperative delirium via its sympatholytic, anti-inflammatory and organ-protective effects (Refs Flanders 2019, Sanders 2021)."

What may also be helpful in the background is acknowledgement that the largest trial (ref 33 Turan at el 800 participants) was negative for DEX, but that even included in the meta analysis (ref 27 Li) DEX still demonstrated benefit for delirium.

Thank you for pointing this out. We have edited the text, line 175-180, and added, line 178:

"This meta-analysis even included the largest trial by Turan et al., with 800 participants, that was negative for dexmedetomidine (ref)."

Of note, ref 35 (Cheng et al Anaesthesia 2019) has been retracted and should not be used.
This changes the context of the sentence (page 12 L172 in that there is now no evidence for benefit in cardiac surgery. Deiner et al was in non-cardiac surgery as well as a secondary outcome.

Thank you for bringing this to our attention! We have deleted the reference and changed the manuscript accordingly, line 181-182:

"To the best of our knowledge, effects of dexmedetomidine upon long time cognitive trajectories have so far not been assessed in this patient population."

Methods:
Depending on jurisdiction initiation of DEX or clonidine started prior to CPB with a primary outcome of delirium could be considered off-label use which the authors may wish to consider given various journals requirements with regards to registration of off-label uses of medication.
The study methodology is well designed.

The trial, including off-label use of these drugs as described in the present manuscript, is approved by the Norwegian Medicines Agency. The lack of evidence regarding use of the drugs in such a context is a major reason for us to carry out the RCT. We allow ourselves to leave to the editor whether (s)he wants us to add a sentence about this in the manuscript.

With regards to secondary outcomes - the authors might wish to consider how they will define changes in cognitive function - will they use the Relative Change Index? Will a decline in any of the cognitive tests they list be considered 'cognitive decline'? Does the decline have to reach a specific threshold? I do realize the authors are examining trajectories (pre-op to postop month 1 and 6) but then what change in trajectory qualifies as a significant change? I may have missed it, but if not ICU length of stay, hospital length of stay would also be worthwhile secondary outcomes.

We realise that this was vaguely worded and have clarified the text. We have not planned to merge results from several cognitive tests into one composite score, but to compare changes in results for separate tests from baseline to follow-up across treatment groups. As MoCA is a global cognitive test, we supplement with tests that assess specific cognitive functions in more detail. As these are considered secondary outcomes, we think it is justified to report the results from each of these tests in parallel. We have not defined a threshold, but will compare the changes from baseline to 1 and 6 months between the groups. We have thoroughly considered ICU LOS as well as total LOS as potentially secondary outcomes, but have dropped this possibility since the participating centres have are differently organised regarding division of responsibilities between ICU, postoperative unit, "step-down" etc, and regarding routines for transfer to local hospitals, making comparisons of LOS potentially unreliable.

The composite secondary endpoint includes coma, delirium or death.

To clarify, we have changed the text in the abstract, line 114, and in the section regarding secondary endpoints, line 323-327:

> *"Secondary endpoints include the composite endpoint of coma, delirium or death, in addition to number of delirium days, delirium severity and motor activity patterns, comparison to inclusion of serum concentrations of neurofilament light (NFL) and p-tau181 1, 3 and 5 days postoperatively, as well as change from inclusion to 1 and 6 months after the operation in different cognitive tests, …"*

With regards to sample size, the study has been powered to a placebo delirium of 30%, clonidine 20% (290 per group) then increased another 290 to account for 3 groups. In effect the authors are expecting a 33% effect size with clonidine, 50% with DEX. These are quite large effect sizes for a condition so multifactorial as delirium but in line with meta-analyses.

We agree these are large effect sizes, however, as the reviewer mention, the expected effect of DEX is based on previous studies and meta-analyses, and we believe that it is realistic to expect a preventive effect of the same magnitude in this study.

Discussion:
Consider rewording the first sentence. The DECADE trial is quite large (800). As the primary outcome is delirium and the study is not adequately powered for cognitive decline (secondary outcome). There is good explanation of the differences in DEX parameters with the DECADE trial. Despite meta-analysis suggesting a 50% effect size for DEX, it is still quite a large expectation and the limitations should acknowledge that is the effect size is lower, the study may be underpowered.

We agree on this. However, ALPHA2PREVENT is to our knowledge the first trial to also include clonidine, and the first to include follow-up cognitive assessments at 1 and 6 months.

