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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

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TITLE PAGE

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ABSTRACT

Introduction: Postoperative delirium is common in older cardiac surgery patients and associated with negative short-term and long-term outcomes. The alpha-2-adrenergic receptor agonist dexmedetomidine shows promise as prophylaxis and treatment for delirium in intensive care units (ICU) and postoperative settings. Clonidine has similar pharmacological properties and can be administered both parenterally and orally. We aim to study whether repurposing of clonidine can represent a novel treatment option for delirium, and the possible effects of dexmedetomidine and clonidine on long-term cognitive trajectories, motor activity patterns and biomarkers of neuronal injury, and whether these effects are associated with frailty status.

Methods and analysis: This five-centre, double blind randomised controlled trial will include 900 cardiac surgery patients aged 70+. Participants will be randomized 1:1:1 to dexmedetomidine or clonidine or placebo. The study drug will be given as a continuous intravenous infusion from the start of cardiopulmonary bypass, at a rate of 0.4 µg/kg/h. The infusion rate will be decreased to 0.2 µg/kg/h postoperatively and be continued until discharge from the ICU or 24 hours postoperatively, whichever happens first.

Primary endpoint is the 7-day cumulative incidence of postoperative delirium (Diagnostic and Statistical Manual of Mental Disorders, 5th edition). Secondary endpoints include the composite endpoint of coma, delirium or death, delirium severity and motor activity patterns, levels of circulating biomarkers of neuronal injury, cognitive function and frailty status 1 and 6 months after surgery.

Ethics and dissemination: This trial is approved by the Regional Committee for Ethics in Medical Research in Norway (South-East Norway) and by the Norwegian Medicines Agency. Dissemination plans include publication in peer-reviewed medical journals and presentation at scientific meetings.

Trial registration number: EudraCT: 2021-001645-12. ClinicalTrials.gov: NCT05029050

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This multicentre trial will provide evidence for prophylactic efficacy of dexmedetomidine and clonidine in reducing the incidence of postoperative delirium as well as decline in cognitive function 1 and 6 months postoperatively in older cardiac surgical patients
- Inclusion of preoperative frailty assessments will provide evidence for frailty as a predictive marker of treatment effect
- The analysis of biomarkers will provide insights into the neural mechanisms in postoperative delirium and long-term cognitive dysfunction
- The analysis of activity by accelerometers will provide insight into motor activity patterns in subtypes of delirium
- The dose of the active drugs may potentially be too low or the duration of treatment too short in order to show effects

BACKGROUND

Delirium represents an acute change in awareness, attention and cognition, precipitated by an acute illness, trauma, intoxication or surgery.[1 2] Common additional features are agitation, hallucinations and poor compliance with medical treatment and care.

Delirium appears in all parts of the health care service, including intensive care units (ICUs) and postoperative settings, regular hospital wards, nursing homes, home nursing services and palliative departments. In a recent meta-analysis, Greaves and co-workers found a delirium prevalence of 24% postoperatively after coronary artery bypass grafting (CABG) surgery, aggregated over all age groups.[3] In a Norwegian study of patients ≥80 years undergoing open aortic valve replacement, the prevalence of postoperative delirium was above 60%.[4] Open heart surgery patients are especially susceptible to delirium. Probable causes may be established cardiovascular disease, micro-embolism from cardiopulmonary bypass (CPB), perioperative circulatory changes including ischemia-reperfusion injuries, systemic inflammation, blood-brain barrier disruption and very deep anaesthesia.[5 6]

Delirium is difficult to handle in clinical settings, increases length of hospital stay and the need for long-term care,[7 8 9] is expensive for the society,[10] represents a frightening experience for the patient and the relatives,[11] and is an independent risk factor for death after cardiac surgery.[12] Delirium is an independent risk factor for cognitive decline in older adults, and induces a more rapid trajectory of deterioration in those who already have dementia.[13 14]

Frailty is a risk factor for delirium,[15] but less is known regarding how frailty assessments can guide prophylactic and therapeutic measures and shared decision making.[16] Frailty is a state of impaired physiologic reserve and decreased resistance to stressors, which increases the risk of an adverse outcome.[17 18] It is a consequence of cumulative decline in many physiological systems.

Conventionally, delirium has been separated into hyperactive and hypoactive subtypes based on clinical impression,[19] but recent research using body-worn sensors indicates a more heterogeneous pattern of motor activity across the clinical delirium motor subtypes.[20 21] Body-worn motor activity sensors may provide objective measures of the effectiveness of delirium treatment intervention, by classifying motor activity patterns in delirious patients. A small postoperative study on cardiac surgery patients showed the possibility of detecting the amount of movement in sedated patients.[22]

Routinely, several actions are taken in perioperative care to minimize the risk of delirium, such as appropriate management of pain and minimizing the use of sedative drugs like benzodiazepines. Further, non-pharmacological multicomponent interventions are essential,[23] but there is currently no compelling evidence to support the use of specific prophylactic pharmacological measures in routine perioperative care for patients at risk of postoperative delirium.[24]

However, dexmedetomidine, a parenterally administered alpha-2-adrenergic receptor agonist that attenuates sympathetic nervous system activity, shows promise as prophylaxis and treatment for delirium in ICUs and postoperative settings.[25 26] In a recent meta-analysis, perioperative use of dexmedetomidine in various surgical procedures was associated with a lower incidence of postoperative delirium. The relative risk (RR) and 95% confidence interval (CI) was 0.52 (0.39-0.70) when compared with placebo.[25] A meta-analysis in cardiac surgery patients showed that dexmedetomidine could reduce the risk of postoperative delirium (Odds Ratio 0.56, 95% CI 0.36-0.89)[27]. Among newer studies, some,[28-31] but not all,[32 33] have found a beneficial short time effect on the incidence of delirium. Effects upon long time cognitive trajectories have so far only been assessed in two studies, with conflicting results.[34 35] Nevertheless, the use of dexmedetomidine in ICUs is rapidly increasing.[26]

An alternative agent is clonidine, which has similar pharmacological properties to dexmedetomidine,[36] even though it's alpha-2-adrenergic selectivity is lower.[37] Clonidine can be administered both parenterally and orally, thus potentially widening its clinical usefulness.[36 37]

Clonidine was originally launched as an antihypertensive agent, but it is also used as an analgesic drug. Further, clonidine has a long tradition as a sedative in patients with hyperactive delirium, and is used by several anaesthesiologists and intensivists.[38] This practice is based on their clinical experiences and knowledge on the drug's properties, but is so far not supported by placebo-controlled clinical trials. A pilot study indicated that clonidine infusion during the period of weaning from mechanical ventilation after surgery for aortic dissection may reduce the severity of delirium.[39] A recent study compared clonidine with dexmedetomidine postoperatively after CABG and found better effect on risk and duration of delirium of dexmedetomidine. Since no placebo control group was included, that study could not assess potential effects of clonidine.[40]

Thus, there is a need for prospective large-scale studies on the potential prophylactic effect of alpha-2-adrenergic receptor agonists on delirium in susceptible patients. The aims of the present planned trial are to study 1) whether repurposing of clonidine can represent a novel treatment option for delirium, and 2) the possible effects of dexmedetomidine and clonidine on long-term cognitive trajectories, motor activity patterns, patient rated outcome measures and biomarkers of neuronal injury, and 3) whether these effects are associated with frailty status.

METHODS AND ANALYSIS

Study design

ALPHA2PREVENT is a nationwide five-centre, double blind randomised controlled trial (RCT). Patients aged 70+ scheduled for open heart surgery will be randomized 1:1:1 to dexmedetomidine or clonidine or placebo. The patients will be cognitively assessed preoperatively, then assessed for any symptoms of delirium according to the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) criteria[41] or subsyndromal delirium[42] postoperatively, and finally assessed for cognitive function after 1 and 6 months (figure 1).

Study locations

The trial will be carried out at Oslo University Hospital (Ullevaal and Rikshospitalet) in Oslo, Haukeland University Hospital in Bergen, Trondheim University Hospital in Trondheim, and the University Hospital of Northern Norway in Tromsø, all in Norway.

Participants, randomisation and blinding

Patients will be assessed for eligibility and asked for participation in cooperation with the responsible thoracic surgeons or anaesthesiologists. A full listing of trial inclusion and exclusion criteria is displayed in table 1. Participants must be ≥70 years old, accepted for cardiac surgery with CPB and capable of giving signed informed consent. The surgical procedures may constitute CABG, valve replacement, surgery on the ascending aorta, or combinations of these. Main exclusion criteria are bradycardia, uncontrolled hypotension, ischemic stroke the last month or acute coronary syndrome last 24 hours,[43] left ventricular ejection fraction < 40%, severe renal failure or hepatic dysfunction, sepsis, planned deep hypothermia and circulatory arrest, as well as emergency surgery.

Table 1. Inclusion and exclusion criteria

Participants are eligible to be included in the study only if all of the following criteria apply:	Participants are excluded from the study if any of the following criteria apply:
1. Participant must be ≥70 years old at the time of signing the informed consent. 2. Participant must be accepted for cardiac surgery with cardiopulmonary bypass. The surgical procedures may constitute 1) coronary bypass grafting, 2) tricuspid, mitral, or aortic valve replacement or repair, 3) the combination of 1 and 2, and 4) surgery on the ascending aorta. 3. Participant must be capable of giving signed informed consent.	4. Preoperative delirium (present at time of potential inclusion) 5. Known hypersensitivity to the active ingredient or components of the product 6. Bradycardia due to sick-sinus-syndrome, 2nd or 3rd degree AV-block (if not treated with pacemaker) or any other reason causing HR <50 bpm at time of inclusion 7. Uncontrolled hypotension 8. Ischemic stroke or transitory ischemic attack the last month or critical peripheral ischemia 9. Acute coronary syndrome last 24 hours. Acute coronary syndrome is defined according to international guidelines 10. Left ventricular ejection fraction < 40% 11. Severe renal impairment (estimated GFR < 20 ml/min) or expected requirement for renal replacement therapy 12. Severe hepatic dysfunction (liver enzyme three times the upper limit of normal together with a serum albumin concentration below the normal reference limit

	13. Reduced peripheral autonomous activity (e.g., spinal cord injury) 14. Current use of tricyclic antidepressants, monoamine reuptake inhibitors or ciclosporin 15. Endocarditis or sepsis 16. Pheochromocytoma 17. Planned deep hypothermia and circulatory arrest 18. Emergency surgery, defined as less than 24 hours from admission to surgery 19. Previously included in this study 20. Not speaking or reading Norwegian 21. Any other condition as evaluated by the treating physician

AV-block, atrioventricular block; HR, heart rate; GFR, glomerular filtration rate

Consenting patients will be randomly assigned 1:1:1, to dexmedetomidine, clonidine or placebo. Randomization will be computer generated with random permuted block sizes of 2 or 4, and stratified according to study centre. Allocation will be concealed by a web-based system that can be accessed no earlier than 3 days before surgery. The study drug will be prepared by an otherwise uninvolved research associate, ensuring that investigators, clinicians and outcome assessors are blinded to the group assignment.

Data collected at study entry

The data collection will take place in connection with routine clinical care at the relevant hospital wards and the ICU (table 2). According to the selection criteria, electrocardiogram (ECG),

creatinine/estimated Glomerular Filtration Rate (eGFR), liver transaminases, albumin, and a recent echo-cardiography will be required, as well as a screening for preoperative delirium. At study entry, demographic data, medical history including cardiovascular and non-cardiovascular co-morbidities, prescription drugs used, sensory impairment, presence or absence of any fall within the past year, functional status including activities of daily living, surgical site and indication for surgery will be obtained. Haemodynamic variables, body mass index, American Society of Anesthesiologists Physical Status (ASA)-classification and Euroscore II will be recorded, and routine blood samples taken prior to surgery will be registered. Blood samples for biomarkers will be drawn preoperatively and on postoperative day 1, 3 and 5. Included patients will undergo preoperative cognitive tests and physical tests for assessment of frailty. Patient rated outcome measures (PROMs) will be assessed by use of the Norwegian version of the EuroQol 5 Dimension 5 Level (EQ-5D-5L) questionnaire.[44] The same tests and questionnaires will be used also after 1 and 6 months, for assessment of cognitive and functional trajectories.

Table 2. Study procedures

Procedure	Screening (up to 30 days before Day 1)	Intervention Period [Days]								Registrations during hospital stay	1 and 6 months
		–1 to -3	1	2	3	4	5	6	7	8	
Assessment of eligibility	X										
Informed consent and randomization	X										
Demographic data		X									X
Physical examination		X									
Past and current medical conditions	X	X									X
Prescribed medications	X	X									X

Routine laboratory tests (e.g., creatinine, liver transaminases, albumin, troponin, proBNP)	X	X									X	
Blood samples for biomarkers		X		X		X		X				
12-lead ECG	X		X									
Vital signs	X	X	X	X	X	X	X	X	X	X		
Cognitive assessments		X										X
Frailty assessments		X										X
PROM (EQ-5D-5L)		X										X
Study intervention			X	X								
How much study drug was given?											X	
ASA-classification and Euroscore II											X	
Peroperative variables (e.g., type of surgery, medications, blood transfusions, vital parameters, duration of surgery and anaesthesia)											X	
Postoperative variables (e.g., vital signs, medications, blood transfusions, re-operations)											X	
Delirium assessments			X	X	X	X	X	X	X	X		X[a]
Postoperative complications											X	
AE review		X	←==========							→	X	
SAE review		X	←==========							→	X	X
Concomitant medication review		X	←==========							→	X	

Death				X	X
Body-worn accelerometers (Trondheim patients only)		X	←==========	X	X

ProBNP, Pro B-type Natriuretic Peptide; ECG, electrocardiogram; PROM, Patient Rated Outcome Measure; ASA-classification, American Society of Anesthesiologists Physical Status Classification; AE, Adverse Event; SAE, Serious AE

[a] No delirium assessment at follow-up after 6 months

Trial interventions

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 for the active drugs. The infusion rate will be decreased to 0.2 µg/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. Clinicians are allowed to decrease, pause or stop administration of study medication if clinically indicated, e.g. if the patient is difficult to wake up after surgery or study drug induced hemodynamic instability is suspected.

Concomitant therapy and rescue medicine

Patients will not be included if they use tricyclic antidepressants, monoamine reuptake inhibitors or cyclosporine. The perioperative anaesthesia will be given per routine at participating institutions. If delirium develops and pharmacological intervention is needed, the study drug will be stopped, and further treatment will be according to local routines and the treating physician's preferences.

Primary endpoint

The primary endpoint for ALPHA2PREVENT is the 7-day cumulative incidence of postoperative delirium. The diagnosis of delirium will be made according to DSM-5 criteria[41] by using a standardized

procedure developed for our previous study[45] and as recommended by others[46]. The methods are refined in order, in a stepwise approach, to assess presence or absence of the diagnostic criteria in DSM-5 and will be carried out by specially trained research assistants. Level of arousal will be assessed using the Norwegian versions of Richmond Agitation Sedation Scale (RASS)[47] and Observational Scale of Level of Arousal (OSLA).[48] Attention and awareness will be evaluated using objective tests (vigilance "A"-test, months of the years backwards, days of the week backwards, and counting down from 20 to 1)[49] and observations by the examiner of the patient´s distractibility, comprehension and tendency to lose the thread of conversation. Presence of additional cognitive disturbances will be assessed by tests for orientation and recall test of three words (different words for each day), as well as information derived from nursing staff and clinical notes. Acute change in the patient´s mental condition, and fluctuations of any disturbance, will be ascertained through informant history from nursing staff and derived from clinical notes.

The Norwegian version of the Confusion Assessment Method for Intensive Care Units (CAM-ICU)[50] will be used as a delirium screening tool by the study nurses. The results from each of the CAM-ICU-items, as well as the total CAM-ICU score, will also be used as a source of information for making the final delirium diagnosis.

Two or more experienced delirium researchers will independently use all available information (including the project assistants' assessments) on each patient to decide if the DSM-5 criteria for delirium are fulfilled. An interrater agreement for the diagnosis of delirium will be calculated and disagreements will be resolved through discussion.

Subsyndromal delirium will be defined as evidence of change, in addition to any one of these: altered arousal, attentional deficits, other cognitive change, delusions or hallucinations. DSM-5 delirium criteria D and E must be met.

Postoperative delirium assessment will start as soon as possible after admission to the ICU, and will continue daily until the seventh postoperative day or until discharge from the university hospital,

whichever happens first. Tests for delirium will also be repeated at the 1-month follow-up, to pick up signs of persistent delirium.

Secondary endpoints

Secondary endpoints include the composite endpoint of coma, delirium or death, 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 between inclusion and after 1 and 6 months in cognitive function, patient rated health status, frailty status, and comparison of change in frailty status between patients with or without postoperative delirium. We will also assess preoperative frailty status as a predictive marker of effect of dexmedetomidine and clonidine treatment, by studying the interaction between preoperative frailty and treatment on delirium and the other mentioned endpoints.

All endpoints will be assessed using Norwegian versions of validated instruments: Delirium severity will be measured using CAM-ICU-7,[51] OSLA[48] and RASS;[47] motor activity patterns using body worn accelerometers; cognitive function using Montreal Cognitive Assessment (MoCA),[52] immediate and delayed recall from The Ten Words Memory Task from The Consortium to Establish a Registry for Alzheimer's Disease,[53] Trail Making Test (TMT) version A and B,[54] semantic and phonemic verbal fluency,[55] digit span forwards and backwards (by Wechsler Adult Intelligence Scale);[56] frailty using a comprehensive geriatric assessment-based Frailty Index[57] and Essential Frailty Toolset;[58] and patient rated health status using the EQ-5D-5L questionnaire.[44]

For assessment of cognitive trajectories, the same cognitive test battery will be performed in a stable phase preoperatively as well as after 1 and 6 months. Information regarding functional status will be obtained from the patient preoperatively and from either the patient or their proxy at follow-up, depending on the patient's ability to provide detailed information.

For a sub-sample of one hundred patients from the Trondheim cohort, motor activity will be measured by 3D accelerometer inertial sensors (AX3 sensors) (Axivity Ltd., Newcastle, UK) sampled at 100 Hz and processed using custom made software. Accelerometers will be attached to the abdomen, the dominant thigh (ventrally, midthigh), and on the dominant wrist pre surgery. Motor activity patterns will be monitored continuously (day and nights) before and the five first days after surgery or until discharge from hospital, and over one week after 1 and 6 months. Sensor data will be analyzed regarding both quantity and quality of movements and compared with the clinical delirium assessments.

Biomarkers

In addition to routine blood tests, blood will be taken in the morning for specific study analyses (serum, plasma and wholeblood) before surgery, and at postoperative day 1, 3 and 5 (or earlier if discharged before day 5) and frozen at –80 °C locally. Frozen samples will then be shipped to the coordinating centre (Oslo) to be stored in a biobank at –80 °C for future analyses. The stored blood samples will be analysed for promising markers such as NFL already known to be associated with delirium,[59] p-tau181 associated with dementia and delirium,[60-62] and possibly other biomarkers of neuronal degeneration, neuroinflammation and neurotransmitters,[63-67] using state-of-the-art ultrasensitive assays to evaluate their association with observed clinical responses to the study drugs.

Standardised training

The research assistants across all sites will receive standardized training for all study measures prior to study initiation, including cognitive tests, delirium assessments and measurements of frailty indicators. Retraining will be provided as necessary. Detailed instructions and operation manuals in Norwegian language, including an instruction video for the MoCA, will be made available to all assessors.

Data management and monitoring

Participant data will be collected by authorized trained personnel, be recorded on electronic Case Report Forms (CRF) and stored on a password protected database. Paper files will be stored in locked cabinets accessible to team members only. Study monitors will perform ongoing source data verification to confirm that data entered into the CRFs are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol, International Conference on Harmonization Good Clinical Practice, and all applicable regulatory requirements. Records and documents, including signed Informed Consent Forms, pertaining to the conduct of this study will be retained by the investigators for 15 years after study completion.

Safety and adverse events management

Immediate safety concerns will be handled by the treating anaesthesiologist, who will determine if the participant should continue or discontinue study intervention. Since patients are closely monitored in the perioperative phase of cardiac surgery, potential adverse circulatory effects will be rapidly revealed and corrected;

- Temporal epicardial pacing wires are placed routinely during cardiac surgery, and bradycardia will be treated with atropine and/or pacemaker as per routine.
- Hypotension will be treated at discretion of the treating anaesthesiologists, who are permitted to reduce dose of the study drug as necessary to preserve haemodynamic stability, following guidelines and local routines. A Mean Arterial Pressure (MAP) >55-60mmHg is recommended.
- If not rapid and satisfactory response on other measures is achieved, the treating anaesthesiologist will consider to turn off the infusion/unblind the study.

Planned time points for safety assessments are provided in table 2.

The following safety indicators will be compared between the three treatment groups with appropriate statistical methods: Highest and lowest heart rate, systolic, diastolic and mean arterial blood pressure, oxygen saturation, PaO2/FiO2 ratio, number of units for blood transfusion, volume of postoperative blood loss, use of pressor substances, use of rescue medication, number of episodes of bradycardia, hypotension or hypoxemia in need of intervention, perioperative myocardial infarction and stroke, postoperative serum concentrations of troponin and Pro B-type Natriuretic Peptide (proBNP), mortality.

An independent Data Monitoring Committee will have unblinded access to all data and meet whenever the members find it necessary.[68] Meetings are pre-planned after inclusion of 20, 50, 100 and 400 participants, to assess safety indicators and to advise on continuation or termination of the study.

Current sample size justification

The proportion of patients experiencing postoperative delirium after open heart surgery for all ages has been reported to be 24%,[3] and higher in the elderly.[4] Since the lower age limit in our trial is 70 years, we estimate that the proportion in the control group will be at least 30%. The most recent meta-analysis of the effect of dexmedetomidine estimates the delirium risk to be reduced to approximately half of the untreated group (*i.e.*, 15%).[25] The effect of clonidine may be weaker but still worth finding. We have thus powered the study based on an estimated delirium incidence of 20% in the clonidine group. 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. To account for dropouts, we aim at including 900 patients.

Statistical analysis

The primary analysis population will be the intention-to-treat population, and all tests will be two-sided. The primary objective in this study is to prevent postoperative delirium. The primary endpoint

is the cumulative incidence of postoperative delirium. The endpoint will be registered when the patient is diagnosed with delirium or receives rescue medication for delirium. The postoperative observation time will vary between patients, as time to discharge or transfer to other hospitals will be different. 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. Patients who are discharged from the university hospital during the observation period or reach the end of the observation period (7 days) without having developed delirium, are regarded as censored. We consider that there is no risk that allocation to treatment group will influence the risk of being censored. Those who die, will also be regarded as censored in the primary analysis, but we will carry out a secondary analysis with the combined endpoint *death or delirium.* The same approach will be applied for those who are comatose, and thus impossible to evaluate for delirium. Additional analyses may also include estimating the incidence of delirium treating deaths as a competing risk by the Fine and Gray method.

All analyses will be adjusted for variables applied in the stratified randomization.

Sensitivity analyses will be carried out by estimating hazard ratios using Cox' proportional hazards model to adjust for potential imbalance of prognostic factors between treatment groups.

Secondary endpoints as the cumulative incidence of death, coma or postoperative delirium will be analysed using the Kaplan Meier estimator and the logrank test as above. Additional analyses by Cox' proportional hazards model may also be performed. Mean duration of delirium; severity of delirium; combination of duration and severity of delirium; cognitive tests after 1 and 6 months; EQ-5D-5L scores after 1 and 6 months; and postoperative plasma concentrations of NFL and p-tau181 will be compared between treatments by linear mixed models with time, treatment group, and strata as fixed factors and constraining the means to be equal in all groups at baseline.

Frailty as risk factor for delirium and for adverse effects of the study medication, will be analysed by linear or logistic regression (as appropriate), adjusted for other known risk factors. The association

between frailty and delirium will be analysed by adding frailty as a covariate in a Cox'proportional hazards model on time to delirium (as above). Any interaction between frailty and treatment will also be assessed. The association between frailty and occurrence of adverse events (AE) will be estimated by logistic regression models including covariates as above.

A detailed statistical analysis plan will be finalized prior to un-blinding.

Ethics and dissemination

This trial is approved by the Regional Committee for Ethics in Medical Research in Norway (South-East Norway) and by the Norwegian Medicines Agency, and will be conducted in accordance with consensus ethical principles derived from international guidelines including the Declaration of Helsinki. The results of this study will be published in peer-reviewed medical journals, as well as presented at scientific meetings

Discussion

To our knowledge, ALPHA2PREVENT will be the first large randomised controlled multicentre trial to study the prophylactic efficacy of dexmedetomidine and clonidine to reduce the incidence of postoperative delirium in older cardiac surgical patients, as well as reducing cognitive decline 1 and 6 months postoperatively.

One should expect that treatment options that can prevent delirium in a short-term perspective, would also improve the long-term cognitive prognosis. Evidence for such an effect is slowly emerging for non-pharmacological interventions,[69] but is lacking regarding drug treatment.

Published studies of dexmedetomidine for prevention of delirium in ICU vary largely with respect to dosing regimens, from 0.1[70 71] to 1.4 µg/kg/h.[32] Many of the authors also administered an initial bolus. In the cardiac surgery context, Turan et al started dexmedetomidine infusion already before start of CPB, gave 0.4 µg/kg/h postoperatively,[33] and found more side effects in the actively treated

than in the placebo group. We have chosen a careful dosage of 0.4 µg/kg/h peroperatively and 0.2 µg/kg/h postoperatively, with no bolus, to reduce the risk of AE, but not so low that we cannot expect an effect on delirium.

Regarding clonidine, the recommended dosage varies greatly between sources, but is mainly in the range 1-1.5 µg/kg/h.[72] We will dose the drug considerably lower, to avoid side effects. A recent meta-analysis indicates that clonidine and dexmedetomidine are approximately equipotent in similar doses.[73] We have thus chosen the same dosage for clonidine as for dexmedetomidine.

To further reduce the risk of hemodynamic instability due to the combination of anaesthesiological procedures and study drug at the start of surgery, we will postpone infusion of study drug until the CPB is established.

Strengths of this trial are the prospective and randomised placebo controlled design, the use of two relevant and much used drugs, inclusion of a high number of patients from multiple sites, adequate statistic strength, repeated cognitive and frailty assessments, use of body-worn accelerometers, and repeated samples of biomarkers. The analyses of biomarkers reflecting neural injury will give us increased understanding of the pathophysiological mechanisms of delirium. Inclusion of preoperative frailty assessments will provide evidence for frailty as a predictive marker of treatment effect and allow for interaction analyses. The use of body-worn accelerometers will provide insight into motor activity patterns in subtypes of delirium.

This trial has, however, some limitations to consider. The exclusion criteria might limit the generalisability of our findings to other patient populations. There might be a problem with statistical power if the incidence of delirium is lower than expected. The dose of the active drugs might be too low or the duration of treatment be too short in order to show effects. As many patients live far away from the study site, there is a potential for missing long-term data.

Should the treatment have a positive effect, it would have important beneficial implications for patients, cares and society, such as alleviating acute patient distress and carer burden. If this treatment could reduce longer-term negative effects of delirium, it might have significant consequences for financial and human resource use in health care.

DECLARATIONS

Patient and public involvement: Panellists from the user panel established by the Norwegian National Advisory Unit on Ageing and Health, participate in the Trial Advisory Board. They have experience as relatives to patients with dementia or delirium, have given valuable input to the project plans and will follow up during the project period.

Ethics approval: The trial is approved by the Regional Committee for Ethics in Medical Research in Norway (South-east Norway) (REK 262384), June 9th 2021, and by the Norwegian Medicines Agency June 17th 2021.

Availability of data and materials: Materials can be available upon reasonable request to the corresponding author. However, availability is dependent on approval from the Regional Ethics Committee and the local data protection officer.

Competing interest: HZ has served at scientific advisory boards and/or as a consultant for Alector, Eisai, Denali, Roche Diagnostics, Wave, Samumed, Siemens Healthineers, Pinteon Therapeutics, Nervgen, AZTherapies, CogRx and Red Abbey Labs, has given lectures in symposia sponsored by Cellectricon, Fujirebio, Alzecure and Biogen, and is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program (outside submitted work).

AJCS is advisor for Prolira, a start-up company that develops an EEG-based delirium monitor. Any (future) profits from EEG-based delirium monitoring will be used for future scientific research only.

GS has participated in one advisory meeting for Biogen. HMN has received lecture fees from Vifor Pharma and Orion Pharma.

The other authors declare that they have no competing interests.

Consent for publication: Not required

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Critical revision of the manuscript for important intellectual content: BEN, RB, RH, JLH, AKK, SAL, IM, HMN, JR, GS, ES, NKS, ES, AS, ØSS, TT, AW, HZ, TBW

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Abbreviations:

Abbreviation	Explanation
AE	Adverse Event
ALPHA2PREVENT	Alpha-2-adrenergic receptor agonists for the prevention of delirium and cognitive decline after open heart surgery: randomised controlled trial
ASA classification	American Society of Anesthesiologists Physical Status Classification
CABG	Coronary Artery Bypass Grafting
CAM-ICU	Confusion Assessment Method for Intensive Care Units
CPB	Cardiopulmonary Bypass
CRF	Case Report Form
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th edition
ECG	Electrocardiogram
EQ-5D-5L	EuroQol 5 Dimension 5 Level
FI	Frailty Index
GFR	Glomerular Filtration Rate
ICU	Intensive Care Unit
MAP	Mean Arterial Pressure
MoCA	Montreal Cognitive Assessment
NFL	Neurofilament light
OSLA	Observational Scale of Level of Arousal
ProBNP	Pro B-type Natriuretic Peptide
PROM	Patient Rated Outcome Measure
RASS	Richmond Agitation Sedation Scale
RCT	Randomised Controlled Trial
SAE	Serious Adverse Event

TMT	Trail Making Test

LEGENDS

Figure 1:

Study schema. MoCA, Montreal Cognitive Assessment; TMT, Trail Making Test; EQ-5D-5L, EuroQol 5 Dimension 5 Level; POD, Postoperative Day

REFERENCES

1. Marcantonio ER. Delirium in Hospitalized Older Adults. *The New England journal of medicine* 2017;377(15):1456-66. doi: 10.1056/NEJMcp1605501 [published Online First: 2017/10/12]
2. Wilson JE, Mart MF, Cunningham C, et al. Delirium. *Nat Rev Dis Primers* 2020;6(1):90. doi: 10.1038/s41572-020-00223-4
3. Greaves D, Psaltis PJ, Ross TJ, et al. Cognitive outcomes following coronary artery bypass grafting: A systematic review and meta-analysis of 91,829 patients. *International journal of cardiology* 2019;289:43-49. doi: 10.1016/j.ijcard.2019.04.065 [published Online First: 2019/05/13]
4. Eide LS, Ranhoff AH, Fridlund B, et al. Comparison of frequency, risk factors, and time course of postoperative delirium in octogenarians after transcatheter aortic valve implantation versus surgical aortic valve replacement. *The American journal of cardiology* 2015;115(6):802-9. doi: 10.1016/j.amjcard.2014.12.043 [published Online First: 2015/02/04]
5. Hollinger A, Siegemund M, Goettel N, et al. Postoperative Delirium in Cardiac Surgery: An Unavoidable Menace? *Journal of cardiothoracic and vascular anesthesia* 2015;29(6):1677-87. doi: 10.1053/j.jvca.2014.08.021 [published Online First: 2015/10/13]
6. Abrahamov D, Levran O, Naparstek S, et al. Blood-Brain Barrier Disruption After Cardiopulmonary Bypass: Diagnosis and Correlation to Cognition. *The Annals of thoracic surgery* 2017;104(1):161-69. doi: 10.1016/j.athoracsur.2016.10.043
7. Gleason LJ, Schmitt EM, Kosar CM, et al. Effect of Delirium and Other Major Complications on Outcomes After Elective Surgery in Older Adults. *JAMA Surg* 2015;150(12):1134-40. doi: 10.1001/jamasurg.2015.2606
8. Witlox J, Eurelings LS, de Jonghe JF, et al. Delirium in elderly patients and the risk of postdischarge mortality, institutionalization, and dementia: a meta-analysis. *JAMA* 2010;304(4):443-51. doi: 304/4/443 [pii];10.1001/jama.2010.1013 [doi]
9. Krogseth M, Wyller TB, Engedal K, et al. Delirium is a risk factor for institutionalization and functional decline in older hip fracture patients. *Journal of psychosomatic research*

2014;76(1):68-74. doi: 10.1016/j.jpsychores.2013.10.006 [published Online First: 2013/12/24]

10. Pezzullo L, Streatfeild J, Hickson J, et al. Economic impact of delirium in Australia: a cost of illness study. *BMJ Open* 2019;9(9):e027514. doi: 10.1136/bmjopen-2018-027514 [published Online First: 2019/09/19]

11. Instenes I, Gjengedal E, Eide LSP, et al. "Eight Days of Nightmares ... " - Octogenarian Patients' Experiences of Postoperative Delirium after Transcatheter or Surgical Aortic Valve Replacement. *Heart, lung & circulation* 2018;27(2):260-66. doi: 10.1016/j.hlc.2017.02.012 [published Online First: 2017/04/12]

12. Gottesman RF, Grega MA, Bailey MM, et al. Delirium after coronary artery bypass graft surgery and late mortality. *Annals of neurology* 2010;67(3):338-44. doi: 10.1002/ana.21899 [published Online First: 2010/04/08]

13. Davis DH, Muniz-Terrera G, Keage HA, et al. Association of Delirium With Cognitive Decline in Late Life: A Neuropathologic Study of 3 Population-Based Cohort Studies. *JAMA Psychiatry* 2017 doi: 10.1001/jamapsychiatry.2016.3423 [published Online First: 2017/01/24]

14. Saczynski JS, Marcantonio ER, Quach L, et al. Cognitive trajectories after postoperative delirium. *The New England journal of medicine* 2012;367(1):30-9. doi: 10.1056/NEJMoa1112923 [published Online First: 2012/07/06]

15. Persico I, Cesari M, Morandi A, et al. Frailty and Delirium in Older Adults: A Systematic Review and Meta-Analysis of the Literature. *Journal of the American Geriatrics Society* 2018;66(10):2022-30. doi: 10.1111/jgs.15503 [published Online First: 2018/09/22]

16. van Beek-Peeters J, van Noort EHM, Faes MC, et al. Shared decision making in older patients with symptomatic severe aortic stenosis: a systematic review. *Heart* 2020;106(9):647-55. doi: 10.1136/heartjnl-2019-316055 [published Online First: 2020/02/01]

17. Clegg A, Young J, Iliffe S, et al. Frailty in elderly people. *Lancet* 2013;381(9868):752-62. doi: S0140-6736(12)62167-9 [pii];10.1016/S0140-6736(12)62167-9 [doi]

18. Guidet B, de Lange DW, Boumendil A, et al. The contribution of frailty, cognition, activity of daily life and comorbidities on outcome in acutely admitted patients over 80 years in European ICUs: the VIP2 study. *Intensive care medicine* 2020;46(1):57-69. doi: 10.1007/s00134-019-05853-1

19. Meagher DJ, Leonard M, Donnelly S, et al. A longitudinal study of motor subtypes in delirium: frequency and stability during episodes. *JPsychosomRes* 2012;72(3):236-41. doi: S0022-3999(11)00298-4 [pii];10.1016/j.jpsychores.2011.11.013 [doi]

20. Godfrey A, Leonard M, Donnelly S, et al. Validating a new clinical subtyping scheme for delirium with electronic motion analysis. *Psychiatry research* 2010;178(1):186-90. doi: 10.1016/j.psychres.2009.04.010 [published Online First: 2010/05/11]

21. Evensen S, Bourke AK, Lydersen S, et al. Motor activity across delirium motor subtypes in geriatric patients assessed using body-worn sensors: a Norwegian cross-sectional study. *BMJ Open* 2019;9(2):e026401. doi: 10.1136/bmjopen-2018-026401 [published Online First: 2019/03/04]

22. Harbo EF, Fuglerud SS, Skjaervold NK. Visualisation of limb movements by accelerometers in sedated patients. *Crit Care* 2020;24(1):283. doi: 10.1186/s13054-020-02975-7 [published Online First: 2020/06/05]

23. Needham MJ, Webb CE, Bryden DC. Postoperative cognitive dysfunction and dementia: what we need to know and do. *British journal of anaesthesia* 2017;119(suppl_1):i115-i25. doi: 10.1093/bja/aex354 [published Online First: 2017/11/22]

24. Siddiqi N, Harrison JK, Clegg A, et al. Interventions for preventing delirium in hospitalised non-ICU patients. *The Cochrane database of systematic reviews* 2016;3:CD005563. doi: 10.1002/14651858.CD005563.pub3 [published Online First: 2016/03/12]

25. Flukiger J, Hollinger A, Speich B, et al. Dexmedetomidine in prevention and treatment of postoperative and intensive care unit delirium: a systematic review and meta-analysis.

Annals of intensive care 2018;8(1):92. doi: 10.1186/s13613-018-0437-z [published Online First: 2018/09/22]

26. Bajwa S, Kulshrestha A. Dexmedetomidine: An Adjuvant Making Large Inroads into Clinical Practice. *Annals of medical and health sciences research* 2013;3(4):475-83. doi: 10.4103/2141-9248.122044 [published Online First: 2014/01/01]

27. Li P, Li LX, Zhao ZZ, et al. Dexmedetomidine reduces the incidence of postoperative delirium after cardiac surgery: a meta-analysis of randomized controlled trials. *BMC anesthesiology* 2021;21(1):153. doi: 10.1186/s12871-021-01370-1 [published Online First: 2021/05/20]

28. Li CJ, Wang BJ, Mu DL, et al. Randomized clinical trial of intraoperative dexmedetomidine to prevent delirium in the elderly undergoing major non-cardiac surgery. *The British journal of surgery* 2020;107(2):e123-e32. doi: 10.1002/bjs.11354 [published Online First: 2020/01/07]

29. Likhvantsev VV, Landoni G, Grebenchikov OA, et al. Perioperative Dexmedetomidine Supplement Decreases Delirium Incidence After Adult Cardiac Surgery: A Randomized, Double-Blind, Controlled Study. *Journal of cardiothoracic and vascular anesthesia* 2020 doi: 10.1053/j.jvca.2020.02.035 [published Online First: 2020/04/09]

30. van Norden J, Spies CD, Borchers F, et al. The effect of peri-operative dexmedetomidine on the incidence of postoperative delirium in cardiac and non-cardiac surgical patients: a randomised, double-blind placebo-controlled trial. *Anaesthesia* 2021 doi: 10.1111/anae.15469 [published Online First: 2021/05/08]

31. Peng K, Shen YP, Ying YY, et al. Perioperative dexmedetomidine and 5-year survival in patients undergoing cardiac surgery. *British journal of anaesthesia* 2021 doi: 10.1016/j.bja.2021.03.040 [published Online First: 2021/06/05]

32. Subramaniam B, Shankar P, Shaefi S, et al. Effect of Intravenous Acetaminophen vs Placebo Combined With Propofol or Dexmedetomidine on Postoperative Delirium Among Older Patients Following Cardiac Surgery: The DEXACET Randomized Clinical Trial. *JAMA* 2019;321(7):686-96. doi: 10.1001/jama.2019.0234 [published Online First: 2019/02/20]

33. 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]

34. Deiner S, Luo X, Lin HM, et al. Intraoperative Infusion of Dexmedetomidine for Prevention of Postoperative Delirium and Cognitive Dysfunction in Elderly Patients Undergoing Major Elective Noncardiac Surgery: A Randomized Clinical Trial. *JAMA Surg* 2017;152(8):e171505. doi: 10.1001/jamasurg.2017.1505 [published Online First: 2017/06/09]

35. Cheng XQ, Mei B, Zuo YM, et al. A multicentre randomised controlled trial of the effect of intra-operative dexmedetomidine on cognitive decline after surgery. *Anaesthesia* 2019;74(6):741-50. doi: 10.1111/anae.14606 [published Online First: 2019/03/06]

36. Pichot C, Ghignone M, Quintin L. Dexmedetomidine and clonidine: from second- to first-line sedative agents in the critical care setting? *Journal of intensive care medicine* 2012;27(4):219-37. doi: 10.1177/0885066610396815 [published Online First: 2011/04/29]

37. Khan ZP, Ferguson CN, Jones RM. alpha-2 and imidazoline receptor agonists. Their pharmacology and therapeutic role. *Anaesthesia* 1999;54(2):146-65.