We have reworded the first sentence in the discussion, line 484-487:

> *"To our knowledge, ALPHA2PREVENT will be the first large randomised controlled multicentre trial to study the prophylactic efficacy of dexmedetomidine as well as clonidine on the incidence of postoperative delirium in older cardiac surgical patients, and also including long-term cognitive trajectories*."

We have added, under limitations, line 520-522

> *"If the incidence of delirium in the placebo group is lower than expected, or if the anticipated effect of the treatment is smaller, the study may be underpowered."*

Reviewer 2: Dr. RC Arora, University of Manitoba
Comments/Concerns:
The following comments/questions are seeking clarification on a few issues (separated by section) to further strengthen the manuscript.
METHODS: The Authors have chosen to limit the study to those over the age of 70. While in agreement that this would be a higher risk patient population, it may be worthwhile to consider inclusion of patient over the age of 60.

We agree that this is worthwhile considering, but since the expected delirium incidence is lower in younger patients, a lower age limit would decrease statistical power considerably. The age limit of 70 is a pragmatic choice between aiming for generalisability and our practical and economic ability to include a sufficient number of patients.

METHODS: Patient awaiting in hospital may have different rates of postoperative delirium. Have the Authors considered looking this factor as part of their analysis?

We agree that patients awaiting in hospital might have more severe underlying conditions, more acute illness, or be frailer, and thus have a higher delirium risk. We do register this variable and will adjust for it in our analyses if unevenly distributed between the randomisation groups. Randomisation is stratified on sites, so differences in logistics or local hospital routines are taken into account.

METHODS: Please clarify the predicted rates of bradycardia and hypotension associated with i.v. dexmedetomine vs. clonidine. In addition, can the Authors provide additional details on the peri-operative teams' ability to stop the drug if bradycardiac or hypotension is encountered (or alternatively, what the algorithm of management would be in these circumstances)?

We expect both bradycardia and hypotension in participants treated with alpha-2-agonists, but exact rates are difficult to predict, as also other variables contribute to this, such as anaesthesia, drugs, frailty status, and surgery. In a similar study by Turan et al. (DECADE),[1] with dosage *0.4 mcg/kg/h* (also postoperatively), clinically important bradycardia occurred in 9 % in the DEX group, vs 11% in the placebo group. Clinically important hypotension was reported in 57% in DEX group, vs 36% in placebo group. To reduce this risk, particularly for hypotension, we have chosen a more careful dosage postoperatively than Turan, but not so low that we cannot expect an effect on delirium.

We have not made a specific algorithm how bradycardia or hypotension will be handled, but leave this up to the treating anaesthesiologist, following local routines, as described in the paragraph Safety and adverse events management. As bradycardia and hypotension is very common in heart surgery patients also without the use of alpa-2 adrenergic drugs, the cardiac anaesthesiologists are under any circumstances extremely aware of such events and have a high preparedness to intervene.

We have added in the paragraph Safety and adverse events management, line 385-388:

> *"If the patient is hemodynamically unstable at any time during infusion of the study medication or difficult to wake up after surgery, the infusion can be temporarily stopped, as decided by the treating physician. In such a case the patient will continue in the study. The reason for temporary discontinuation will be recorded*."

METHODS: The Authors have described the use of the CAM-ICU for the ICU, what tool will be used on the post-operative ward? In addition, can the Authors provide additional details on the timing of the delirium assessments (i.e. time of day) and if this will be standardized across sites.

We have added, line 317:

> *Table 3. Diagnostic algorithm for DSM-5 delirium*

We have added, line 289:

> *" .. will be carried out <u>once daily</u> by specially trained research assistants"*

We have tried to clarify, and added to the manuscript, line 299-302

> *"<u>Nurses will, as part of their routine and for each shift (i.e., three times daily),</u> actively register symptoms of delirium in the case notes, as well as screen for delirium using the Norwegian version of the Confusion Assessment Method for Intensive Care Units (CAM-ICU)(ref) and RASS. The same delirium assessment tools will be used for the ICU, step-down and bed wards."*

METHODS: Please provide additional details on the frailty testing (and timing) to be undertaken postoperatively (if any are to be investigated).