38. Wang JG, Belley-Cote E, Burry L, et al. Clonidine for sedation in the critically ill: a systematic review and meta-analysis. *Crit Care* 2017;21(1):75. doi: 10.1186/s13054-017-1610-8 [published Online First: 2017/03/24]

39. Rubino AS, Onorati F, Caroleo S, et al. Impact of clonidine administration on delirium and related respiratory weaning after surgical correction of acute type-A aortic dissection: results of a pilot study. *InteractCardiovascThoracSurg* 2010;10(1):58-62. doi: icvts.2009.217562 [pii];10.1510/icvts.2009.217562 [doi]

40. Shokri H, Ali I. A randomized control trial comparing prophylactic dexmedetomidine versus clonidine on rates and duration of delirium in older adult patients undergoing coronary

artery bypass grafting. *Journal of clinical anesthesia* 2020;61:109622. doi: 10.1016/j.jclinane.2019.09.016 [published Online First: 2019/11/02]

41. AmericanPsychiatricAssociation. Diagnostic and Statistical Manual of Mental Disorders: DSM-5 (5th ed.). Washington DC: American Psychiatric Association 2013.

42. Cole MG, Ciampi A, Belzile E, et al. Subsyndromal delirium in older people: a systematic review of frequency, risk factors, course and outcomes. *Int J Geriatr Psychiatry* 2013;28(8):771-80. doi: 10.1002/gps.3891

43. Collet JP, Thiele H, Barbato E, et al. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *European heart journal* 2021;42(14):1289-367. doi: 10.1093/eurheartj/ehaa575 [published Online First: 2020/08/30]

44. EuroQol G. EuroQol--a new facility for the measurement of health-related quality of life. *Health policy (Amsterdam, Netherlands)* 1990;16(3):199-208. doi: 10.1016/0168-8510(90)90421-9 [published Online First: 1990/11/05]

45. Neerland BE, Hov KR, Bruun Wyller V, et al. The protocol of the Oslo Study of Clonidine in Elderly Patients with Delirium; LUCID: a randomised placebo-controlled trial. *BMC geriatrics* 2015;15(1):7. doi: 10.1186/s12877-015-0006-3 [published Online First: 2015/04/19]

46. Oh ES, Akeju O, Avidan MS, et al. A roadmap to advance delirium research: Recommendations from the NIDUS Scientific Think Tank. *Alzheimer's & dementia : the journal of the Alzheimer's Association* 2020;16(5):726-33. doi: 10.1002/alz.12076 [published Online First: 2020/04/16]

47. Sessler CN, Gosnell MS, Grap MJ, et al. The Richmond Agitation-Sedation Scale: validity and reliability in adult intensive care unit patients. *AmJRespirCrit Care Med* 2002;166(10):1338-44. doi: 10.1164/rccm.2107138 [doi];166/10/1338 [pii]

48. Tieges Z, McGrath A, Hall RJ, et al. Abnormal level of arousal as a predictor of delirium and inattention: an exploratory study. *The American journal of geriatric psychiatry : official*

journal of the American Association for Geriatric Psychiatry 2013;21(12):1244-53. doi: 10.1016/j.jagp.2013.05.003

49. Hall RJ, Meagher DJ, Maclullich AM. Delirium detection and monitoring outside the ICU. *BestPractResClinAnaesthesiol* 2012;26(3):367-83. doi: S1521-6896(12)00035-3 [pii];10.1016/j.bpa.2012.07.002 [doi]

50. Ely EW, Inouye SK, Bernard GR, et al. Delirium in mechanically ventilated patients: validity and reliability of the confusion assessment method for the intensive care unit (CAM-ICU). *JAMA* 2001;286(21):2703-10. doi: 10.1001/jama.286.21.2703 [published Online First: 2001/12/26]

51. Khan BA, Perkins AJ, Gao S, et al. The Confusion Assessment Method for the ICU-7 Delirium Severity Scale: A Novel Delirium Severity Instrument for Use in the ICU. *Crit Care Med* 2017;45(5):851-57. doi: 10.1097/CCM.0000000000002368

52. Nasreddine ZS, Phillips NA, Bedirian V, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *Journal of the American Geriatrics Society* 2005;53(4):695-9. doi: 10.1111/j.1532-5415.2005.53221.x [published Online First: 2005/04/09]

53. Morris JC, Heyman A, Mohs RC, et al. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part I. Clinical and neuropsychological assessment of Alzheimer's disease. *Neurology* 1989;39(9):1159-65. [published Online First: 1989/09/01]

54. Tombaugh TN. Trail Making Test A and B: normative data stratified by age and education. *Archives of clinical neuropsychology : the official journal of the National Academy of Neuropsychologists* 2004;19(2):203-14. doi: 10.1016/S0887-6177(03)00039-8 [published Online First: 2004/03/11]

55. Tombaugh TN, Kozak J, Rees L. Normative data stratified by age and education for two measures of verbal fluency: FAS and animal naming. *Archives of clinical neuropsychology : the official journal of the National Academy of Neuropsychologists* 1999;14(2):167-77. [published Online First: 2003/11/01]

56. Wechsler D NH, Nordvik H. Wais-III Wechsler Adult Intelligence Scale : manual. 3. Ed. Stockholm: Psykologiförlaget 2003.

57. Kim DH, Afilalo J, Shi SM, et al. Evaluation of Changes in Functional Status in the Year After Aortic Valve Replacement. *JAMA Intern Med* 2019;179(3):383-91. doi: 10.1001/jamainternmed.2018.6738 [published Online First: 2019/02/05]

58. Afilalo J, Lauck S, Kim DH, et al. Frailty in Older Adults Undergoing Aortic Valve Replacement: The FRAILTY-AVR Study. *J Am Coll Cardiol* 2017;70(6):689-700. doi: 10.1016/j.jacc.2017.06.024 [published Online First: 2017/07/12]

59. Halaas NB, Blennow K, Idland AV, et al. Neurofilament Light in Serum and Cerebrospinal Fluid of Hip Fracture Patients with Delirium. *Dementia and geriatric cognitive disorders* 2018;46(5-6):346-57. doi: 10.1159/000494754 [published Online First: 2018/12/07]

60. Karikari TK, Pascoal TA, Ashton NJ, et al. Blood phosphorylated tau 181 as a biomarker for Alzheimer's disease: a diagnostic performance and prediction modelling study using data from four prospective cohorts. *The Lancet Neurology* 2020;19(5):422-33. doi: 10.1016/S1474-4422(20)30071-5 [published Online First: 2020/04/26]

61. Ballweg T, White M, Parker M, et al. Association between plasma tau and postoperative delirium incidence and severity: a prospective observational study. *British journal of anaesthesia* 2021;126(2):458-66. doi: 10.1016/j.bja.2020.08.061 [published Online First: 2020/11/25]

62. Yu L, Wen G, Zhu S, et al. Abnormal phosphorylation of tau protein and neuroinflammation induced by laparotomy in an animal model of postoperative delirium. *Experimental brain research* 2021 doi: 10.1007/s00221-020-06007-2 [published Online First: 2021/01/08]

63. Sajjad MU, Blennow K, Knapskog AB, et al. Cerebrospinal Fluid Levels of Interleukin-8 in Delirium, Dementia, and Cognitively Healthy Patients. *Journal of Alzheimer's disease : JAD* 2020;73(4):1363-72. doi: 10.3233/JAD-190941 [published Online First: 2020/01/14]

64. Hov KR, Bolstad N, Idland AV, et al. Cerebrospinal Fluid S100B and Alzheimer's Disease Biomarkers in Hip Fracture Patients with Delirium. *Dementia and geriatric cognitive disorders extra* 2017;7(3):374-85. doi: 10.1159/000481853 [published Online First: 2017/12/29]

65. Neerland BE, Hall RJ, Seljeflot I, et al. Associations Between Delirium and Preoperative Cerebrospinal Fluid C-Reactive Protein, Interleukin-6, and Interleukin-6 Receptor in Individuals with Acute Hip Fracture. *Journal of the American Geriatrics Society* 2016;64(7):1456-63. doi: 10.1111/jgs.14238 [published Online First: 2016/06/25]

66. Balaganapathy P, Baik SH, Mallilankaraman K, et al. Interplay between Notch and p53 promotes neuronal cell death in ischemic stroke. *Journal of cerebral blood flow and metabolism : official journal of the International Society of Cerebral Blood Flow and Metabolism* 2018;38(10):1781-95. doi: 10.1177/0271678X17715956

67. Wedervang-Resell K, Ueland T, Aukrust P, et al. Reduced levels of circulating adhesion molecules in adolescents with early-onset psychosis. *NPJ Schizophr* 2020;6(1):20. doi: 10.1038/s41537-020-00112-5

68. Fleming TR, DeMets DL, Roe MT, et al. Data monitoring committees: Promoting best practices to address emerging challenges. *Clin Trials* 2017;14(2):115-23. doi: 10.1177/1740774516688915

69. Wang YY, Yue JR, Xie DM, et al. Effect of the Tailored, Family-Involved Hospital Elder Life Program on Postoperative Delirium and Function in Older Adults A Randomized Clinical Trial. *Jama Internal Medicine* 2020;180(1):17-25. doi: 10.1001/jamainternmed.2019.4446

70. Su X, Meng ZT, Wu XH, et al. Dexmedetomidine for prevention of delirium in elderly patients after non-cardiac surgery: a randomised, double-blind, placebo-controlled trial. *Lancet* 2016 doi: 10.1016/S0140-6736(16)30580-3

71. Shehabi Y, Grant P, Wolfenden H, et al. Prevalence of delirium with dexmedetomidine compared with morphine based therapy after cardiac surgery: a randomized controlled trial (DEXmedetomidine COmpared to Morphine-DEXCOM Study). *Anesthesiology* 2009;111(5):1075-84. doi: 10.1097/ALN.0b013e3181b6a783 [doi]

72. Jamadarkhana S, Gopal S. Clonidine in adults as a sedative agent in the intensive care unit. *Journal of anaesthesiology, clinical pharmacology* 2010;26(4):439-45. [published Online First: 2011/05/07]

73. 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]

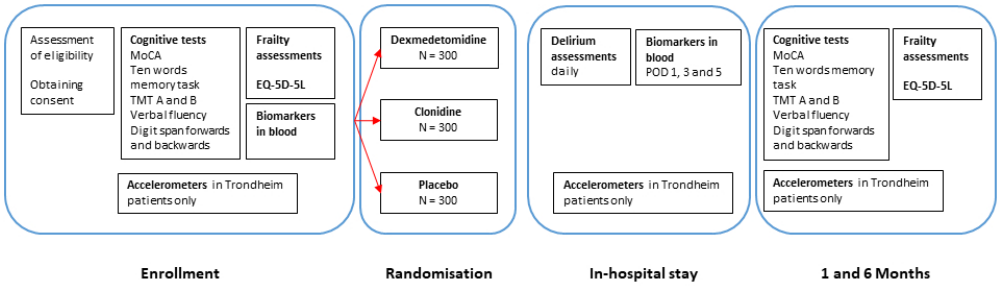

Figure 1:
Study schema. MoCA, Montreal Cognitive Assessment; TMT, Trail Making Test; EQ-5D-5L, EuroQol 5 Dimension 5 Level; POD, Postoperative Day

254x190mm (96 x 96 DPI)

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

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Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

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		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	6
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	11
Protocol version	#3	Date and version identifier	NA

Funding	#4	Sources and types of financial, material, and other support	26
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1-3,26
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	25-26
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	26
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	19-21
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	8-10,16,23
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	11
Objectives	#7	Specific objectives or hypotheses	10
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	11

Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	11
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	11-13
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	16
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	16, 20-21
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	21
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	16
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	16-19

Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	11-16, Table 2, Figure 1
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	21
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	11
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	13
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	13
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	11-13
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	13

Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	20-21
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	13,16-19, Table 2
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	21-22
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	19-20
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	21-23
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	21-23
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	21-23

Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	21
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	21
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	20-21
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	21
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	6,23,25
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	23
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	11
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	11

Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	19,20
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	25-26
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	20,25
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	20-21
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	6,23
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	23
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	25
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	11
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	14,19

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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

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TITLE PAGE

Title: 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

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ABSTRACT

Introduction: Postoperative delirium is common in older cardiac surgery patients and associated with negative short-term and long-term outcomes. The alpha-2-adrenergic receptor agonist dexmedetomidine shows promise as prophylaxis and treatment for delirium in intensive care units (ICU) and postoperative settings. Clonidine has similar pharmacological properties and can be administered both parenterally and orally. We aim to study whether repurposing of clonidine can represent a novel treatment option for delirium, and the possible effects of dexmedetomidine and clonidine on long-term cognitive trajectories, motor activity patterns and biomarkers of neuronal injury, and whether these effects are associated with frailty status.

Methods and analysis: This five-centre, double blind randomised controlled trial will include 900 cardiac surgery patients aged 70+. Participants will be randomized 1:1:1 to dexmedetomidine or clonidine or placebo. The study drug will be given as a continuous intravenous infusion from the start of cardiopulmonary bypass, at a rate of 0.4 µg/kg/h. The infusion rate will be decreased to 0.2 µg/kg/h postoperatively and be continued until discharge from the ICU or 24 hours postoperatively, whichever happens first.

Primary endpoint is the 7-day cumulative incidence of postoperative delirium (Diagnostic and Statistical Manual of Mental Disorders, 5th edition). Secondary endpoints include the composite endpoint of coma, delirium or death, in addition to delirium severity and motor activity patterns, levels of circulating biomarkers of neuronal injury, cognitive function and frailty status 1 and 6 months after surgery.

Ethics and dissemination: This trial is approved by the Regional Committee for Ethics in Medical Research in Norway (South-East Norway) and by the Norwegian Medicines Agency. Dissemination plans include publication in peer-reviewed medical journals and presentation at scientific meetings.

Trial registration number: EudraCT: 2021-001645-12. ClinicalTrials.gov: NCT05029050

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This multicentre trial will provide evidence for prophylactic efficacy of dexmedetomidine and clonidine in reducing the incidence of postoperative delirium as well as decline in cognitive function 1 and 6 months postoperatively in older cardiac surgical patients
- Inclusion of preoperative frailty assessments will provide evidence for frailty as a predictive marker of treatment effect
- The analysis of biomarkers will provide insights into the neural mechanisms in postoperative delirium and long-term cognitive dysfunction
- The analysis of activity by accelerometers will provide insight into motor activity patterns in subtypes of delirium
- The dose of the active drugs may potentially be too low or the duration of treatment too short in order to show effects

BACKGROUND

Delirium represents an acute change in awareness, attention and cognition, precipitated by an acute illness, trauma, intoxication or surgery.[1 2] Common additional features are agitation, hallucinations and poor compliance with medical treatment and care.

Delirium appears in all parts of the health care service, including intensive care units (ICUs) and postoperative settings, regular hospital wards, nursing homes, home nursing services and palliative departments. In a recent meta-analysis, Greaves and co-workers found a delirium prevalence of 24% postoperatively after coronary artery bypass grafting (CABG) surgery, aggregated over all age groups.[3] In a Norwegian study of patients ≥80 years undergoing open aortic valve replacement, the prevalence of postoperative delirium was above 60%.[4] Open heart surgery patients are especially susceptible to delirium. Probable causes may be established cardiovascular disease, micro-embolism from cardiopulmonary bypass (CPB), perioperative circulatory changes including ischemia-reperfusion injuries, systemic inflammation, blood-brain barrier disruption and very deep anaesthesia.[5 6]

Delirium is difficult to handle in clinical settings, increases length of hospital stay and the need for long-term care,[7 8 9] is expensive for the society,[10] represents a frightening experience for the patient and the relatives,[11] and is an independent risk factor for death after cardiac surgery.[12] Delirium is an independent risk factor for cognitive decline in older adults, and induces a more rapid trajectory of deterioration in those who already have dementia.[13 14]

Frailty is a risk factor for delirium,[15] but less is known regarding how frailty assessments can guide prophylactic and therapeutic measures and shared decision making.[16] Frailty is a state of impaired physiologic reserve and decreased resistance to stressors, which increases the risk of an adverse outcome.[17 18] It is a consequence of cumulative decline in many physiological systems.

Conventionally, delirium has been separated into hyperactive and hypoactive subtypes based on clinical impression,[19] but recent research using body-worn sensors indicates a more heterogeneous pattern of motor activity across the clinical delirium motor subtypes.[20 21] 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. A small postoperative study on cardiac surgery patients showed the possibility of detecting the amount of movement in sedated patients.[22]

Delirium is multifactorial and relate to both predisposing and to precipitating factors.[1,2] Routinely, several actions are taken in perioperative care to minimize the risk of delirium, such as appropriate management of pain and minimizing the use of sedative drugs like benzodiazepines. Further, non-pharmacological multicomponent interventions are essential,[23] but there is currently no compelling evidence to support the use of specific prophylactic pharmacological measures in routine perioperative care for patients at risk of postoperative delirium.[24]

However, dexmedetomidine, a parenterally administered alpha-2-adrenergic receptor agonist that attenuates sympathetic nervous system activity, shows promise as prophylaxis and treatment for delirium in ICUs and postoperative settings.[25 26] It has been hypothesised that dexmedetomidine may reduce postoperative delirium via its sympatholytic, anti-inflammatory and organ-protective effects.[27 28] In a recent meta-analysis, perioperative use of dexmedetomidine in various surgical procedures was associated with a lower incidence of postoperative delirium. The relative risk (RR) and 95% confidence interval (CI) was 0.52 (0.39-0.70) when compared with placebo.[25] Among newer studies in cardiac surgery, some,[29-32] but not all,[33 34] have found a beneficial short time effect on the incidence of delirium. A meta-analysis in cardiac surgery patients showed that dexmedetomidine could reduce the risk of postoperative delirium (Odds Ratio 0.56, 95% CI 0.36-0.89).[35] This meta-analysis even included the largest trial by Turan et al., with 800 participants, that was negative for dexmedetomidine.[34]. To the best of our knowledge, effects of dexmedetomidine upon long time

cognitive trajectories have so far not been assessed in this patient population. Nevertheless, the use of dexmedetomidine in ICUs is rapidly increasing.[26]

An alternative agent is clonidine, which has similar pharmacological properties to dexmedetomidine,[36] even though it's alpha-2-adrenergic selectivity is lower.[37] Clonidine can be administered both parenterally and orally, thus potentially widening its clinical usefulness.[36 37] Clonidine was originally launched as an antihypertensive agent, but it is also used as an analgesic drug. Further, clonidine has a long tradition as a sedative in patients with hyperactive delirium, and is used by several anaesthesiologists and intensivists.[38] This practice is based on their clinical experiences and knowledge on the drug's properties, but is so far not supported by placebo-controlled clinical trials. A pilot study indicated that clonidine infusion during the period of weaning from mechanical ventilation after surgery for aortic dissection may reduce the severity of delirium.[39] A recent study compared clonidine with dexmedetomidine postoperatively after CABG and found better effect on risk and duration of delirium of dexmedetomidine. Since no placebo control group was included, that study could not assess potential effects of clonidine.[40]

Thus, there is a need for prospective large-scale studies on the potential prophylactic effect of alpha-2-adrenergic receptor agonists on delirium in susceptible patients. The aims of the present planned trial are to study 1) whether repurposing of clonidine can represent a novel treatment option for delirium, and 2) the possible effects of dexmedetomidine and clonidine on long-term cognitive trajectories, motor activity patterns, patient rated outcome measures and biomarkers of neuronal injury, and 3) whether these effects are associated with frailty status.

METHODS AND ANALYSIS

Study design

ALPHA2PREVENT is a nationwide five-centre, double blind randomised controlled trial (RCT). Patients aged 70+ scheduled for open heart surgery will be randomized 1:1:1 to dexmedetomidine or clonidine or placebo. The patients will be cognitively assessed preoperatively, then assessed for any symptoms of delirium according to the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) criteria[41] or subsyndromal delirium[42] postoperatively, and finally assessed for cognitive function after 1 and 6 months (figure 1).

Study locations

The trial will be carried out at Oslo University Hospital (Ullevaal and Rikshospitalet) in Oslo, Haukeland University Hospital in Bergen, Trondheim University Hospital in Trondheim, and the University Hospital of Northern Norway in Tromsø, all in Norway.