We have added a more thorough description on frailty assessments, line 338-343:

"… frailty will be measured by a comprehensive geriatric assessment (including medical history, number of prescribed drugs, sensory impairment, activity of daily living, gait speed, handgrip strength, chair stand and nutritional status) calculating a frailty-index (range, 0-1; higher values indicate greater frailty) based on the accumulation of deficits model of frailty[57] and by the shorter Essential Frailty Toolset;[58]"

Patients will be assessed for frailty preoperatively, and 1 and 6 months after surgery (Table 2)

METHODS: Can the Authors if they utilize any enhancing recovery after surgery (ERAS) protocols for their cardiac surgery patients at their centres?

Unfortunately, no such standardized protocols as ERAS are used for cardiac surgery in Norway. However, the cardiac surgery in Norway is performed by permanent teams that follow well-developed and standardized routines pre- and postoperatively. All cardiac surgery patients are included in a national registry.

METHODS: The Authors have indicated "duration of delirium " (ln 399) as a secondary endpoint. Can the Authors provide a definition of how they will determine an episode of delirium to have ended?

This is an important, relevant and difficult question in all delirium research. We define delirium according to the DSM-5 criteria, and consider the patient to be delirious when all criteria are met *(we have added Table 3).* If all criteria are not met, the patient is not delirious according to this definition. However, since delirium is not a dichotomous size, but a continuous concept, we also want to classify subsyndromal delirium. Furthermore, we believe that it is a strength that we also register individual tests and delirium severity as continuous scales, for more refined analyses. It is an advantage that we know the results of preoperative cognitive tests (including attentions tests). This makes it easier to assess whether the patient is back to their normal mental level or not.

STATISTICS: Power analysis: have the Authors factored perioperative mortality in their calculations?

Perioperative mortality was not specifically factored into the power calculations, however the approach used was conservative considering the planned analyses and was increased by 10 patients per group to allow for dropouts (which would include perioperative mortality). We have now described this more clearly (lines 425-435) and included *a supplementary description of sample size calculations* under different situations (Supplementary file 1). Lines 427-435 now reads:

"An initial, conservative sample size calculation based on comparison of two proportions indicated that a sample size of 290 in each group (870 altogether) will give a power of 80% with a significance level of 5% to detect such a difference between the clonidine and the placebo group in the proportion developing delirium within 7 days postoperatively. To account for dropouts, we aim at including 900 patients. This sample size calculation approach was conservative considering the use of time-to-delirium analysis strategy, accommodating for both a higher dropout rate and that this trial has three arms. We have further confirmed the adequacy of this sample size estimate for the logrank test with differing rates of dropout and considering the three-arms (Supplementary file 1)."

STATISTICS: Can the Author provide additional details on the planned modeling of examining the interaction of frailty and the occurrence of delirium?

We have added details on this. Line 470-473 now reads:

"Additionally, we will assess if the presence of frailty modifies the effect of the treatment by including an interaction term between frailty and treatment allocation in the Cox proportional hazards model."

Correspondingly, we have also changed the wording in line 329-332 to:

"We will also assess if preoperative frailty status modifies the effect of dexmedetomidine and clonidine treatment, by studying the interaction between preoperative frailty and treatment on delirium and the other mentioned endpoints."

Minor Concerns:
1. Suggest to change the title from "open heart" to "cardiac surgery" as open heart refers to valve operations as the more general term cardiac surgery refers to CABG + valvular surgery.

We have probably not been fully aware of this nuance when we decided on the title of the study. However, the trial has already been registered several places with this title, and it will take a lot of work to change this. In addition, a name change will now contribute to confusion, and might be interpreted as if there are in fact two different studies. We have registered that several places the two terms seem to be used interchangeably, so we hope it is acceptable to keep it as it is.

2. Suggest to change the term "elderly" to "older adult" where used in the manuscript

Thank you for pointing this out. We have changed the text accordingly, line 422.

Reviewer: 3 Dr. Gregory Bryson, University of Ottawa, The Ottawa Hospital Research Institute
Comments to the Author:
Thank you for the opportunity to review this protocol for a multicentre, randomized controlled trial evaluating the influence of dexmedetomidine, clonidine, and placebo on the incidence of delirium 7-days following cardiac surgery. My review will reference the SPIRIT statement for the reporting of protocols for randomized controlled trials https://doi.org/10.7326/0003-4819-158-3-201302050-00583.
SPIRIT 2. This trial is registered with both EUDRA CT and ClinicalTrials.gov. This manuscript is concordant with the registration on both platforms.
SPIRIT 6. The selection of parenteral clonidine as a comparator requires a bit more explanation, at least for North Americans for whom it is not readily available. Similarly, a brief discussion of the discordance between the 12-24 h duration of alpha-2 agonist therapy and the 7-day window for the primary outcome would be welcome.