Participants, randomisation and blinding

Patients will be assessed for eligibility and asked for participation in cooperation with the responsible thoracic surgeons or anaesthesiologists. A full listing of trial inclusion and exclusion criteria is displayed in table 1. Participants must be ≥70 years old, accepted for cardiac surgery with CPB and capable of giving signed informed consent. The surgical procedures may constitute CABG, valve replacement, surgery on the ascending aorta, or combinations of these. Main exclusion criteria are bradycardia, uncontrolled hypotension, ischemic stroke the last month or acute coronary syndrome last 24 hours,[43] left ventricular ejection fraction < 40%, severe renal failure or hepatic dysfunction, sepsis, planned deep hypothermia and circulatory arrest, as well as emergency surgery.

Table 1. Inclusion and exclusion criteria

Participants are eligible to be included in the study only if all of the following criteria apply:	Participants are excluded from the study if any of the following criteria apply:
1. Participant must be ≥70 years old at the time of signing the informed consent. 2. Participant must be accepted for cardiac surgery with cardiopulmonary bypass. 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. 3. Participant must be capable of giving signed informed consent.	4. Preoperative delirium (present at time of potential inclusion) 5. Known hypersensitivity to the active ingredient or components of the product 6. Bradycardia due to sick-sinus-syndrome, 2nd or 3rd degree AV-block (if not treated with pacemaker) or any other reason causing HR <50 bpm at time of inclusion 7. Uncontrolled hypotension 8. Ischemic stroke or transitory ischemic attack the last month or critical peripheral ischemia 9. Acute coronary syndrome last 24 hours. Acute coronary syndrome is defined according to international guidelines 10. Left ventricular ejection fraction < 40% 11. Severe renal impairment (estimated GFR < 20 ml/min) or expected requirement for renal replacement therapy 12. Severe hepatic dysfunction (liver enzyme three times the upper limit of normal together with a serum albumin concentration below the normal reference limit

	13. Reduced peripheral autonomous activity (e.g., spinal cord injury) 14. Current use of tricyclic antidepressants, monoamine reuptake inhibitors or ciclosporin 15. Endocarditis or sepsis 16. Pheochromocytoma 17. Planned deep hypothermia and circulatory arrest 18. Emergency surgery, defined as less than 24 hours from admission to surgery 19. Previously included in this study 20. Not speaking or reading Norwegian 21. Any other condition as evaluated by the treating physician

AV-block, atrioventricular block; HR, heart rate; GFR, glomerular filtration rate

Consenting patients will be randomly assigned 1:1:1, to dexmedetomidine, clonidine or placebo. Randomization will be computer generated with random permuted block sizes of 3 or 6, and stratified according to study centre. Allocation will be concealed by a web-based system that can be accessed no earlier than 3 days before surgery. The study drug will be prepared by an otherwise uninvolved research associate, ensuring that investigators, clinicians, outcome assessors and statisticians are blinded to the group assignment.

Data collected at study entry

The data collection will take place in connection with routine clinical care at the relevant hospital wards and the ICU (table 2). According to the selection criteria, electrocardiogram (ECG),

creatinine/estimated Glomerular Filtration Rate (eGFR), liver transaminases, albumin, and a recent echo-cardiography will be required, as well as a screening for preoperative delirium. At study entry, demographic data, medical history including cardiovascular and non-cardiovascular co-morbidities, prescription drugs used, sensory impairment, presence or absence of any fall within the past year, functional status including activities of daily living, surgical site and indication for surgery will be obtained. Haemodynamic variables, body mass index, American Society of Anesthesiologists Physical Status (ASA)-classification and Euroscore II will be recorded, and routine blood samples taken prior to surgery will be registered. Blood samples for biomarkers will be drawn preoperatively and on postoperative day 1, 3 and 5. Included patients will undergo preoperative cognitive tests and physical tests for assessment of frailty. Patient rated outcome measures (PROMs) will be assessed by use of the Norwegian version of the EuroQol 5 Dimension 5 Level (EQ-5D-5L) questionnaire.[44] The same tests and questionnaires will be used also after 1 and 6 months, for assessment of cognitive and functional trajectories.

Table 2. Study procedures

	Screening	**Baseline**	**Surgery**	**Postoperative day number:**								**1 and 6 months**
Procedure	**≤30 days before Day 0**	**-3 to -1 days before Day 0**	**Day 0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**Hospital discharge**	
Informed consent	X											
Assessment of eligibility	X											
Routine blood tests (i.e. creatinine, liver transaminases, albumin, troponin, proBNP)	X										X	
ECG	X			X								
Physical examination	X											

Past and current medical conditions	X										X
Vital signs	X	X	X	X	X	X	X	X	X	X	
Randomization		X									
Prescribed medications		X									
Demographic data		X									X
Blood samples for biomarkers		X		X		X		X			
ASA-classification and Euroscore II		X									
Cognitive assessments		X									X
Frailty assessments		X									X
PROM (EQ-5D-5L)		X									X
Body worn accelerometers (St Olav only)		X		X	X	X	X	X	X	X	X
Study intervention			X	X							
Safety review (incl hemodynamic variables, AE/SAE-review, death)			X	X	X	X	X	X	X		X
Postoperative variables (e.g., vital signs, medications, transfusions, re-operations, respiratory support)				X	X	X	X	X	X		
Routine assessments of delirium, 3x/day (by nursing staff); CAM-ICU, RASS			X	X	X	X	X	X	X		
Delirium assessments DSM-5 based, 1x/day (by research assistant)				X	X	X	X	X	X		X[a]
Pain assessment (NRS)				X	X	X	X	X	X		
Registration of per-operative variables (e.g., type of surgery, medications, transfusions,										X	

vital parameters, duration of surgery/anaesthesia)											
Registration of post-operative complications										X	
Registration of total dose and duration of study medication										X	

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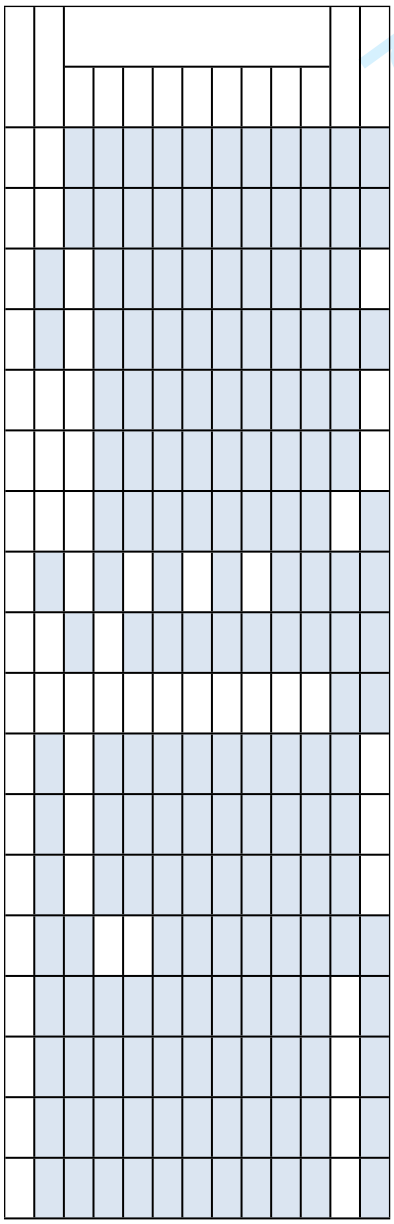

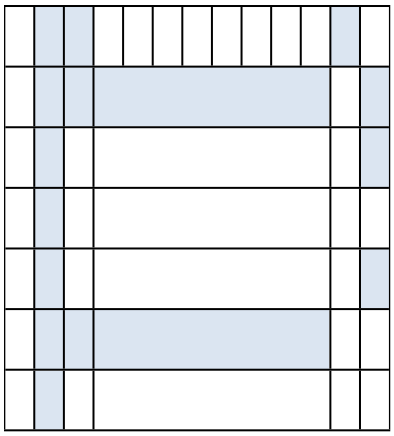

ProBNP, Pro B-type Natriuretic Peptide; ECG, electrocardiogram; PROM, Patient Rated Outcome Measure; ASA-classification, American Society of Anesthesiologists Physical Status Classification; AE, Adverse Event; SAE, Serious AE; CAM-ICU, Confusion Assessment Method for Intensive Care Units; RASS, Richmond Agitation Sedation Scale; DSM-5, Diagnostic and Statistical Manual of Mental Disorders, 5th edition; NRS, Numerical Rating Scale

[a] No delirium assessment at follow-up after 6 months

Trial interventions

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 the step-down unit, 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.

Concomitant therapy and rescue medicine

Patients will not be included if they use tricyclic antidepressants, monoamine reuptake inhibitors or cyclosporine. The perioperative anaesthesia will be given per routine at participating institutions. If

delirium develops and pharmacological intervention is needed, the study drug will be stopped, and further treatment will be according to local routines and the treating physician's preferences.

Primary endpoint

The primary endpoint for ALPHA2PREVENT is the cumulative incidence of postoperative delirium within 7 days. Postoperative delirium assessment will start as soon as possible after admission to the ICU, and will continue daily until the seventh postoperative day or until discharge from the university hospital, whichever happens first. To allow for differences in the duration of the postoperative observation period, time until delirium diagnosis will be recorded and the cumulative incidence will be assessed using Kaplan Meier estimates and compared between groups with the log-rank test as described below. A clinical assessment for delirium will also be repeated at the 1-month follow-up, to pick up signs of persistent delirium.

The diagnosis of delirium will be ascertained using all available information, and will be determined to be present if participants meet all DSM-5 criteria[41] by using a standardized procedure developed for our previous study[45] and as recommended by others[46], table 3. The methods are refined in order, in a stepwise approach, to assess presence or absence of the diagnostic criteria in DSM-5 and will be carried out once daily by specially trained research assistants. Level of arousal will be assessed using the Norwegian versions of Richmond Agitation Sedation Scale (RASS)[47] and Observational Scale of Level of Arousal (OSLA).[48] Attention and awareness will be evaluated using objective tests (vigilance "A"-test, months of the years backwards, days of the week backwards, and counting down from 20 to 1)[49] and observations by the examiner of the patient´s distractibility, comprehension and tendency to lose the thread of conversation. Presence of additional cognitive disturbances will be assessed by tests for orientation and recall test of three words (different words for each day), as well as information derived from nursing staff and clinical notes. Acute change in the patient´s mental condition, and fluctuations of any disturbance, will be ascertained through informant history from nursing staff and derived from clinical notes. Nurses will, as part of their routine and for each shift

(i.e., three times daily), 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)[50] and RASS. The same delirium assessment tools will be used for the ICU, step-down and bed wards. .The results from each of the CAM-ICU-items, as well as the total CAM-ICU score, will also be used as a source of information for making the final delirium diagnosis.

Finally, as a quality assurance, two or more highly experienced delirium researchers will independently use all available information (including the research assistants' assessments) on each patient to decide if the DSM-5 criteria for delirium are fulfilled. An interrater agreement for the diagnosis of delirium will be calculated and disagreements will be resolved through discussion.

Subsyndromal delirium (table 3) will be defined as evidence of change, in addition to any one of these: altered arousal, attentional deficits, other cognitive change, delusions or hallucinations. DSM-5 delirium criteria D and E must be met.

Table 3. Diagnostic algorithm for DSM-5 delirium.

DSM-5 criteria	**Tests to be performed or information needed**		**Criterium fulfilled?**	
			Yes	**No**
A. Disturbance in **attention** (i.e., reduced ability to direct, focus, sustain, and shift attention) and **awareness** (reduced orientation to the environment).	**TEST**	**Cut off (definition of inattention)**		
	Digit span forward	less than 5 forward		
	SAVEAHAART	more than 2 errors		
	Days of the week backwards	any error		

	<table><tr><td>**Months of the year backwards**</td><td>unable to pass June</td></tr><tr><td>**Count backwards from 20 to 1**</td><td>any error</td></tr><tr><td>**Digit span backwards**</td><td><5 digits</td></tr></table> <u>Observation (by the examiner during the interview):</u> Distractibility. Comprehension. Tendency to lose the tread of conversation Level of arousal measured using RASS and OSLA		
B. The disturbance develops over a **short period of time** (usually hours to a few days), represents a **change** from baseline attention and awareness, and tends to **fluctuate** in severity during the course of a day.	Acute onset and/or fluctuation obtained from informant history from nursing staff and clinical notes <u>Questions to carer/ nursing staff or derived from clinical notes:</u> Has there been a sudden change in the patient´s mental state? Does the patient seem to be better at any period in the day compared to other times? Has the level of consciousness been altered (drowsy/ not interacting or agitated)? Sleep-wake cycle disturbances?		

C. An additional disturbance in **cognition** (e.g., memory deficit, disorientation, language, visuospatial ability, or perception).	Questions to the patient: Orientation to time, place and person 3 item recall at three minutes Questions from CAM-ICU: Why are you in hospital? Will a stone float in water? Are there fish in the sea? Questions to carer/ nursing staff or derived from clinical notes: Any evidence of perceptual disturbances as illusions or hallucinations? Memory disturbances? Psychotic symptoms? Psychomotor abnormalities?		
D. The disturbances in criteria A and C are **not explained by another preexisting, established, or evolving neurocognitive disorder** and do not occur in the context of a severely reduced level of arousal, such as coma.	Information from history/chart/clinical assessment		
E. There is evidence from the history, physical examination, or laboratory findings that the disturbance is a direct **physiologic consequence** of another medical condition, substance intoxication or withdrawal (i.e., because of	By virtue of the surgery, all participants are considered to fulfil this criterion.		

a drug of abuse or to a medication), or exposure to a toxin or is because of multiple etiologies.			
Delirium based on the tests and information above?	All DSM-5 criteria fulfilled		
Subsyndromal delirium based on the tests and information above?	Defined as evidence of change, in addition to any one of these: (a) altered arousal, (b) attentional deficits, (c) other cognitive change, (d) delusions or hallucinations. Criteria D and E must be met.		

DSM-5, Diagnostic and Statistical Manual of Mental Disorders, 5th edition; RASS, Richmond Agitation Sedation Scale; OSLA, Observational Scale of Level of Arousal; CAM-ICU, Confusion Assessment Method for Intensive Care Units

Secondary endpoints

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, patient rated health status, frailty status, and comparison of change in frailty status. In explorative analyses, the secondary outcomes will also be assessed between patients with or without postoperative delirium. 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.

All endpoints will be assessed using Norwegian versions of validated instruments: Delirium severity will be measured using CAM-ICU-7,[51] OSLA[48] and RASS;[47] motor activity patterns using body worn accelerometers; cognitive function using Montreal Cognitive Assessment (MoCA),[52] immediate and delayed recall from The Ten Words Memory Task from The Consortium to Establish a Registry for Alzheimer's Disease,[53] Trail Making Test (TMT) version A and B,[54] semantic and phonemic verbal fluency,[55] digit span forwards and backwards (by Wechsler Adult Intelligence Scale);[56] 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 58] and by the shorter Essential Frailty Toolset;[59] and patient rated health status using the EQ-5D-5L questionnaire.[44]

For assessment of cognitive trajectories, the same cognitive tests will be performed in a stable phase preoperatively as well as after 1 and 6 months. Information regarding functional status will be obtained from the patient preoperatively and from either the patient or their proxy at follow-up, depending on the patient's ability to provide detailed information.

For a sub-sample of one hundred patients from the Trondheim cohort, motor activity will be measured by 3D accelerometer inertial sensors (AX3 sensors) (Axivity Ltd., Newcastle, UK) sampled at 100 Hz and processed using custom made software. Accelerometers will be attached to the frontal part of the waist, the dominant thigh (ventrally, midthigh), and on the dominant wrist pre surgery. Motor activity patterns will be monitored continuously (day and nights) before and the five first days after surgery or until discharge from hospital, and over one week after 1 and 6 months. Sensor data will be analyzed regarding both quantity and quality of movements and compared with the clinical delirium assessments.

Biomarkers

In addition to routine blood tests, blood will be taken in the morning for specific study analyses (serum, plasma and wholeblood) before surgery, and at postoperative day 1, 3 and 5 (or earlier if discharged before day 5) and frozen at –80 °C locally. Frozen samples will then be shipped to the coordinating centre (Oslo) to be stored in a biobank at –80 °C for future analyses. The stored blood samples will be analysed for promising markers such as NFL already known to be associated with delirium,[609] p-tau181 associated with dementia and delirium,[61-63] and possibly other biomarkers of neuronal degeneration, neuroinflammation and neurotransmitters,[64-68] using state-of-the-art ultrasensitive assays to evaluate their association with observed clinical responses to the study drugs.

Standardised training

The research assistants across all sites will receive standardized training for all study measures prior to study initiation, including cognitive tests, delirium assessments and measurements of frailty indicators. Retraining will be provided as necessary. Detailed instructions and operation manuals in Norwegian language, including an instruction video for the MoCA, will be made available to all assessors.

Data management and monitoring

Participant data will be collected by authorized trained personnel, be recorded on electronic Case Report Forms (CRF) and stored on a password protected database. Paper files will be stored in locked cabinets accessible to team members only. Study monitors will perform ongoing source data verification to confirm that data entered into the CRFs are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol, International Conference on Harmonization Good Clinical Practice, and all applicable regulatory requirements. Records and documents, including signed Informed Consent Forms, pertaining to the conduct of this study will be retained by the investigators for 15 years after study completion.

Safety and adverse events management

Immediate safety concerns will be handled by the treating anaesthesiologist, who will determine if the participant should continue or discontinue study intervention. 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. Since patients are closely monitored in the perioperative phase of cardiac surgery, potential adverse circulatory effects will be rapidly revealed and corrected;

- Temporal epicardial pacing wires are placed routinely during cardiac surgery, and bradycardia will be treated with atropine and/or pacemaker as per routine.
- Hypotension will be treated at discretion of the treating anaesthesiologists, who are permitted to reduce dose of the study drug as necessary to preserve haemodynamic stability, following guidelines and local routines. A Mean Arterial Pressure (MAP) >55-60mmHg is recommended.
- If not rapid and satisfactory response on other measures is achieved, the treating anaesthesiologist will consider to turn off the infusion/unblind the study.

Planned time points for safety assessments are provided in table 2.

The following safety indicators will be compared between the three treatment groups with appropriate statistical methods: Highest and lowest heart rate and mean arterial blood pressure, oxygen saturation, number of units for blood transfusion, volume of postoperative blood loss, use of pressor substances, use of rescue medication, number of episodes of bradycardia, hypotension or hypoxemia in need of intervention, perioperative myocardial infarction and stroke, postoperative serum concentrations of troponin and Pro B-type Natriuretic Peptide (proBNP), mortality.

An independent Data Monitoring Committee will have unblinded access to all data and meet at pre-planned inclusion milestones and whenever the members find it necessary.[69] Meetings are pre-planned after inclusion of 20, 50, 100 and 400 participants, to assess safety indicators and to advise on continuation or termination of the study. 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.

Current sample size justification

The proportion of patients experiencing postoperative delirium after open heart surgery for all ages has been reported to be 24%,[3] and higher in older adults.[4] Since the lower age limit in our trial is 70 years, we estimate that the proportion in the control group will be at least 30%. The most recent meta-analysis of the effect of dexmedetomidine estimates the delirium risk to be reduced to approximately half of the untreated group (*i.e.*, 15%).[25] We anticipate that the effect of clonidine may be weaker, but still clinically relevant. We have thus powered the study based on an estimated delirium incidence of 20% in the clonidine group. 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 drop-out 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 drop-out and considering the three-arms (Supplementary file 1).

Statistical analysis

The primary analysis population will be the intention-to-treat population, and all tests will be two-sided. The primary objective in this study is to prevent postoperative delirium. The primary endpoint is the cumulative incidence of postoperative delirium. In the analysis of this endpoint, time to diagnosis of delirium will be used to account for the varying postoperative observation time due to difference in time to discharge or transfer to other hospitals will be different. The cumulative incidence will therefore be estimated using 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. Patients who are discharged from the university hospital during the observation period or reach the end of the observation period (7 days) without having developed delirium, are regarded as censored. We consider that treatment group allocation will not influence the risk of being censored. Those who die prior to 7 days, will also be regarded as censored in the primary analysis, but we will carry out a secondary analysis with the combined endpoint *death or delirium.* The same approach will be applied for those who are comatose, and thus impossible to evaluate for delirium. Additional analyses may also include estimating the incidence of delirium treating deaths as a competing risk by the Fine and Gray method.

All analyses will be adjusted for study centre which was used to as a stratification variable in the randomisation process.

Sensitivity analyses will be carried out by estimating hazard ratios using Cox' proportional hazards model to adjust for potential imbalance of prognostic factors between treatment groups.

Secondary endpoints as the cumulative incidence of death, coma or postoperative delirium will be analysed using the Kaplan Meier estimator and the logrank test as above. Additional analyses by Cox' proportional hazards model may also be performed. Mean duration of delirium; severity of delirium; combination of duration and severity of delirium; cognitive tests after 1 and 6 months; EQ-5D-5L scores after 1 and 6 months; and postoperative plasma concentrations of NFL and p-tau181 will be compared between treatments with appropriate regression models which will be defined in a Statistical Analysis Plan prior to analysis.

Frailty as risk factor for delirium and for adverse effects of the study medication, will be analysed by linear or logistic regression (as appropriate), adjusted for other known risk factors. The association between frailty and delirium will be analysed by adding frailty as a covariate in a Cox'proportional hazards model on time to delirium (as above). 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. The association between frailty and occurrence of adverse events (AE) will be estimated by logistic regression models including covariates as above.

No interim analyses of the efficacy of the treatments are planned. A detailed statistical analysis plan will be finalized prior to unblinding.

Ethics and dissemination

This trial is approved by the Regional Committee for Ethics in Medical Research in Norway (South-East Norway) and by the Norwegian Medicines Agency, and will be conducted in accordance with consensus ethical principles derived from international guidelines including the Declaration of Helsinki. The results of this study will be published in peer-reviewed medical journals, as well as presented at scientific meetings

Discussion

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.

One should expect that treatment options that can prevent delirium in a short-term perspective, would also improve the long-term cognitive prognosis. Evidence for such an effect is slowly emerging for non-pharmacological interventions,[70] but is lacking regarding drug treatment.

Published studies of dexmedetomidine for prevention of delirium in ICU vary largely with respect to dosing regimens, from 0.1[71 72] to 1.4 µg/kg/h.[33] Many of the authors also administered an initial bolus. In the cardiac surgery context, Turan et al started dexmedetomidine infusion already before start of CPB, gave 0.4 µg/kg/h postoperatively,[34] and found more side effects in the actively treated than in the placebo group. We have chosen a careful dosage of 0.4 µg/kg/h peroperatively and 0.2 µg/kg/h postoperatively, with no bolus, to reduce the risk of AE, but not so low that we cannot expect an effect on delirium.

Regarding clonidine, the recommended dosage varies greatly between sources, but is mainly in the range 1-1.5 µg/kg/h.[73] We will dose the drug considerably lower, to avoid side effects. There is a shortage of studies comparing i.v. dexmedetomidine and i.v. clonidine in ICU or postoperative settings.[74] 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[74] and a recent meta-analysis favour equipotency mg per mg.[75] Thus, our choice is fairly pragmatic, but the doses are similar to that currently used in many ICUs as part of routine practice.

To further reduce the risk of hemodynamic instability due to the combination of anaesthesiological procedures and study drug at the start of surgery, we will postpone infusion of study drug until the CPB is established. 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.

Strengths of this trial are the prospective and randomised placebo controlled design, the use of two relevant and much used drugs, inclusion of a high number of patients from multiple sites, adequate statistic strength, repeated cognitive and frailty assessments, use of body-worn accelerometers, and repeated samples of biomarkers. The analyses of biomarkers reflecting neural injury will give us increased understanding of the pathophysiological mechanisms of delirium. Inclusion of preoperative frailty assessments will provide evidence for frailty as a predictive marker of treatment effect and allow for interaction analyses. The use of body-worn accelerometers will provide insight into motor activity patterns in subtypes of delirium.

This trial has, however, some limitations to consider. The exclusion criteria might limit the generalisability of our findings to other patient populations. 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. The dose of the active drugs might be too low or the duration of treatment be too short in order to show effects. As many patients live far away from the study site, there is a potential for missing long-term data.

Should the treatment have a positive effect, it would have important beneficial implications for patients, carers and society, such as alleviating acute patient distress and carer burden. If this treatment could reduce longer-term negative effects of delirium, it might have significant consequences for financial and human resource use in health care.

DECLARATIONS

Patient and public involvement: Panellists from the user panel established by the Norwegian National Advisory Unit on Ageing and Health, participate in the Trial Advisory Board. They have experience as relatives to patients with dementia or delirium, have given valuable input to the project plans and will follow up during the project period.

Ethics approval: The trial is approved by the Regional Committee for Ethics in Medical Research in Norway (South-east Norway) (REK 262384), June 9th 2021, and by the Norwegian Medicines Agency June 17th 2021.

Availability of data and materials: Materials can be available upon reasonable request to the corresponding author. However, availability is dependent on approval from the Regional Ethics Committee and the local data protection officer.

Competing interest: HZ has served at scientific advisory boards and/or as a consultant for Alector, Eisai, Denali, Roche Diagnostics, Wave, Samumed, Siemens Healthineers, Pinteon Therapeutics, Nervgen, AZTherapies, CogRx and Red Abbey Labs, has given lectures in symposia sponsored by Cellectricon, Fujirebio, Alzecure and Biogen, and is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program (outside submitted work).

AJCS is advisor for Prolira, a start-up company that develops an EEG-based delirium monitor. Any (future) profits from EEG-based delirium monitoring will be used for future scientific research only.

GS has participated in one advisory meeting for Biogen. HMN has received lecture fees from Vifor Pharma and Orion Pharma.

The other authors declare that they have no competing interests.

Consent for publication: Not required

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Author contributions:

Drafting of the manuscript: BEN

Critical revision of the manuscript for important intellectual content: BEN, RB, RH, JLH, AKK, SAL, IM, HMN, JR, GS, ES, NKS, ES, AS, ØSS, TT, AW, HZ, TBW, MRS

Obtained funding: TBW

All authors contributed to the writing of the manuscript and approved the final version.

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Abbreviations:

Abbreviation	**Explanation**
AE	Adverse Event
ALPHA2PREVENT	Alpha-2-adrenergic receptor agonists for the prevention of delirium and cognitive decline after open heart surgery: randomised controlled trial
ASA classification	American Society of Anesthesiologists Physical Status Classification
CABG	Coronary Artery Bypass Grafting
CAM-ICU	Confusion Assessment Method for Intensive Care Units
CPB	Cardiopulmonary Bypass
CRF	Case Report Form
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th edition
ECG	Electrocardiogram
EQ-5D-5L	EuroQol 5 Dimension 5 Level

FI	Frailty Index
GFR	Glomerular Filtration Rate
ICU	Intensive Care Unit
MAP	Mean Arterial Pressure
MoCA	Montreal Cognitive Assessment
NFL	Neurofilament light
NRS	Numerical Rating Scale
OSLA	Observational Scale of Level of Arousal
ProBNP	Pro B-type Natriuretic Peptide
PROM	Patient Rated Outcome Measure
RASS	Richmond Agitation Sedation Scale
RCT	Randomised Controlled Trial
SAE	Serious Adverse Event
TMT	Trail Making Test

LEGENDS

Figure 1:

Study schema. MoCA, Montreal Cognitive Assessment; TMT, Trail Making Test; EQ-5D-5L, EuroQol 5 Dimension 5 Level; POD, Postoperative Day

REFERENCES

1. Marcantonio ER. Delirium in Hospitalized Older Adults. *The New England journal of medicine* 2017;377(15):1456-66. doi: 10.1056/NEJMcp1605501 [published Online First: 2017/10/12]
2. Wilson JE, Mart MF, Cunningham C, et al. Delirium. *Nat Rev Dis Primers* 2020;6(1):90. doi: 10.1038/s41572-020-00223-4
3. Greaves D, Psaltis PJ, Ross TJ, et al. Cognitive outcomes following coronary artery bypass grafting: A systematic review and meta-analysis of 91,829 patients. *International journal of cardiology* 2019;289:43-49. doi: 10.1016/j.ijcard.2019.04.065 [published Online First: 2019/05/13]
4. Eide LS, Ranhoff AH, Fridlund B, et al. Comparison of frequency, risk factors, and time course of postoperative delirium in octogenarians after transcatheter aortic valve implantation versus surgical aortic valve replacement. *The American journal of cardiology* 2015;115(6):802-9. doi: 10.1016/j.amjcard.2014.12.043 [published Online First: 2015/02/04]
5. Hollinger A, Siegemund M, Goettel N, et al. Postoperative Delirium in Cardiac Surgery: An Unavoidable Menace? *Journal of cardiothoracic and vascular anesthesia* 2015;29(6):1677-87. doi: 10.1053/j.jvca.2014.08.021 [published Online First: 2015/10/13]
6. Abrahamov D, Levran O, Naparstek S, et al. Blood-Brain Barrier Disruption After Cardiopulmonary Bypass: Diagnosis and Correlation to Cognition. *The Annals of thoracic surgery* 2017;104(1):161-69. doi: 10.1016/j.athoracsur.2016.10.043
7. Gleason LJ, Schmitt EM, Kosar CM, et al. Effect of Delirium and Other Major Complications on Outcomes After Elective Surgery in Older Adults. *JAMA Surg* 2015;150(12):1134-40. doi: 10.1001/jamasurg.2015.2606
8. Witlox J, Eurelings LS, de Jonghe JF, et al. Delirium in elderly patients and the risk of postdischarge mortality, institutionalization, and dementia: a meta-analysis. *JAMA* 2010;304(4):443-51. doi: 304/4/443 [pii];10.1001/jama.2010.1013 [doi]
9. Krogseth M, Wyller TB, Engedal K, et al. Delirium is a risk factor for institutionalization and functional decline in older hip fracture patients. *Journal of psychosomatic research*

2014;76(1):68-74. doi: 10.1016/j.jpsychores.2013.10.006 [published Online First: 2013/12/24]

10. Pezzullo L, Streatfeild J, Hickson J, et al. Economic impact of delirium in Australia: a cost of illness study. *BMJ Open* 2019;9(9):e027514. doi: 10.1136/bmjopen-2018-027514 [published Online First: 2019/09/19]

11. Instenes I, Gjengedal E, Eide LSP, et al. "Eight Days of Nightmares ... " - Octogenarian Patients' Experiences of Postoperative Delirium after Transcatheter or Surgical Aortic Valve Replacement. *Heart, lung & circulation* 2018;27(2):260-66. doi: 10.1016/j.hlc.2017.02.012 [published Online First: 2017/04/12]

12. Gottesman RF, Grega MA, Bailey MM, et al. Delirium after coronary artery bypass graft surgery and late mortality. *Annals of neurology* 2010;67(3):338-44. doi: 10.1002/ana.21899 [published Online First: 2010/04/08]

13. Davis DH, Muniz-Terrera G, Keage HA, et al. Association of Delirium With Cognitive Decline in Late Life: A Neuropathologic Study of 3 Population-Based Cohort Studies. *JAMA Psychiatry* 2017 doi: 10.1001/jamapsychiatry.2016.3423 [published Online First: 2017/01/24]

14. Saczynski JS, Marcantonio ER, Quach L, et al. Cognitive trajectories after postoperative delirium. *The New England journal of medicine* 2012;367(1):30-9. doi: 10.1056/NEJMoa1112923 [published Online First: 2012/07/06]

15. Persico I, Cesari M, Morandi A, et al. Frailty and Delirium in Older Adults: A Systematic Review and Meta-Analysis of the Literature. *Journal of the American Geriatrics Society* 2018;66(10):2022-30. doi: 10.1111/jgs.15503 [published Online First: 2018/09/22]

16. van Beek-Peeters J, van Noort EHM, Faes MC, et al. Shared decision making in older patients with symptomatic severe aortic stenosis: a systematic review. *Heart* 2020;106(9):647-55. doi: 10.1136/heartjnl-2019-316055 [published Online First: 2020/02/01]

17. Clegg A, Young J, Iliffe S, et al. Frailty in elderly people. *Lancet* 2013;381(9868):752-62. doi: S0140-6736(12)62167-9 [pii];10.1016/S0140-6736(12)62167-9 [doi]

18. Guidet B, de Lange DW, Boumendil A, et al. The contribution of frailty, cognition, activity of daily life and comorbidities on outcome in acutely admitted patients over 80 years in European ICUs: the VIP2 study. *Intensive care medicine* 2020;46(1):57-69. doi: 10.1007/s00134-019-05853-1

19. Meagher DJ, Leonard M, Donnelly S, et al. A longitudinal study of motor subtypes in delirium: frequency and stability during episodes. *JPsychosomRes* 2012;72(3):236-41. doi: S0022-3999(11)00298-4 [pii];10.1016/j.jpsychores.2011.11.013 [doi]

20. Godfrey A, Leonard M, Donnelly S, et al. Validating a new clinical subtyping scheme for delirium with electronic motion analysis. *Psychiatry research* 2010;178(1):186-90. doi: 10.1016/j.psychres.2009.04.010 [published Online First: 2010/05/11]

21. Evensen S, Bourke AK, Lydersen S, et al. Motor activity across delirium motor subtypes in geriatric patients assessed using body-worn sensors: a Norwegian cross-sectional study. *BMJ Open* 2019;9(2):e026401. doi: 10.1136/bmjopen-2018-026401 [published Online First: 2019/03/04]

22. Harbo EF, Fuglerud SS, Skjaervold NK. Visualisation of limb movements by accelerometers in sedated patients. *Crit Care* 2020;24(1):283. doi: 10.1186/s13054-020-02975-7 [published Online First: 2020/06/05]

23. Needham MJ, Webb CE, Bryden DC. Postoperative cognitive dysfunction and dementia: what we need to know and do. *British journal of anaesthesia* 2017;119(suppl_1):i115-i25. doi: 10.1093/bja/aex354 [published Online First: 2017/11/22]

24. Siddiqi N, Harrison JK, Clegg A, et al. Interventions for preventing delirium in hospitalised non-ICU patients. *The Cochrane database of systematic reviews* 2016;3:CD005563. doi: 10.1002/14651858.CD005563.pub3 [published Online First: 2016/03/12]

25. Flukiger J, Hollinger A, Speich B, et al. Dexmedetomidine in prevention and treatment of postoperative and intensive care unit delirium: a systematic review and meta-analysis.

Annals of intensive care 2018;8(1):92. doi: 10.1186/s13613-018-0437-z [published Online First: 2018/09/22]

26. Bajwa S, Kulshrestha A. Dexmedetomidine: An Adjuvant Making Large Inroads into Clinical Practice. *Annals of medical and health sciences research* 2013;3(4):475-83. doi: 10.4103/2141-9248.122044 [published Online First: 2014/01/01]

27. Flanders CA, Rocke AS, Edwardson SA, et al. The effect of dexmedetomidine and clonidine on the inflammatory response in critical illness: a systematic review of animal and human studies. *Crit Care* 2019;23(1):402. doi: 10.1186/s13054-019-2690-4 [published Online First: 2019/12/13]

28. Sanders RD, Wehrman J, Irons J, et al. Meta-analysis of randomised controlled trials of perioperative dexmedetomidine to reduce delirium and mortality after cardiac surgery. *British journal of anaesthesia* 2021; 127(5):e168-e70. doi: 10.1016/j.bja.2021.08.009

29. Li CJ, Wang BJ, Mu DL, et al. Randomized clinical trial of intraoperative dexmedetomidine to prevent delirium in the elderly undergoing major non-cardiac surgery. *The British journal of surgery* 2020;107(2):e123-e32. doi: 10.1002/bjs.11354 [published Online First: 2020/01/07]

30. Likhvantsev VV, Landoni G, Grebenchikov OA, et al. Perioperative Dexmedetomidine Supplement Decreases Delirium Incidence After Adult Cardiac Surgery: A Randomized, Double-Blind, Controlled Study. *Journal of cardiothoracic and vascular anesthesia* 2020 doi: 10.1053/j.jvca.2020.02.035 [published Online First: 2020/04/09]

31. van Norden J, Spies CD, Borchers F, et al. The effect of peri-operative dexmedetomidine on the incidence of postoperative delirium in cardiac and non-cardiac surgical patients: a randomised, double-blind placebo-controlled trial. *Anaesthesia* 2021 doi: 10.1111/anae.15469 [published Online First: 2021/05/08]

32. Peng K, Shen YP, Ying YY, et al. Perioperative dexmedetomidine and 5-year survival in patients undergoing cardiac surgery. *British journal of anaesthesia* 2021 doi: 10.1016/j.bja.2021.03.040 [published Online First: 2021/06/05]

33. Subramaniam B, Shankar P, Shaefi S, et al. Effect of Intravenous Acetaminophen vs Placebo Combined With Propofol or Dexmedetomidine on Postoperative Delirium Among Older Patients Following Cardiac Surgery: The DEXACET Randomized Clinical Trial. *JAMA* 2019;321(7):686-96. doi: 10.1001/jama.2019.0234 [published Online First: 2019/02/20]

34. 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]

35. Li P, Li LX, Zhao ZZ, et al. Dexmedetomidine reduces the incidence of postoperative delirium after cardiac surgery: a meta-analysis of randomized controlled trials. BMC anesthesiology 2021;21(1):153. doi: 10.1186/s12871-021-01370-1 [published Online First: 2021/05/20]

36. Pichot C, Ghignone M, Quintin L. Dexmedetomidine and clonidine: from second- to first-line sedative agents in the critical care setting? *Journal of intensive care medicine* 2012;27(4):219-37. doi: 10.1177/0885066610396815 [published Online First: 2011/04/29]

37. Khan ZP, Ferguson CN, Jones RM. alpha-2 and imidazoline receptor agonists. Their pharmacology and therapeutic role. *Anaesthesia* 1999;54(2):146-65.

38. Wang JG, Belley-Cote E, Burry L, et al. Clonidine for sedation in the critically ill: a systematic review and meta-analysis. *Crit Care* 2017;21(1):75. doi: 10.1186/s13054-017-1610-8 [published Online First: 2017/03/24]

39. Rubino AS, Onorati F, Caroleo S, et al. Impact of clonidine administration on delirium and related respiratory weaning after surgical correction of acute type-A aortic dissection: results of a pilot study. *InteractCardiovascThoracSurg* 2010;10(1):58-62. doi: icvts.2009.217562 [pii];10.1510/icvts.2009.217562 [doi]

40. Shokri H, Ali I. A randomized control trial comparing prophylactic dexmedetomidine versus clonidine on rates and duration of delirium in older adult patients undergoing coronary

679 artery bypass grafting. *Journal of clinical anesthesia* 2020;61:109622. doi:
680 10.1016/j.jclinane.2019.09.016 [published Online First: 2019/11/02]
681 41. AmericanPsychiatricAssociation. Diagnostic and Statistical Manual of Mental Disorders: DSM-5
682 (5th ed.). Washington DC: American Psychiatric Association 2013.
683 42. Cole MG, Ciampi A, Belzile E, et al. Subsyndromal delirium in older people: a systematic review of
684 frequency, risk factors, course and outcomes. *Int J Geriatr Psychiatry* 2013;28(8):771-80. doi:
685 10.1002/gps.3891
686 43. Collet JP, Thiele H, Barbato E, et al. 2020 ESC Guidelines for the management of acute coronary
687 syndromes in patients presenting without persistent ST-segment elevation. *European heart*
688 *journal* 2021;42(14):1289-367. doi: 10.1093/eurheartj/ehaa575 [published Online First:
689 2020/08/30]
690 44. EuroQol G. EuroQol--a new facility for the measurement of health-related quality of life. *Health*
691 *policy (Amsterdam, Netherlands)* 1990;16(3):199-208. doi: 10.1016/0168-8510(90)90421-9
692 [published Online First: 1990/11/05]
693 45. Neerland BE, Hov KR, Bruun Wyller V, et al. The protocol of the Oslo Study of Clonidine in Elderly
694 Patients with Delirium; LUCID: a randomised placebo-controlled trial. *BMC geriatrics*
695 2015;15(1):7. doi: 10.1186/s12877-015-0006-3 [published Online First: 2015/04/19]
696 46. Oh ES, Akeju O, Avidan MS, et al. A roadmap to advance delirium research: Recommendations
697 from the NIDUS Scientific Think Tank. *Alzheimer's & dementia : the journal of the Alzheimer's*
698 *Association* 2020;16(5):726-33. doi: 10.1002/alz.12076 [published Online First: 2020/04/16]
699 47. Sessler CN, Gosnell MS, Grap MJ, et al. The Richmond Agitation-Sedation Scale: validity and
700 reliability in adult intensive care unit patients. *AmJRespirCrit Care Med* 2002;166(10):1338-
701 44. doi: 10.1164/rccm.2107138 [doi];166/10/1338 [pii]
702 48. Tieges Z, McGrath A, Hall RJ, et al. Abnormal level of arousal as a predictor of delirium and
703 inattention: an exploratory study. *The American journal of geriatric psychiatry : official*

journal of the American Association for Geriatric Psychiatry 2013;21(12):1244-53. doi: 10.1016/j.jagp.2013.05.003

49. Hall RJ, Meagher DJ, Maclullich AM. Delirium detection and monitoring outside the ICU. *BestPractResClinAnaesthesiol* 2012;26(3):367-83. doi: S1521-6896(12)00035-3 [pii];10.1016/j.bpa.2012.07.002 [doi]

50. Ely EW, Inouye SK, Bernard GR, et al. Delirium in mechanically ventilated patients: validity and reliability of the confusion assessment method for the intensive care unit (CAM-ICU). *JAMA* 2001;286(21):2703-10. doi: 10.1001/jama.286.21.2703 [published Online First: 2001/12/26]

51. Khan BA, Perkins AJ, Gao S, et al. The Confusion Assessment Method for the ICU-7 Delirium Severity Scale: A Novel Delirium Severity Instrument for Use in the ICU. *Crit Care Med* 2017;45(5):851-57. doi: 10.1097/CCM.0000000000002368

52. Nasreddine ZS, Phillips NA, Bedirian V, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *Journal of the American Geriatrics Society* 2005;53(4):695-9. doi: 10.1111/j.1532-5415.2005.53221.x [published Online First: 2005/04/09]

53. Morris JC, Heyman A, Mohs RC, et al. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part I. Clinical and neuropsychological assessment of Alzheimer's disease. *Neurology* 1989;39(9):1159-65. [published Online First: 1989/09/01]

54. Tombaugh TN. Trail Making Test A and B: normative data stratified by age and education. *Archives of clinical neuropsychology : the official journal of the National Academy of Neuropsychologists* 2004;19(2):203-14. doi: 10.1016/S0887-6177(03)00039-8 [published Online First: 2004/03/11]

55. Tombaugh TN, Kozak J, Rees L. Normative data stratified by age and education for two measures of verbal fluency: FAS and animal naming. *Archives of clinical neuropsychology : the official journal of the National Academy of Neuropsychologists* 1999;14(2):167-77. [published Online First: 2003/11/01]

56. Wechsler D NH, Nordvik H. Wais-III Wechsler Adult Intelligence Scale : manual. 3. Ed. Stockholm: Psykologiförlaget 2003.