We have chosen clonidine as a comparator because clonidine has similar pharmacological properties to dexmedetomidine, in addition to the advantage that it can be administered orally as well as parenterally, potentially widening its usefulness.

We have added to the discussion, line 509-510:
"If clonidine is both effective and safe to administer, then it may be relevant to conduct more studies on per oral treatment with clonidine in other patient groups later on."

We consider the surgical procedure to be the main trigger of postoperative delirium, via inflammation, sympathetic activation and physiological disturbances. Thus, we plan to administer the intervention when these stressful events are at their most intense, to prevent activation of pathophysiological cascades that presumably may trigger delirium. Although we consider the risk of triggering delirium to be highest immediately after the operation, we know that many patients become delirious later in the postoperative course. The reasons for tis can be other than the trauma itself, e.g. pain, infection, cardiac events or other postoperative complications. Moreover, we cannot rule out that the study medicine itself may increase the risk of delirium, so we believe it is important to have several days of delirium registration.

SPIRIT 7. I suggest that the hypothesis (hypotheses) be stated as distinct PICO questions and aligned with the analysis plan.

We agree that this is something to consider. However, we are not used to see this in protocol articles from BMJ Open, and find that the text may become more difficult to read if it is broken up that way. We hope it is okay that we leave to the editor to decide whether we should to this.

The statistical analysis plan will be finalized prior to unblinding and it will include a more technical and detailed description of the statistical analyses.

SPIRIT 11a.
The reader would benefit from a discussion (and reference) attesting to the equipotency of clonidine and dexmedetomidine. While potency regarding delirium prevention is unknown, data attesting to their relative sedative and anti-hypertensive effects. Perhaps some of the Discussion (P23L51 to P24L18) could be moved to Introduction.

We agree that the evidence regarding equipotency of dexmedetomidine and intravenous (i.v) use of clonidine in delirium prevention is unknown, and that is in fact one of the reasons we are conducting this trial. There is a shortage of studies comparing iv dexmedetomidine and iv clonidine in ICU or postoperative settings.[2] To our knowledge, a widely agreed evidence-based i.v. dosage regimen has not been developed for i.v clonidine. We have only found the study by Grest [2] and meta-analysis by Wang,[3] and this favours equipotency mg per mg. Thus, our choice is fairly pragmatic, but the doses are similar to that currently used in many ICUs as part of routine practice. Clinical guidelines suggest, for example, to administer clonidine intravenously in doses from 0.5 mcg/kg/h, and monitoring hemodynamic responses (https://www.bsuh.nhs.uk/library/wp-content/uploads/sites/8/2020/09/clonidine.pdf). We are aware of another multicentre RCT evaluating the efficacy of dexmedetomidine versus clonidine in ICU patients (NCT03653832), including their effects on delirium. In that study, similar doses for i.v. clonidine and i.v. dexmedetomidine are used, and the two drugs are regarded as equipotent.

We have added to the discussion, line 499-504, that now reads:

> *"… There is a shortage of studies comparing i.v. dexmedetomidine and i.v. clonidine in ICU or postoperative settings. To our knowledge, a widely agreed evidence-based i.v. dosage regimen has not been developed for i.v clonidine. A study by Grest in critically ill patients after cardiac surgery (ref) and a recent meta-analysis favour equipotency mg per mg.(ref). Thus, our choice is fairly pragmatic, but the doses are similar to that currently used in many ICUs as part of routine practice."*

While the doses of clonidine and dexmedetomidine are similar, in the absence of drug concentration it is unclear how the infusions will be adjusted to ensure masking (particularly for the placebo group).

Both dexmedetomidine and clonidine concentrations will be 4 µg/ml, and both drugs will be administered as a continuous infusion: 0.4 µg/kg/hour (i.e., 0.1 ml/kg/h) from the start of cardiopulmonary bypass until the patient leaves the operation theatre, followed by 0.2 µg/kg/hour (i.e., 0.05 ml/kg/h) for up to 24 hours postoperatively in NaCl 9 mg/ml. To ensure masking, placebo will be given as a continuous infusion of the same volume of saline, at 0.1 ml/kg/h, followed by 0.05 ml/kg/h.