57. 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]

58. Kim DH, Afilalo J, Shi SM, et al. Evaluation of Changes in Functional Status in the Year After Aortic Valve Replacement. *JAMA Intern Med* 2019;179(3):383-91. doi: 10.1001/jamainternmed.2018.6738 [published Online First: 2019/02/05]

59. Afilalo J, Lauck S, Kim DH, et al. Frailty in Older Adults Undergoing Aortic Valve Replacement: The FRAILTY-AVR Study. *J Am Coll Cardiol* 2017;70(6):689-700. doi: 10.1016/j.jacc.2017.06.024 [published Online First: 2017/07/12]

60. Halaas NB, Blennow K, Idland AV, et al. Neurofilament Light in Serum and Cerebrospinal Fluid of Hip Fracture Patients with Delirium. *Dementia and geriatric cognitive disorders* 2018;46(5-6):346-57. doi: 10.1159/000494754 [published Online First: 2018/12/07]

61. Karikari TK, Pascoal TA, Ashton NJ, et al. Blood phosphorylated tau 181 as a biomarker for Alzheimer's disease: a diagnostic performance and prediction modelling study using data from four prospective cohorts. *The Lancet Neurology* 2020;19(5):422-33. doi: 10.1016/S1474-4422(20)30071-5 [published Online First: 2020/04/26]

62. Ballweg T, White M, Parker M, et al. Association between plasma tau and postoperative delirium incidence and severity: a prospective observational study. *British journal of anaesthesia* 2021;126(2):458-66. doi: 10.1016/j.bja.2020.08.061 [published Online First: 2020/11/25]

63. Yu L, Wen G, Zhu S, et al. Abnormal phosphorylation of tau protein and neuroinflammation induced by laparotomy in an animal model of postoperative delirium. *Experimental brain research* 2021 doi: 10.1007/s00221-020-06007-2 [published Online First: 2021/01/08]

64. Sajjad MU, Blennow K, Knapskog AB, et al. Cerebrospinal Fluid Levels of Interleukin-8 in Delirium, Dementia, and Cognitively Healthy Patients. *Journal of Alzheimer's disease : JAD* 2020;73(4):1363-72. doi: 10.3233/JAD-190941 [published Online First: 2020/01/14]

65. Hov KR, Bolstad N, Idland AV, et al. Cerebrospinal Fluid S100B and Alzheimer's Disease Biomarkers in Hip Fracture Patients with Delirium. *Dementia and geriatric cognitive disorders extra* 2017;7(3):374-85. doi: 10.1159/000481853 [published Online First: 2017/12/29]

66. Neerland BE, Hall RJ, Seljeflot I, et al. Associations Between Delirium and Preoperative Cerebrospinal Fluid C-Reactive Protein, Interleukin-6, and Interleukin-6 Receptor in Individuals with Acute Hip Fracture. *Journal of the American Geriatrics Society* 2016;64(7):1456-63. doi: 10.1111/jgs.14238 [published Online First: 2016/06/25]

67. Balaganapathy P, Baik SH, Mallilankaraman K, et al. Interplay between Notch and p53 promotes neuronal cell death in ischemic stroke. *Journal of cerebral blood flow and metabolism : official journal of the International Society of Cerebral Blood Flow and Metabolism* 2018;38(10):1781-95. doi: 10.1177/0271678X17715956

68. Wedervang-Resell K, Ueland T, Aukrust P, et al. Reduced levels of circulating adhesion molecules in adolescents with early-onset psychosis. *NPJ Schizophr* 2020;6(1):20. doi: 10.1038/s41537-020-00112-5

69. Fleming TR, DeMets DL, Roe MT, et al. Data monitoring committees: Promoting best practices to address emerging challenges. *Clin Trials* 2017;14(2):115-23. doi: 10.1177/1740774516688915

70. Wang YY, Yue JR, Xie DM, et al. Effect of the Tailored, Family-Involved Hospital Elder Life Program on Postoperative Delirium and Function in Older Adults A Randomized Clinical Trial. *Jama Internal Medicine* 2020;180(1):17-25. doi: 10.1001/jamainternmed.2019.4446

71. Su X, Meng ZT, Wu XH, et al. Dexmedetomidine for prevention of delirium in elderly patients after non-cardiac surgery: a randomised, double-blind, placebo-controlled trial. *Lancet* 2016 doi: 10.1016/S0140-6736(16)30580-3

72. Shehabi Y, Grant P, Wolfenden H, et al. Prevalence of delirium with dexmedetomidine compared with morphine based therapy after cardiac surgery: a randomized controlled trial (DEXmedetomidine COmpared to Morphine-DEXCOM Study). *Anesthesiology* 2009;111(5):1075-84. doi: 10.1097/ALN.0b013e3181b6a783 [doi]

73. Jamadarkhana S, Gopal S. Clonidine in adults as a sedative agent in the intensive care unit. *Journal of anaesthesiology, clinical pharmacology* 2010;26(4):439-45. [published Online First: 2011/05/07]

74. 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]

75. 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]

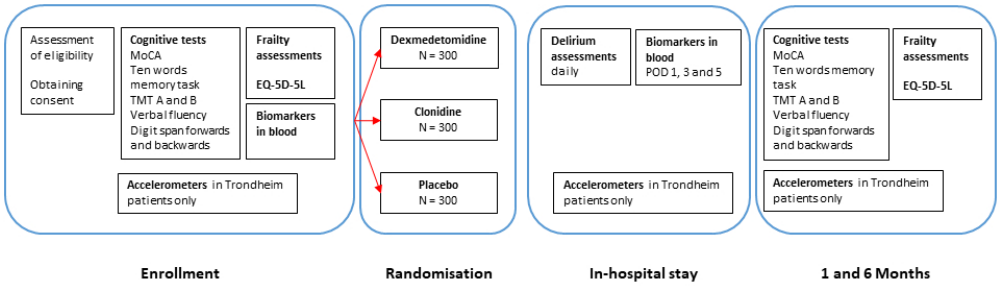


Figure 1:
Study schema. MoCA, Montreal Cognitive Assessment; TMT, Trail Making Test; EQ-5D-5L, EuroQol 5 Dimension 5 Level; POD, Postoperative Day

254x190mm (96 x 96 DPI)

Supplementary File 1

Detailed explanation of sample size calculations

The following parameters were considered in the samples size calculation strategy and confirmations:

Parameter		Explanation / justification
Proportions	**% delirium within 7 days**	
Placebo	30 %	Proportion of patients experiencing postoperative delirium after open heart surgery for all ages has been reported to be 24%,[1] and higher in the elderly.[2] With participants over 70 years in this trial, we expect the proportion to be at least 30%.
Dexmedetomidine (DEX)	15 %	Recent meta-analysis indicated dexmedetomidine approximately halves the risk of delirium[3]
Clonidine	20 %	Clonidine is anticipated to have similar effect to DEX, however 10 percentage point reduction would also be clinically significant
Power	80 %	
Significance level	5 %	
Duration of follow-up	7-days	
Accrual period	0-days*	

*Observation period starts with operation for all participants

Conservative sample size: As described the initial, conservative samples 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 of 20 % delirium in the clonidine and 30 % in 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 a higher drop-out rate. Furthermore, the study will be more than adequately powered to find the greater expected reduction in delirium in the dexmedetomidine group.

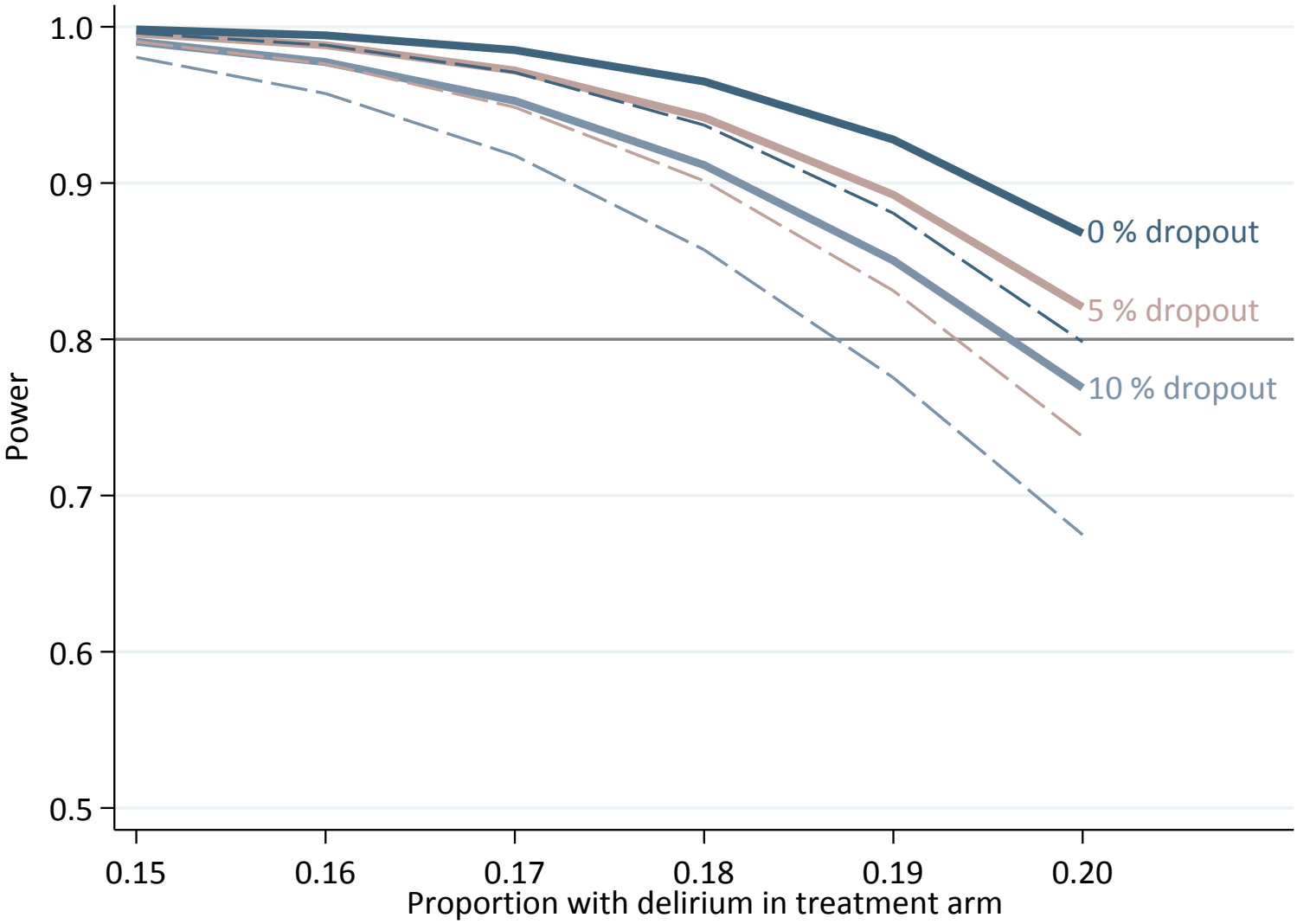
Since we intend to use the logrank test to account for difference in the observation period, we confirmed that the calculated sample size was adequate using the more flexible calculation options in PASS Sample size software (version 20, NCSS, Kaysville, Utah, USA).

Logrank test: A two-sided logrank test with an overall sample size of 498 subjects (249 in the control group and 249 in the treatment group) achieves 80 % power at a 5 % significance level to a reduction in the proportion with delirium from 30 % in the control arm to 20 % in the clonidine arm (equivalent to a hazard ratio of 1.34). By including 300 participants in each group, we will still achieve

80 % power with up to 7 % drop-out rate over the first seven postoperative days. Drop out rates lower than 7 % will result in a higher power. Even with 10 % drop out rate, we will still achieve 80 % to detect a slightly larger difference between the groups (10.4 percentage point reduction, rather than 10 percentage points) (Figure S1).

Multiplicity: The planned comparisons for this trial are between dexmedetomidine versus placebo and clonidine versus placebo. Any comparison between dexmedetomidine and clonidine groups will be explorative and clearly stated as such. The extension of the CONSORT 2010 Statement for multi-arm parallel-group randomised trials recommend that adjustments for multiple comparisons are generally not necessary in trials comparing two or more independent treatments to placebo as we are here.[4] This has therefore not been factored into the sample size calculation. However, even with the very conservative Bonferroni adjustment for two comparisons a sample size of 300 participants per arm will be sufficient if there were no drop-outs and only minimally affect the difference in proportions which we can hope to identify with 80 % power if there is up to 10 % drop-out (Figure S1). For example, with 5 % dropout we can detect a 10.6 percentage point reduction in delirium cumulative incidence with 80 % and 2.5 % significance level (to account for multiplicity), or 11.3 percentage points if there was 10 % dropout (Figure S1).

Figure S1: Power depending differing drop-out rates over the proportion with delirium in the treatment arm and where the proportion in the control arm is 30 %. The solid lines indicate the power with 5 % significance level for studies with no dropout (dark blue), 5 % dropout (pink) or 10 % dropout (medium blue). The corresponding broken lines indicate the power with 2.5 % significance level, a Bonferroni adjustment for the two planned comparisons.



1. Greaves D, Psaltis PJ, Ross TJ, et al. Cognitive outcomes following coronary artery bypass grafting: A systematic review and meta-analysis of 91,829 patients. *International journal of cardiology* 2019;289:43-49. doi: 10.1016/j.ijcard.2019.04.065 [published Online First: 2019/05/13]
2. Eide LS, Ranhoff AH, Fridlund B, et al. Comparison of frequency, risk factors, and time course of postoperative delirium in octogenarians after transcatheter aortic valve implantation versus surgical aortic valve replacement. *The American journal of cardiology* 2015;115(6):802-9. doi: 10.1016/j.amjcard.2014.12.043 [published Online First: 2015/02/04]
3. Flukiger J, Hollinger A, Speich B, et al. Dexmedetomidine in prevention and treatment of postoperative and intensive care unit delirium: a systematic review and meta-analysis. *Annals of intensive care* 2018;8(1):92. doi: 10.1186/s13613-018-0437-z [published Online First: 2018/09/22]
4. Juszczak E, Altman DG, Hopewell S, et al. Reporting of Multi-Arm Parallel-Group Randomized Trials: Extension of the CONSORT 2010 Statement. *JAMA* 2019;321(16):1610-20. doi: 10.1001/jama.2019.3087

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	6
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	11
Protocol version	#3	Date and version identifier	NA

Funding	#4	Sources and types of financial, material, and other support	26
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1-3,26
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	25-26
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	26
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	19-21
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	8-10,16,23
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	11
Objectives	#7	Specific objectives or hypotheses	10
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	11

Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	11
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	11-13
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	16
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	16, 20-21
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	21
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	16
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	16-19

Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	11-16, Table 2, Figure 1
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	21
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	11
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	13
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	13
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	11-13
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	13

Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	20-21
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	13,16-19, Table 2
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	21-22
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	19-20
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	21-23
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	21-23
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	21-23

Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	21
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Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	20-21
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Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	6,23,25
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	23
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	11
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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

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TITLE PAGE

Title: 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

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ABSTRACT

Introduction: Postoperative delirium is common in older cardiac surgery patients and associated with negative short-term and long-term outcomes. The alpha-2-adrenergic receptor agonist dexmedetomidine shows promise as prophylaxis and treatment for delirium in intensive care units (ICU) and postoperative settings. Clonidine has similar pharmacological properties and can be administered both parenterally and orally. We aim to study whether repurposing of clonidine can represent a novel treatment option for delirium, and the possible effects of dexmedetomidine and clonidine on long-term cognitive trajectories, motor activity patterns and biomarkers of neuronal injury, and whether these effects are associated with frailty status.

Methods and analysis: This five-centre, double blind randomised controlled trial will include 900 cardiac surgery patients aged 70+. Participants will be randomized 1:1:1 to dexmedetomidine or clonidine or placebo. The study drug will be given as a continuous intravenous infusion from the start of cardiopulmonary bypass, at a rate of 0.4 µg/kg/h. The infusion rate will be decreased to 0.2 µg/kg/h postoperatively and be continued until discharge from the ICU or 24 hours postoperatively, whichever happens first.

Primary endpoint is the 7-day cumulative incidence of postoperative delirium (Diagnostic and Statistical Manual of Mental Disorders, 5th edition). Secondary endpoints include the composite endpoint of coma, delirium or death, in addition to delirium severity and motor activity patterns, levels of circulating biomarkers of neuronal injury, cognitive function and frailty status 1 and 6 months after surgery.

Ethics and dissemination: This trial is approved by the Regional Committee for Ethics in Medical Research in Norway (South-East Norway) and by the Norwegian Medicines Agency. Dissemination plans include publication in peer-reviewed medical journals and presentation at scientific meetings.

Trial registration number: EudraCT: 2021-001645-12. ClinicalTrials.gov: NCT05029050

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This multicentre trial will provide evidence for prophylactic efficacy of dexmedetomidine and clonidine in reducing the incidence of postoperative delirium as well as decline in cognitive function 1 and 6 months postoperatively in older cardiac surgical patients
- Inclusion of preoperative frailty assessments will provide evidence for frailty as a predictive marker of treatment effect
- The analysis of biomarkers will provide insights into the neural mechanisms in postoperative delirium and long-term cognitive dysfunction
- The analysis of activity by accelerometers will provide insight into motor activity patterns in subtypes of delirium
- The dose of the active drugs may potentially be too low or the duration of treatment too short in order to show effects

BACKGROUND

Delirium represents an acute change in awareness, attention and cognition, precipitated by an acute illness, trauma, intoxication or surgery.[1 2] Common additional features are agitation, hallucinations and poor compliance with medical treatment and care.

Delirium appears in all parts of the health care service, including intensive care units (ICUs) and postoperative settings, regular hospital wards, nursing homes, home nursing services and palliative departments. In a recent meta-analysis, Greaves and co-workers found a delirium prevalence of 24% postoperatively after coronary artery bypass grafting (CABG) surgery, aggregated over all age groups.[3] In a Norwegian study of patients ≥80 years undergoing open aortic valve replacement, the prevalence of postoperative delirium was above 60%.[4] Open heart surgery patients are especially susceptible to delirium. Probable causes may be established cardiovascular disease, micro-embolism from cardiopulmonary bypass (CPB), perioperative circulatory changes including ischemia-reperfusion injuries, systemic inflammation, blood-brain barrier disruption and very deep anaesthesia.[5 6]

Delirium is difficult to handle in clinical settings, increases length of hospital stay and the need for long-term care,[7 8 9] is expensive for the society,[10] represents a frightening experience for the patient and the relatives,[11] and is an independent risk factor for death after cardiac surgery.[12] Delirium is an independent risk factor for cognitive decline in older adults, and induces a more rapid trajectory of deterioration in those who already have dementia.[13 14]

Frailty is a risk factor for delirium,[15] but less is known regarding how frailty assessments can guide prophylactic and therapeutic measures and shared decision making.[16] Frailty is a state of impaired physiologic reserve and decreased resistance to stressors, which increases the risk of an adverse outcome.[17 18] It is a consequence of cumulative decline in many physiological systems.

Conventionally, delirium has been separated into hyperactive and hypoactive subtypes based on clinical impression,[19] but recent research using body-worn sensors indicates a more heterogeneous pattern of motor activity across the clinical delirium motor subtypes.[20 21] 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. A small postoperative study on cardiac surgery patients showed the possibility of detecting the amount of movement in sedated patients.[22]

Delirium is multifactorial and relate to both predisposing and to precipitating factors.[1,2] Routinely, several actions are taken in perioperative care to minimize the risk of delirium, such as appropriate management of pain and minimizing the use of sedative drugs like benzodiazepines. Further, non-pharmacological multicomponent interventions are essential,[23] but there is currently no compelling evidence to support the use of specific prophylactic pharmacological measures in routine perioperative care for patients at risk of postoperative delirium.[24]

However, dexmedetomidine, a parenterally administered alpha-2-adrenergic receptor agonist that attenuates sympathetic nervous system activity, shows promise as prophylaxis and treatment for delirium in ICUs and postoperative settings.[25 26] It has been hypothesised that dexmedetomidine may reduce postoperative delirium via its sympatholytic, anti-inflammatory and organ-protective effects.[27 28] In a recent meta-analysis, perioperative use of dexmedetomidine in various surgical procedures was associated with a lower incidence of postoperative delirium. The relative risk (RR) and 95% confidence interval (CI) was 0.52 (0.39-0.70) when compared with placebo.[25] Among newer studies in cardiac surgery, some,[29-32] but not all,[33 34] have found a beneficial short time effect on the incidence of delirium. A meta-analysis in cardiac surgery patients showed that dexmedetomidine could reduce the risk of postoperative delirium (Odds Ratio 0.56, 95% CI 0.36-0.89).[35] This meta-analysis even included the largest trial by Turan et al., with 800 participants, that was negative for dexmedetomidine.[34]. To the best of our knowledge, effects of dexmedetomidine upon long time

cognitive trajectories have so far not been assessed in this patient population. Nevertheless, the use of dexmedetomidine in ICUs is rapidly increasing.[26]

An alternative agent is clonidine, which has similar pharmacological properties to dexmedetomidine,[36] even though it's alpha-2-adrenergic selectivity is lower.[37] Clonidine can be administered both parenterally and orally, thus potentially widening its clinical usefulness.[36 37] Clonidine was originally launched as an antihypertensive agent, but it is also used as an analgesic drug. Further, clonidine has a long tradition as a sedative in patients with hyperactive delirium, and is used by several anaesthesiologists and intensivists.[38] This practice is based on their clinical experiences and knowledge on the drug's properties, but is so far not supported by placebo-controlled clinical trials. A pilot study indicated that clonidine infusion during the period of weaning from mechanical ventilation after surgery for aortic dissection may reduce the severity of delirium.[39] A recent study compared clonidine with dexmedetomidine postoperatively after CABG and found better effect on risk and duration of delirium of dexmedetomidine. Since no placebo control group was included, that study could not assess potential effects of clonidine.[40]

Thus, there is a need for prospective large-scale studies on the potential prophylactic effect of alpha-2-adrenergic receptor agonists on delirium in susceptible patients. The aims of the present planned trial are to study 1) whether repurposing of clonidine can represent a novel treatment option for delirium, and 2) the possible effects of dexmedetomidine and clonidine on long-term cognitive trajectories, motor activity patterns, patient rated outcome measures and biomarkers of neuronal injury, and 3) whether these effects are associated with frailty status.

METHODS AND ANALYSIS

Study design

ALPHA2PREVENT is a nationwide five-centre, double blind randomised controlled trial (RCT). Patients aged 70+ scheduled for open heart surgery will be randomized 1:1:1 to dexmedetomidine or clonidine or placebo. The patients will be cognitively assessed preoperatively, then assessed for any symptoms of delirium according to the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) criteria[41] or subsyndromal delirium[42] postoperatively, and finally assessed for cognitive function after 1 and 6 months (figure 1).

Study locations

The trial will be carried out at Oslo University Hospital (Ullevaal and Rikshospitalet) in Oslo, Haukeland University Hospital in Bergen, Trondheim University Hospital in Trondheim, and the University Hospital of Northern Norway in Tromsø, all in Norway.

Participants, randomisation and blinding

Patients will be assessed for eligibility and asked for participation in cooperation with the responsible thoracic surgeons or anaesthesiologists. A full listing of trial inclusion and exclusion criteria is displayed in table 1. Participants must be ≥70 years old, accepted for cardiac surgery with CPB and capable of giving signed informed consent. The surgical procedures may constitute CABG, valve replacement, surgery on the ascending aorta, or combinations of these. Main exclusion criteria are bradycardia, uncontrolled hypotension, ischemic stroke the last month or acute coronary syndrome last 24 hours,[43] left ventricular ejection fraction < 40%, severe renal failure or hepatic dysfunction, sepsis, planned deep hypothermia and circulatory arrest, as well as emergency surgery.

Table 1. Inclusion and exclusion criteria

Participants are eligible to be included in the study only if all of the following criteria apply:	Participants are excluded from the study if any of the following criteria apply:
1. Participant must be ≥70 years old at the time of signing the informed consent. 2. Participant must be accepted for cardiac surgery with cardiopulmonary bypass. 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. 3. Participant must be capable of giving signed informed consent.	4. Preoperative delirium (present at time of potential inclusion) 5. Known hypersensitivity to the active ingredient or components of the product 6. Bradycardia due to sick-sinus-syndrome, 2nd or 3rd degree AV-block (if not treated with pacemaker) or any other reason causing HR <50 bpm at time of inclusion 7. Uncontrolled hypotension 8. Ischemic stroke or transitory ischemic attack the last month or critical peripheral ischemia 9. Acute coronary syndrome last 24 hours. Acute coronary syndrome is defined according to international guidelines 10. Left ventricular ejection fraction < 40% 11. Severe renal impairment (estimated GFR < 20 ml/min) or expected requirement for renal replacement therapy 12. Severe hepatic dysfunction (liver enzyme three times the upper limit of normal together with a serum albumin concentration below the normal reference limit

	13. Reduced peripheral autonomous activity (e.g., spinal cord injury) 14. Current use of tricyclic antidepressants, monoamine reuptake inhibitors or ciclosporin 15. Endocarditis or sepsis 16. Pheochromocytoma 17. Planned deep hypothermia and circulatory arrest 18. Emergency surgery, defined as less than 24 hours from admission to surgery 19. Previously included in this study 20. Not speaking or reading Norwegian 21. Any other condition as evaluated by the treating physician

AV-block, atrioventricular block; HR, heart rate; GFR, glomerular filtration rate

Consenting patients will be randomly assigned 1:1:1, to dexmedetomidine, clonidine or placebo. Randomization will be computer generated with random permuted block sizes of 3 or 6, and stratified according to study centre. Allocation will be concealed by a web-based system that can be accessed no earlier than 3 days before surgery. The study drug will be prepared by an otherwise uninvolved research associate, ensuring that investigators, clinicians, outcome assessors and statisticians are blinded to the group assignment.

Data collected at study entry

The data collection will take place in connection with routine clinical care at the relevant hospital wards and the ICU (table 2). According to the selection criteria, electrocardiogram (ECG),

creatinine/estimated Glomerular Filtration Rate (eGFR), liver transaminases, albumin, and a recent echo-cardiography will be required, as well as a screening for preoperative delirium. At study entry, demographic data, medical history including cardiovascular and non-cardiovascular co-morbidities, prescription drugs used, sensory impairment, presence or absence of any fall within the past year, functional status including activities of daily living, surgical site and indication for surgery will be obtained. Haemodynamic variables, body mass index, American Society of Anesthesiologists Physical Status (ASA)-classification and Euroscore II will be recorded, and routine blood samples taken prior to surgery will be registered. Blood samples for biomarkers will be drawn preoperatively and on postoperative day 1, 3 and 5. Included patients will undergo preoperative cognitive tests and physical tests for assessment of frailty. Patient rated outcome measures (PROMs) will be assessed by use of the Norwegian version of the EuroQol 5 Dimension 5 Level (EQ-5D-5L) questionnaire.[44] The same tests and questionnaires will be used also after 1 and 6 months, for assessment of cognitive and functional trajectories.

Table 2. Study procedures

	Screening	**Baseline**	**Surgery**	**Postoperative day number:**								**1 and 6 months**
Procedure	**≤30 days before Day 0**	**-3 to -1 days before Day 0**	**Day 0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**Hospital discharge**	
Informed consent	X											
Assessment of eligibility	X											
Routine blood tests (i.e. creatinine, liver transaminases, albumin, troponin, proBNP)	X										X	
ECG	X			X								
Physical examination	X											

Past and current medical conditions	X										X
Vital signs	X	X	X	X	X	X	X	X	X	X	
Randomization		X									
Prescribed medications		X									
Demographic data		X									X
Blood samples for biomarkers		X		X		X		X			
ASA-classification and Euroscore II		X									
Cognitive assessments		X									X
Frailty assessments		X									X
PROM (EQ-5D-5L)		X									X
Body worn accelerometers (St Olav only)		X		X	X	X	X	X	X	X	X
Study intervention			X	X							
Safety review (incl hemodynamic variables, AE/SAE-review, death)			X	X	X	X	X	X	X		X
Postoperative variables (e.g., vital signs, medications, transfusions, re-operations, respiratory support)				X	X	X	X	X	X		
Routine assessments of delirium, 3x/day (by nursing staff); CAM-ICU, RASS			X	X	X	X	X	X	X		
Delirium assessments DSM-5 based, 1x/day (by research assistant)				X	X	X	X	X	X		X[a]
Pain assessment (NRS)				X	X	X	X	X	X		
Registration of per-operative variables (e.g., type of surgery, medications, transfusions,										X	

vital parameters, duration of surgery/anaesthesia)											
Registration of post-operative complications										X	
Registration of total dose and duration of study medication										X	

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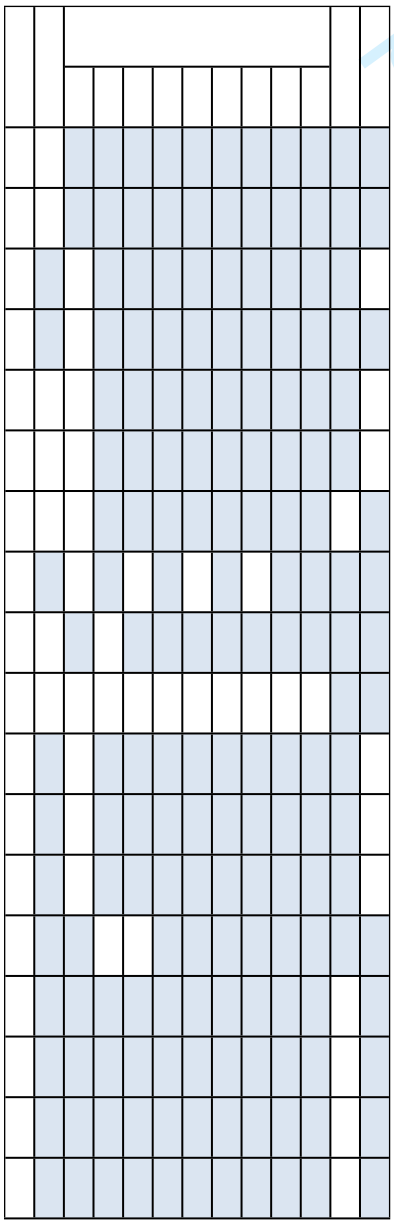

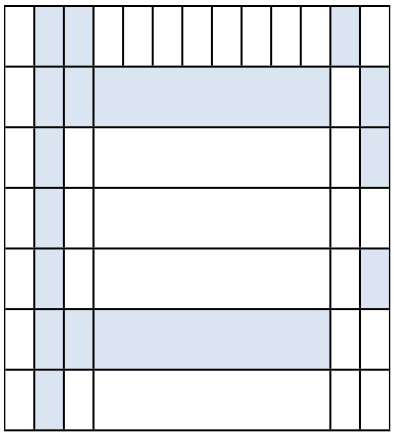

ProBNP, Pro B-type Natriuretic Peptide; ECG, electrocardiogram; PROM, Patient Rated Outcome Measure; ASA-classification, American Society of Anesthesiologists Physical Status Classification; AE, Adverse Event; SAE, Serious AE; CAM-ICU, Confusion Assessment Method for Intensive Care Units; RASS, Richmond Agitation Sedation Scale; DSM-5, Diagnostic and Statistical Manual of Mental Disorders, 5th edition; NRS, Numerical Rating Scale

[a] No delirium assessment at follow-up after 6 months

Trial interventions

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 the step-down unit, 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.

Concomitant therapy and rescue medicine

Patients will not be included if they use tricyclic antidepressants, monoamine reuptake inhibitors or cyclosporine. The perioperative anaesthesia will be given per routine at participating institutions. If

delirium develops and pharmacological intervention is needed, the study drug will be stopped, and further treatment will be according to local routines and the treating physician's preferences.

Primary endpoint

The primary endpoint for ALPHA2PREVENT is the cumulative incidence of postoperative delirium within 7 days. Postoperative delirium assessment will start as soon as possible after admission to the ICU, and will continue daily until the seventh postoperative day or until discharge from the university hospital, whichever happens first. To allow for differences in the duration of the postoperative observation period, time until delirium diagnosis will be recorded and the cumulative incidence will be assessed using Kaplan Meier estimates and compared between groups with the log-rank test as described below. A clinical assessment for delirium will also be repeated at the 1-month follow-up, to pick up signs of persistent delirium.

The diagnosis of delirium will be ascertained using all available information, and will be determined to be present if participants meet all DSM-5 criteria[41] by using a standardized procedure developed for our previous study[45] and as recommended by others[46], table 3. The methods are refined in order, in a stepwise approach, to assess presence or absence of the diagnostic criteria in DSM-5 and will be carried out once daily by specially trained research assistants. Level of arousal will be assessed using the Norwegian versions of Richmond Agitation Sedation Scale (RASS)[47] and Observational Scale of Level of Arousal (OSLA).[48] Attention and awareness will be evaluated using objective tests (vigilance "A"-test, months of the years backwards, days of the week backwards, and counting down from 20 to 1)[49] and observations by the examiner of the patient´s distractibility, comprehension and tendency to lose the thread of conversation. Presence of additional cognitive disturbances will be assessed by tests for orientation and recall test of three words (different words for each day), as well as information derived from nursing staff and clinical notes. Acute change in the patient´s mental condition, and fluctuations of any disturbance, will be ascertained through informant history from nursing staff and derived from clinical notes. Nurses will, as part of their routine and for each shift

(i.e., three times daily), 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)[50] and RASS. The same delirium assessment tools will be used for the ICU, step-down and bed wards. .The results from each of the CAM-ICU-items, as well as the total CAM-ICU score, will also be used as a source of information for making the final delirium diagnosis.

Finally, as a quality assurance, two or more highly experienced delirium researchers will independently use all available information (including the research assistants' assessments) on each patient to decide if the DSM-5 criteria for delirium are fulfilled. An interrater agreement for the diagnosis of delirium will be calculated and disagreements will be resolved through discussion.

Subsyndromal delirium (table 3) will be defined as evidence of change, in addition to any one of these: altered arousal, attentional deficits, other cognitive change, delusions or hallucinations. DSM-5 delirium criteria D and E must be met.

Table 3. Diagnostic algorithm for DSM-5 delirium.

DSM-5 criteria	**Tests to be performed or information needed**		**Criterium fulfilled?**	
			Yes	**No**
A. Disturbance in **attention** (i.e., reduced ability to direct, focus, sustain, and shift attention) and **awareness** (reduced orientation to the environment).	**TEST**	**Cut off (definition of inattention)**		
	Digit span forward	less than 5 forward		
	SAVEAHAART	more than 2 errors		
	Days of the week backwards	any error		

	<table><tr><td>**Months of the year backwards**</td><td>unable to pass June</td></tr><tr><td>**Count backwards from 20 to 1**</td><td>any error</td></tr><tr><td>**Digit span backwards**</td><td><5 digits</td></tr></table> <u>Observation (by the examiner during the interview):</u> Distractibility. Comprehension. Tendency to lose the tread of conversation Level of arousal measured using RASS and OSLA		
B. The disturbance develops over a **short period of time** (usually hours to a few days), represents a **change** from baseline attention and awareness, and tends to **fluctuate** in severity during the course of a day.	Acute onset and/or fluctuation obtained from informant history from nursing staff and clinical notes <u>Questions to carer/ nursing staff or derived from clinical notes:</u> Has there been a sudden change in the patient´s mental state? Does the patient seem to be better at any period in the day compared to other times? Has the level of consciousness been altered (drowsy/ not interacting or agitated)? Sleep-wake cycle disturbances?		

C. An additional disturbance in **cognition** (e.g., memory deficit, disorientation, language, visuospatial ability, or perception).	Questions to the patient: Orientation to time, place and person 3 item recall at three minutes Questions from CAM-ICU: Why are you in hospital? Will a stone float in water? Are there fish in the sea? Questions to carer/ nursing staff or derived from clinical notes: Any evidence of perceptual disturbances as illusions or hallucinations? Memory disturbances? Psychotic symptoms? Psychomotor abnormalities?		
D. The disturbances in criteria A and C are **not explained by another preexisting, established, or evolving neurocognitive disorder** and do not occur in the context of a severely reduced level of arousal, such as coma.	Information from history/chart/clinical assessment		
E. There is evidence from the history, physical examination, or laboratory findings that the disturbance is a direct **physiologic consequence** of another medical condition, substance intoxication or withdrawal (i.e., because of	By virtue of the surgery, all participants are considered to fulfil this criterion.		

a drug of abuse or to a medication), or exposure to a toxin or is because of multiple etiologies.			
Delirium based on the tests and information above?	All DSM-5 criteria fulfilled		
Subsyndromal delirium based on the tests and information above?	Defined as evidence of change, in addition to any one of these: (a) altered arousal, (b) attentional deficits, (c) other cognitive change, (d) delusions or hallucinations. Criteria D and E must be met.		

DSM-5, Diagnostic and Statistical Manual of Mental Disorders, 5th edition; RASS, Richmond Agitation Sedation Scale; OSLA, Observational Scale of Level of Arousal; CAM-ICU, Confusion Assessment Method for Intensive Care Units

Secondary endpoints

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, patient rated health status, frailty status, and comparison of change in frailty status. In explorative analyses, the secondary outcomes will also be assessed between patients with or without postoperative delirium. 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.

All endpoints will be assessed using Norwegian versions of validated instruments: Delirium severity will be measured using CAM-ICU-7,[51] OSLA[48] and RASS;[47] motor activity patterns using body worn accelerometers; cognitive function using Montreal Cognitive Assessment (MoCA),[52] immediate and delayed recall from The Ten Words Memory Task from The Consortium to Establish a Registry for Alzheimer's Disease,[53] Trail Making Test (TMT) version A and B,[54] semantic and phonemic verbal fluency,[55] digit span forwards and backwards (by Wechsler Adult Intelligence Scale);[56] 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 58] and by the shorter Essential Frailty Toolset;[59] and patient rated health status using the EQ-5D-5L questionnaire.[44]

For assessment of cognitive trajectories, the same cognitive tests will be performed in a stable phase preoperatively as well as after 1 and 6 months. Information regarding functional status will be obtained from the patient preoperatively and from either the patient or their proxy at follow-up, depending on the patient's ability to provide detailed information.