To clarify this, we have added text, lines 260-266, that now reads:

> *"Dexmedetomidine and clonidine concentrations will be 4 µg/ml in NaCl 9 mg/ml. Dexmedetomidine, clonidine or placebo (saline), will be given as a continuous intravenous infusion, without a loading dose, from the start of CPB, at a rate of 0.4 µg/kg/h (i.e., 0.1 ml/kg/h) for the active drugs. The infusion rate will be decreased to 0.2 µg/kg/h (i.e., 0.05 ml/kg/h) postoperatively and maintained for at least 12 hours after end of surgery. The infusion will be continued until discharge from the ICU or 24 hours postoperatively, whichever happens first. To ensure masking, placebo will be given as a continuous infusion of the same volume of saline at the same infusion rate."*

SPIRIT 11b. A more detailed description of the criteria clinicians will use to "decrease, pause or stop administration of study medication" would be welcome. Information in Safety and Adverse Events Management (P20L26) is vague.

To avoid misunderstandings, we have removed and edited a sentence from the paragraph “trial interventions” lines 266-268, to the section about safety management, lines 385-388, that now reads:

> *“If the patient is hemodynamically unstable at any time during infusion of the study medication or difficult to wake up after surgery, the infusion can be temporarily stopped, as decided by the treating physician. In such a case the patient will continue in the study. The reason for temporary discontinuation will be recorded.”*

SPIRIT 12. While the association of frailty and delirium plays a key role in this protocol, it’s the 3rd aim of the study (P6L33), there is little information regarding the measurement of frailty. Rather than drive your reader to the electronic supplement of reference 57, I suggest this be discussed more directly in the protocol. Note that the approach used in reference 57 is idiosyncratic and will be less familiar to the perioperative frailty research community.

We agree, and a more thorough information of the frailty assessments has been included, line 338-343, please see response to Reviewer 2.
Regarding choosing the accumulation of deficit model, we have added in the manuscript, the reference from Searle et al, 2008, to clarify; “A standard procedure for creating a frailty index».[4]

SPIRIT 14. The sample size estimate quoted on P21L30 suggests the study has been powered to detect an absolute difference in delirium of 10% between placebo (CER 30%) and clonidine (TER 20%). The 300 participant estimate in this two group comparison (I’ve confirmed it assuming a chi-square test) is cloned for the dexmedetomidine group yielding the final sample size of 900. However, the statistical analysis as described on P22L10 “We will thus estimate cumulative incidence by the Kaplan Meier estimator with time to first delirium as the dependent variable and compare time to event curves between treatments by the logrank test” suggests a time to event function and a three group comparison. A dexmedetomidine vs clonidine comparison would appear to be underpowered and no alpha-preserving function has been described. Please clarify and align hypothesis, estimate, and analysis plan.

Thank you for pointing out that our sample size estimate and analysis plan did not appear to be aligned. Clinically, the cumulative incidence of delirium within 7-days was considered to be the most important outcome for this trial. However, due to varying lengths of follow-up (due to discharge, transfers, or deaths), a simple comparison of proportions may be misleading. We therefore opted to use the Kaplan Meier estimator and the logrank test to compare the event curves. We appreciate that this strategy will indicate if there is any difference in survival at any timepoint, however we believe this to be a more appropriate test given the known variability that will arise in observation time.
As described in response to reviewer 2, we have now included a clearer description that the initial samples size calculation was based on a simple comparison of proportions (line 427-435). We have also included a more detailed explanation of how this (pragmatic) approach is conservative and the consequence of different dropout rates (new suppl. Information).

SPIRIT 16. I’m sure it will wash out in a 900-patient trial, but it is curious that “random permuted block sizes of 2 or 4, and stratified according to study centre” have been chosen. One wonders why the block sizes are not multiples of the number of study groups.

Thank you for pointing this out, this was a typo and has been corrected to 3 or 6 as originally planned in the randomisation protocol.

SPIRIT 18. Operationalizing the DSM-5 criteria is a key feature of this study’s methods. Rather than drive your reader to the protocol for the LUCID study, I suggest you recreate Table 4 from that document in the present manuscript.

We agree and have added Table 3, line 317.

SPIRIT 20a. The second objective of this study is to determine “the possible effects of dexmedetomidine and clonidine on long-term cognitive trajectories. P10L31” This manuscript should describe how the battery of cognitive tests will be summarized into a single assessment of postoperative neurocognitive disorder. Note that training effects and population norms must be accounted for, see https://doi.org/10.1034/j.1399-6576.2001.045003275.x.

As also emphasised in our answer to Reviewer 1, we realize that our wording could be misunderstood regarding the cognitive tests. We hope the wordings are better now, please see lines 323-329 and 345. We have not planned to aggregate the test results into one single assessment, but to treat the results of each single cognitive test as a separate, secondary outcome. Norwegian Population norms are available for most of the tests. We do indeed agree that training effects are inevitable, but consider this to be acceptable in a parallel group design.

SPIRIT 21b. Interim analysis, stopping rules, futility analyses, etc are not described.

We have added to the manuscript, line 475

“No interim analyses of the efficacy of the treatment are planned.”

We have added, line 410 - 418

All safety data collected will be summarized and reviewed by the DMC for agreement of next steps. In particular, data will be reviewed by for identification of the following events that would potentially contribute to a requirement to pause or stop the study: Any deaths, regardless of causality; cerebral infarctions; haemodynamic variables (time during surgery with MAP<50 mmHg, highest/lowest MAP and HR, lowest SpO2); need for vasopressor, non-invasive ventilation, active pacing, respiratory support or extracorporeal membrane oxygenation (ECMO); postoperative troponin values. If a pausing/stopping rule is met, a decision will be made, based on the review, as to whether enrolment in the study will be allowed to resume. Case unblinding will be performed for above reviews if necessary.”

Overall, this is a solid report of the protocol of the ALPHA2PREVENT trial. The clinical question, delirium following cardiac surgery, is of significant importance to both patients and clinicians. The involvement of patient partners in the design of this trial (P25L19) is to be commended. I encourage the investigators to make the data of this trial freely available rather than await a “reasonable request.”

The data cannot be made readily available because of Norwegian regulations and conditions for informed consent. However, any external party can approach the co-investigators to request access to the trial data. Such access to the trial dataset will be given when a majority of the members of the trial management group and the sponsor approve it.

Reviewer: 4 Dr. J. Yeung, University of Birmingham
Comments to the Author:Thank you for opportunity to review this manuscript.

My comments below:

1. Please can the authors comment on why the age of included patients are set at 70 and above - seemed overly restrictive?

Please, see our response to Reviewer 2, first paragraph.

2. The use of alpha 2 receptor agonists in cardiac patients may run into problems with hypotension and bradycardia. There is mention of adverse events management in the protocol - How will the investigators handle managing potential side effects without the need to unblind every patient who may have bradycardia/hypotension due to surgery rather than trial intervention?

Please, also see our response to Reviewer 2. Clinicians are allowed to decrease, pause or stop administration of study medication if clinically indicated. The study drug can be temporarily stopped, or infusion rate can be reduced, without unblinding the patient.

3. Drop out rate is estimated at 5% by investigators and appear a little conservative in a relatively older population having major cardiac surgery. The authors should consider increasing sample size for to account for loss to follow up or drop out to study.

Please see also our response to Reviewer 2. The sample size calculation section has been revised and now describes how the initial calculation was conservative given the statistical analysis strategy (line 427-435), and we have included a supplementary document to describe the adequacy of this sample size with varying rates of dropout (new suppl. Information).

4. The authors should consider including a flow diagram to explain delirium assessment that may explain the stepwise approach more succinctly.

We agree and have tried to clarify by adding Table 3, line 317.

Additional amendments

We have also updated the manuscript according to minor amendments in the revised protocol version 2.0 (Nov 29th 2021):

- Table 2. Study procedures: *The table has been replaced by an updated version*
    - We have added the variable Numerical rating scale (NRS), for assessment of pain
    - We have extended the registration of adverse events from 5 to 7 days postoperatively

- Added text, line 264-265

  "The infusion will be continued until discharge from the ICU or the step-down unit, or 24 hours postoperatively, whichever happens first."

- Table 1. Inclusion and exclusion criteria: We have changed the wording of the inclusion criteria #2 to avoid misunderstandings. We do not have changed on which patients can be included:

  "*The surgical procedures may constitute 1) coronary bypass grafting, 2) tricuspid, mitral, or aortic valve replacement or repair, 3) surgery on the ascending aorta, and 4) the combination of any of these procedures"*

We carefully ask if Melanie Rae Simpson can be added as a co-author, line 15, 44, 81, 560. She is a biostatistician in this trial and joined the project shortly after the first version of the manuscript was submitted. She has a significant role in the further analyses and has contributed substantially with the revision of the present manuscript.

We have made the text regarding body-worn accelerometers more precise:

Lines 158-160 now reads: "*Small light-weight body-worn accelerometers may provide objective measures of the effectiveness of delirium treatment intervention on motor activity level and types of patterns*."

Lines 351-352 now reads: *"Accelerometers will be attached to the frontal part of the waist,.."*

References

1. Turan A, Duncan A, Leung S, et al. Dexmedetomidine for reduction of atrial fibrillation and delirium after cardiac surgery (DECADE): a randomised placebo-controlled trial. *Lancet* 2020;396(10245):177-85. doi: 10.1016/S0140-6736(20)30631-0 [published Online First: 2020/07/20]
2. Grest A, Kurmann J, Muller M, et al. Cardiovascular Safety of Clonidine and Dexmedetomidine in Critically Ill Patients after Cardiac Surgery. *Crit Care Res Pract* 2020;2020:4750615. doi: 10.1155/2020/4750615 [published Online First: 2020/05/27]
3. Wang N, Wang Z, Song X, et al. Intravenous dexmedetomidine versus intravenous clonidine for post spinal anesthesia shivering: a meta-analysis of randomized controlled trials. *Scottish medical journal* 2020;65(3):94-102. doi: 10.1177/0036933020936283 [published Online First: 2020/06/24]
4. Searle SD, Mitnitski A, Gahbauer EA, et al. A standard procedure for creating a frailty index. *BMC geriatrics* 2008;8:24. doi: 10.1186/1471-2318-8-24 [published Online First: 2008/10/02]

VERSION 2 – REVIEW

REVIEWER	Bryson, Gregory University of Ottawa, Anesthesiology and Pain Medicine
REVIEW RETURNED	03-Mar-2022

GENERAL COMMENTS	Thank you for the opportunity to review this thoughtful revision of the report of the ALPHA2PREVENT protocol. You have addressed many of the concerns raised in my review of the original submission. Several small small points remain. 1. Thank you for the supplementary appendix describing the sample size estimate in detail. I find it a bit hard to believe that a dexmedetomidine v clonidine comparison is "explorative and clearly stated as such." I am reassured by the stated Bonferroni correction demonstrating a clinically important difference demonstrated at P = 0.0025 but would it not have been simpler to plan for all pairwise comparisons and set alpha at 0.0167? 2. I appreciate the expanded rationale regarding the use of clonidine for delirium prevention in this population. The potential to use this drug orally is a potential benefit when compared with dexmedetomidine. While I recognize the design issues involved in exploring clonidine's oral use in this trial, the focus on short term intravenous therapy for both drugs in this trial fails to capitalize on the putative advantage of clonidine. The short description of future trials at the bottom of page 29 could be expanded to reinforce that efficacy must be first demonstrated and found comparable to existing parenteral treatment (dexmedetomidine) before future trials with longer, oral use could be explored. 3. This extended prophylaxis, in part, animated my question regarding the short exposure (24h) to study drug and relatively long (7d) outcome assessment. I remain unconvinced that prophylaxis during surgery and 24h periop period will be sufficient to influence an ongoing inflammatory process. This limitation could be better

	described in the discussion. 4. The before and after measurements of individual neurocognitive tests treated as simple independent measures is inconsistent with best practice as described by ISPOCD. Reliable change methodology correcting for population norms and learning effects is encouraged. Thank you once again for the privilege of reviewing this protocol. I practice open peer review, Gregory L Bryson, MD, FRCPC, MSc uOttawa Anesthesiology and Pain Medicine.

REVIEWER	Yeung, J. University of Birmingham
REVIEW RETURNED	13-Mar-2022

GENERAL COMMENTS	Thank you for the opportunity to review the amended manuscript. I would like to thank the authors for their detailed responses. I am content that they have addressed the comments.

VERSION 2 – AUTHOR RESPONSE

Thank you for useful comments. Here are our point-by-point responses:

1. Thank you for the supplementary appendix describing the sample size estimate in detail. I find it a bit hard to believe that a dexmedetomidine v clonidine comparison is "explorative and clearly stated as such." I am reassured by the stated Bonferroni correction demonstrating a clinically important difference demonstrated at P = 0.0025 but would it not have been simpler to plan for all pairwise comparisons and set alpha at 0.0167?

We are pleased that the reviewer is reassured by our detailed description of the sample size estimate. It would of course have been possible also to plan for a formal comparison of dexmedetomidine vs clonidine, but that would have led to a larger sample size, which would have prolonged inclusion and costs.

2. I appreciate the expanded rationale regarding the use of clonidine for delirium prevention in this population. The potential to use this drug orally is a potential benefit when compared with dexmedetomidine. While I recognize the design issues involved in exploring clonidine's oral use in this trial, the focus on short term intravenous therapy for both drugs in this trial fails to capitalize on the putative advantage of clonidine. The short description of future trials at the bottom of page 29 could be expanded to reinforce that efficacy must be first demonstrated and found comparable to existing parenteral treatment (dexmedetomidine) before future trials with longer, oral use could be explored.

We appreciate this suggestion, and have added, line 486, page 29:

> *"Efficacy must first be demonstrated and found comparable to existing parenteral treatment before future trials with oral, longer use could be explored"*

3. This extended prophylaxis, in part, animated my question regarding the short exposure (24h) to study drug and relatively long (7d) outcome assessment. I remain unconvinced that prophylaxis during surgery and 24h periop period will be sufficient to influence an ongoing inflammatory process. This limitation could be better described in the discussion.

We have added in the discussion, line 500-1, page 30:

"The dose of the active drugs might be too low or the duration of treatment be too short to influence an ongoing pathophysiological process, in order to show effects."

4. The before and after measurements of individual neurocognitive tests treated as simple independent measures is inconsistent with best practice as described by ISPOCD. Reliable change methodology correcting for population norms and learning effects is encouraged.

We are well aware of the ISPOC methodology, in fact we took part in some of the studies (1-3). Although the use of a non-operated reference population is necessary to identify the true incidences of cognitive dysfunction caused by surgery/anesthesia, this is not the purpose of the present study as we aim for identifying any differences between the two treatment arms. For this purpose a standardized test battery at defined points will do, with head-to-head comparison between the groups before the code for double-blinding is broken. We see that it may be a good idea to use the Reliable Change Index, which we will consider following in spin-off studies later. However, we do not want to change the protocol now since the study is already underway.

References

1. Is peri-operative cortisol secretion related to post-operative cognitive dysfunction? Rasmussen LS, O'Brien JT, Silverstein JH, Johnson TW, Siersma VD, Canet J, Jolles J, Hanning CD, Kuipers HM, Abildstrom H, Papaioannou A, Raeder J, Yli-Hankala A, Sneyd JR, Munoz L, Moller JT; ISPOCD2 Investigators. Acta Anaesthesiol Scand. 2005 Oct;49(9):1225-31.

1. Cognitive dysfunction after minor surgery in the elderly. Canet J, Raeder J, Rasmussen LS, Enlund M, Kuipers HM, Hanning CD, Jolles J, Korttila K, Siersma VD, Dodds C, Abildstrom H, Sneyd JR, Vila P, Johnson T, Muñoz Corsini L, Silverstein JH, Nielsen IK, Moller JT; ISPOCD2 investigators. Acta Anaesthesiol Scand. 2003 Nov;47(10):1204-10.

1. Does anaesthesia cause postoperative cognitive dysfunction? A randomised study of regional versus general anaesthesia in 438 elderly patients. Rasmussen LS, Johnson T, Kuipers HM, Kristensen D, Siersma VD, Vila P, Jolles J, Papaioannou A, Abildstrom H, Silverstein JH, Bonal JA, Raeder J, Nielsen IK, Korttila K, Munoz L, Dodds C, Hanning CD, Moller JT; ISPOCD2(International Study of Postoperative Cognitive Dysfunction) Investigators. Acta Anaesthesiol Scand. 2003 Mar;47(3):260-6.