For a sub-sample of one hundred patients from the Trondheim cohort, motor activity will be measured by 3D accelerometer inertial sensors (AX3 sensors) (Axivity Ltd., Newcastle, UK) sampled at 100 Hz and processed using custom made software. Accelerometers will be attached to the frontal part of the waist, the dominant thigh (ventrally, midthigh), and on the dominant wrist pre surgery. Motor activity patterns will be monitored continuously (day and nights) before and the five first days after surgery or until discharge from hospital, and over one week after 1 and 6 months. Sensor data will be analyzed regarding both quantity and quality of movements and compared with the clinical delirium assessments.

Biomarkers

In addition to routine blood tests, blood will be taken in the morning for specific study analyses (serum, plasma and wholeblood) before surgery, and at postoperative day 1, 3 and 5 (or earlier if discharged before day 5) and frozen at –80 °C locally. Frozen samples will then be shipped to the coordinating centre (Oslo) to be stored in a biobank at –80 °C for future analyses. The stored blood samples will be analysed for promising markers such as NFL already known to be associated with delirium,[60] p-tau181 associated with dementia and delirium,[61-63] and possibly other biomarkers of neuronal degeneration, neuroinflammation and neurotransmitters,[64-68] using state-of-the-art ultrasensitive assays to evaluate their association with observed clinical responses to the study drugs.

Standardised training

The research assistants across all sites will receive standardized training for all study measures prior to study initiation, including cognitive tests, delirium assessments and measurements of frailty indicators. Retraining will be provided as necessary. Detailed instructions and operation manuals in Norwegian language, including an instruction video for the MoCA, will be made available to all assessors.

Data management and monitoring

Participant data will be collected by authorized trained personnel, be recorded on electronic Case Report Forms (CRF) and stored on a password protected database. Paper files will be stored in locked cabinets accessible to team members only. Study monitors will perform ongoing source data verification to confirm that data entered into the CRFs are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol, International Conference on Harmonization Good Clinical Practice, and all applicable regulatory requirements. Records and documents, including signed Informed Consent Forms, pertaining to the conduct of this study will be retained by the investigators for 15 years after study completion.

Safety and adverse events management

Immediate safety concerns will be handled by the treating anaesthesiologist, who will determine if the participant should continue or discontinue study intervention. 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. Since patients are closely monitored in the perioperative phase of cardiac surgery, potential adverse circulatory effects will be rapidly revealed and corrected;

- Temporal epicardial pacing wires are placed routinely during cardiac surgery, and bradycardia will be treated with atropine and/or pacemaker as per routine.
- Hypotension will be treated at discretion of the treating anaesthesiologists, who are permitted to reduce dose of the study drug as necessary to preserve haemodynamic stability, following guidelines and local routines. A Mean Arterial Pressure (MAP) >55-60mmHg is recommended.
- If not rapid and satisfactory response on other measures is achieved, the treating anaesthesiologist will consider to turn off the infusion/unblind the study.

Planned time points for safety assessments are provided in table 2.

The following safety indicators will be compared between the three treatment groups with appropriate statistical methods: Highest and lowest heart rate and mean arterial blood pressure, oxygen saturation, number of units for blood transfusion, volume of postoperative blood loss, use of pressor substances, use of rescue medication, number of episodes of bradycardia, hypotension or hypoxemia in need of intervention, perioperative myocardial infarction and stroke, postoperative serum concentrations of troponin and Pro B-type Natriuretic Peptide (proBNP), mortality.

An independent Data Monitoring Committee will have unblinded access to all data and meet at pre-planned inclusion milestones and whenever the members find it necessary.[69] Meetings are pre-planned after inclusion of 20, 50, 100 and 400 participants, to assess safety indicators and to advise on continuation or termination of the study. 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.

Current sample size justification

The proportion of patients experiencing postoperative delirium after open heart surgery for all ages has been reported to be 24%,[3] and higher in older adults.[4] Since the lower age limit in our trial is 70 years, we estimate that the proportion in the control group will be at least 30%. The most recent meta-analysis of the effect of dexmedetomidine estimates the delirium risk to be reduced to approximately half of the untreated group (*i.e.*, 15%).[25] We anticipate that the effect of clonidine may be weaker, but still clinically relevant. We have thus powered the study based on an estimated delirium incidence of 20% in the clonidine group. 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 drop-out 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 drop-out and considering the three-arms (Figure S1, Supplementary file 1).

Statistical analysis

The primary analysis population will be the intention-to-treat population, and all tests will be two-sided. The primary objective in this study is to prevent postoperative delirium. The primary endpoint is the cumulative incidence of postoperative delirium. In the analysis of this endpoint, time to diagnosis of delirium will be used to account for the varying postoperative observation time due to difference in time to discharge or transfer to other hospitals will be different. The cumulative incidence will therefore be estimated using 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. Patients who are discharged from the university hospital during the observation period or reach the end of the observation period (7 days) without having developed delirium, are regarded as censored. We consider that treatment group allocation will not influence the risk of being censored. Those who die prior to 7 days, will also be regarded as censored in the primary analysis, but we will carry out a secondary analysis with the combined endpoint *death or delirium.* The same approach will be applied for those who are comatose, and thus impossible to evaluate for delirium. Additional analyses may also include estimating the incidence of delirium treating deaths as a competing risk by the Fine and Gray method.

All analyses will be adjusted for study centre which was used to as a stratification variable in the randomisation process.

Sensitivity analyses will be carried out by estimating hazard ratios using Cox' proportional hazards model to adjust for potential imbalance of prognostic factors between treatment groups.

Secondary endpoints as the cumulative incidence of death, coma or postoperative delirium will be analysed using the Kaplan Meier estimator and the logrank test as above. Additional analyses by Cox' proportional hazards model may also be performed. Mean duration of delirium; severity of delirium; combination of duration and severity of delirium; cognitive tests after 1 and 6 months; EQ-5D-5L scores after 1 and 6 months; and postoperative plasma concentrations of NFL and p-tau181 will be compared between treatments with appropriate regression models which will be defined in a Statistical Analysis Plan prior to analysis.

Frailty as risk factor for delirium and for adverse effects of the study medication, will be analysed by linear or logistic regression (as appropriate), adjusted for other known risk factors. The association between frailty and delirium will be analysed by adding frailty as a covariate in a Cox'proportional hazards model on time to delirium (as above). 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. The association between frailty and occurrence of adverse events (AE) will be estimated by logistic regression models including covariates as above.

No interim analyses of the efficacy of the treatments are planned. A detailed statistical analysis plan will be finalized prior to unblinding.

Ethics and dissemination

This trial is approved by the Regional Committee for Ethics in Medical Research in Norway (South-East Norway) and by the Norwegian Medicines Agency, and will be conducted in accordance with consensus ethical principles derived from international guidelines including the Declaration of Helsinki. The results of this study will be published in peer-reviewed medical journals, as well as presented at scientific meetings

Discussion

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.

One should expect that treatment options that can prevent delirium in a short-term perspective, would also improve the long-term cognitive prognosis. Evidence for such an effect is slowly emerging for non-pharmacological interventions,[70] but is lacking regarding drug treatment.

Published studies of dexmedetomidine for prevention of delirium in ICU vary largely with respect to dosing regimens, from 0.1[71 72] to 1.4 µg/kg/h.[33] Many of the authors also administered an initial bolus. In the cardiac surgery context, Turan et al started dexmedetomidine infusion already before start of CPB, gave 0.4 µg/kg/h postoperatively,[34] and found more side effects in the actively treated than in the placebo group. We have chosen a careful dosage of 0.4 µg/kg/h peroperatively and 0.2 µg/kg/h postoperatively, with no bolus, to reduce the risk of AE, but not so low that we cannot expect an effect on delirium.

Regarding clonidine, the recommended dosage varies greatly between sources, but is mainly in the range 1-1.5 µg/kg/h.[73] We will dose the drug considerably lower, to avoid side effects. There is a shortage of studies comparing i.v. dexmedetomidine and i.v. clonidine in ICU or postoperative settings.[74] 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[74] and a recent meta-analysis favour equipotency mg per mg.[75] Thus, our choice is fairly pragmatic, but the doses are similar to that currently used in many ICUs as part of routine practice.

To further reduce the risk of hemodynamic instability due to the combination of anaesthesiological procedures and study drug at the start of surgery, we will postpone infusion of study drug until the CPB is established. 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. Efficacy

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

Strengths of this trial are the prospective and randomised placebo controlled design, the use of two relevant and much used drugs, inclusion of a high number of patients from multiple sites, adequate statistic strength, repeated cognitive and frailty assessments, use of body-worn accelerometers, and repeated samples of biomarkers. The analyses of biomarkers reflecting neural injury will give us increased understanding of the pathophysiological mechanisms of delirium. Inclusion of preoperative frailty assessments will provide evidence for frailty as a predictive marker of treatment effect and allow for interaction analyses. The use of body-worn accelerometers will provide insight into motor activity patterns in subtypes of delirium.

This trial has, however, some limitations to consider. The exclusion criteria might limit the generalisability of our findings to other patient populations. 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. 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. As many patients live far away from the study site, there is a potential for missing long-term data.

Should the treatment have a positive effect, it would have important beneficial implications for patients, carers and society, such as alleviating acute patient distress and carer burden. If this treatment could reduce longer-term negative effects of delirium, it might have significant consequences for financial and human resource use in health care.

DECLARATIONS

Patient and public involvement: Panellists from the user panel established by the Norwegian National Advisory Unit on Ageing and Health, participate in the Trial Advisory Board. They have

experience as relatives to patients with dementia or delirium, have given valuable input to the project plans and will follow up during the project period.

Ethics approval: The trial is approved by the Regional Committee for Ethics in Medical Research in Norway (South-east Norway) (REK 262384), June 9th 2021, and by the Norwegian Medicines Agency June 17th 2021.

Availability of data and materials: Materials can be available upon reasonable request to the corresponding author. However, availability is dependent on approval from the Regional Ethics Committee and the local data protection officer.

Competing interest: HZ has served at scientific advisory boards and/or as a consultant for Alector, Eisai, Denali, Roche Diagnostics, Wave, Samumed, Siemens Healthineers, Pinteon Therapeutics, Nervgen, AZTherapies, CogRx and Red Abbey Labs, has given lectures in symposia sponsored by Cellectricon, Fujirebio, Alzecure and Biogen, and is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program (outside submitted work).

AJCS is advisor for Prolira, a start-up company that develops an EEG-based delirium monitor. Any (future) profits from EEG-based delirium monitoring will be used for future scientific research only.

GS has participated in one advisory meeting for Biogen. HMN has received lecture fees from Vifor Pharma and Orion Pharma.

The other authors declare that they have no competing interests.

Consent for publication: Not required

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Author contributions:

Drafting of the manuscript: BEN

Critical revision of the manuscript for important intellectual content: BEN, RB, RH, JLH, AKK, SAL, IM, HMN, JR, GS, ES, NKS, ES, AS, ØSS, TT, AW, HZ, TBW, MRS

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All authors contributed to the writing of the manuscript and approved the final version.

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Abbreviations:

Abbreviation	**Explanation**
AE	Adverse Event
ALPHA2PREVENT	Alpha-2-adrenergic receptor agonists for the prevention of delirium and cognitive decline after open heart surgery: randomised controlled trial
ASA classification	American Society of Anesthesiologists Physical Status Classification
CABG	Coronary Artery Bypass Grafting
CAM-ICU	Confusion Assessment Method for Intensive Care Units
CPB	Cardiopulmonary Bypass

CRF	Case Report Form
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th edition
ECG	Electrocardiogram
EQ-5D-5L	EuroQol 5 Dimension 5 Level
FI	Frailty Index
GFR	Glomerular Filtration Rate
ICU	Intensive Care Unit
MAP	Mean Arterial Pressure
MoCA	Montreal Cognitive Assessment
NFL	Neurofilament light
NRS	Numerical Rating Scale
OSLA	Observational Scale of Level of Arousal
ProBNP	Pro B-type Natriuretic Peptide
PROM	Patient Rated Outcome Measure
RASS	Richmond Agitation Sedation Scale
RCT	Randomised Controlled Trial
SAE	Serious Adverse Event
TMT	Trail Making Test

LEGENDS

Figure 1:

Study schema. MoCA, Montreal Cognitive Assessment; TMT, Trail Making Test; EQ-5D-5L, EuroQol 5 Dimension 5 Level; POD, Postoperative Day

REFERENCES

1. Marcantonio ER. Delirium in Hospitalized Older Adults. *The New England journal of medicine* 2017;377(15):1456-66. doi: 10.1056/NEJMcp1605501 [published Online First: 2017/10/12]
2. Wilson JE, Mart MF, Cunningham C, et al. Delirium. *Nat Rev Dis Primers* 2020;6(1):90. doi: 10.1038/s41572-020-00223-4
3. Greaves D, Psaltis PJ, Ross TJ, et al. Cognitive outcomes following coronary artery bypass grafting: A systematic review and meta-analysis of 91,829 patients. *International journal of cardiology* 2019;289:43-49. doi: 10.1016/j.ijcard.2019.04.065 [published Online First: 2019/05/13]
4. Eide LS, Ranhoff AH, Fridlund B, et al. Comparison of frequency, risk factors, and time course of postoperative delirium in octogenarians after transcatheter aortic valve implantation versus surgical aortic valve replacement. *The American journal of cardiology* 2015;115(6):802-9. doi: 10.1016/j.amjcard.2014.12.043 [published Online First: 2015/02/04]
5. Hollinger A, Siegemund M, Goettel N, et al. Postoperative Delirium in Cardiac Surgery: An Unavoidable Menace? *Journal of cardiothoracic and vascular anesthesia* 2015;29(6):1677-87. doi: 10.1053/j.jvca.2014.08.021 [published Online First: 2015/10/13]
6. Abrahamov D, Levran O, Naparstek S, et al. Blood-Brain Barrier Disruption After Cardiopulmonary Bypass: Diagnosis and Correlation to Cognition. *The Annals of thoracic surgery* 2017;104(1):161-69. doi: 10.1016/j.athoracsur.2016.10.043
7. Gleason LJ, Schmitt EM, Kosar CM, et al. Effect of Delirium and Other Major Complications on Outcomes After Elective Surgery in Older Adults. *JAMA Surg* 2015;150(12):1134-40. doi: 10.1001/jamasurg.2015.2606
8. Witlox J, Eurelings LS, de Jonghe JF, et al. Delirium in elderly patients and the risk of postdischarge mortality, institutionalization, and dementia: a meta-analysis. *JAMA* 2010;304(4):443-51. doi: 304/4/443 [pii];10.1001/jama.2010.1013 [doi]
9. Krogseth M, Wyller TB, Engedal K, et al. Delirium is a risk factor for institutionalization and functional decline in older hip fracture patients. *Journal of psychosomatic research*

2014;76(1):68-74. doi: 10.1016/j.jpsychores.2013.10.006 [published Online First: 2013/12/24]

10. Pezzullo L, Streatfeild J, Hickson J, et al. Economic impact of delirium in Australia: a cost of illness study. *BMJ Open* 2019;9(9):e027514. doi: 10.1136/bmjopen-2018-027514 [published Online First: 2019/09/19]

11. Instenes I, Gjengedal E, Eide LSP, et al. "Eight Days of Nightmares ... " - Octogenarian Patients' Experiences of Postoperative Delirium after Transcatheter or Surgical Aortic Valve Replacement. *Heart, lung & circulation* 2018;27(2):260-66. doi: 10.1016/j.hlc.2017.02.012 [published Online First: 2017/04/12]

12. Gottesman RF, Grega MA, Bailey MM, et al. Delirium after coronary artery bypass graft surgery and late mortality. *Annals of neurology* 2010;67(3):338-44. doi: 10.1002/ana.21899 [published Online First: 2010/04/08]

13. Davis DH, Muniz-Terrera G, Keage HA, et al. Association of Delirium With Cognitive Decline in Late Life: A Neuropathologic Study of 3 Population-Based Cohort Studies. *JAMA Psychiatry* 2017 doi: 10.1001/jamapsychiatry.2016.3423 [published Online First: 2017/01/24]

14. Saczynski JS, Marcantonio ER, Quach L, et al. Cognitive trajectories after postoperative delirium. *The New England journal of medicine* 2012;367(1):30-9. doi: 10.1056/NEJMoa1112923 [published Online First: 2012/07/06]

15. Persico I, Cesari M, Morandi A, et al. Frailty and Delirium in Older Adults: A Systematic Review and Meta-Analysis of the Literature. *Journal of the American Geriatrics Society* 2018;66(10):2022-30. doi: 10.1111/jgs.15503 [published Online First: 2018/09/22]

16. van Beek-Peeters J, van Noort EHM, Faes MC, et al. Shared decision making in older patients with symptomatic severe aortic stenosis: a systematic review. *Heart* 2020;106(9):647-55. doi: 10.1136/heartjnl-2019-316055 [published Online First: 2020/02/01]

17. Clegg A, Young J, Iliffe S, et al. Frailty in elderly people. *Lancet* 2013;381(9868):752-62. doi: S0140-6736(12)62167-9 [pii];10.1016/S0140-6736(12)62167-9 [doi]

18. Guidet B, de Lange DW, Boumendil A, et al. The contribution of frailty, cognition, activity of daily life and comorbidities on outcome in acutely admitted patients over 80 years in European ICUs: the VIP2 study. *Intensive care medicine* 2020;46(1):57-69. doi: 10.1007/s00134-019-05853-1

19. Meagher DJ, Leonard M, Donnelly S, et al. A longitudinal study of motor subtypes in delirium: frequency and stability during episodes. *JPsychosomRes* 2012;72(3):236-41. doi: S0022-3999(11)00298-4 [pii];10.1016/j.jpsychores.2011.11.013 [doi]

20. Godfrey A, Leonard M, Donnelly S, et al. Validating a new clinical subtyping scheme for delirium with electronic motion analysis. *Psychiatry research* 2010;178(1):186-90. doi: 10.1016/j.psychres.2009.04.010 [published Online First: 2010/05/11]

21. Evensen S, Bourke AK, Lydersen S, et al. Motor activity across delirium motor subtypes in geriatric patients assessed using body-worn sensors: a Norwegian cross-sectional study. *BMJ Open* 2019;9(2):e026401. doi: 10.1136/bmjopen-2018-026401 [published Online First: 2019/03/04]

22. Harbo EF, Fuglerud SS, Skjaervold NK. Visualisation of limb movements by accelerometers in sedated patients. *Crit Care* 2020;24(1):283. doi: 10.1186/s13054-020-02975-7 [published Online First: 2020/06/05]

23. Needham MJ, Webb CE, Bryden DC. Postoperative cognitive dysfunction and dementia: what we need to know and do. *British journal of anaesthesia* 2017;119(suppl_1):i115-i25. doi: 10.1093/bja/aex354 [published Online First: 2017/11/22]

24. Siddiqi N, Harrison JK, Clegg A, et al. Interventions for preventing delirium in hospitalised non-ICU patients. *The Cochrane database of systematic reviews* 2016;3:CD005563. doi: 10.1002/14651858.CD005563.pub3 [published Online First: 2016/03/12]

25. Flukiger J, Hollinger A, Speich B, et al. Dexmedetomidine in prevention and treatment of postoperative and intensive care unit delirium: a systematic review and meta-analysis.

Annals of intensive care 2018;8(1):92. doi: 10.1186/s13613-018-0437-z [published Online First: 2018/09/22]

26. Bajwa S, Kulshrestha A. Dexmedetomidine: An Adjuvant Making Large Inroads into Clinical Practice. *Annals of medical and health sciences research* 2013;3(4):475-83. doi: 10.4103/2141-9248.122044 [published Online First: 2014/01/01]

27. Flanders CA, Rocke AS, Edwardson SA, et al. The effect of dexmedetomidine and clonidine on the inflammatory response in critical illness: a systematic review of animal and human studies. *Crit Care* 2019;23(1):402. doi: 10.1186/s13054-019-2690-4 [published Online First: 2019/12/13]

28. Sanders RD, Wehrman J, Irons J, et al. Meta-analysis of randomised controlled trials of perioperative dexmedetomidine to reduce delirium and mortality after cardiac surgery. *British journal of anaesthesia* 2021; 127(5):e168-e70. doi: 10.1016/j.bja.2021.08.009

29. Li CJ, Wang BJ, Mu DL, et al. Randomized clinical trial of intraoperative dexmedetomidine to prevent delirium in the elderly undergoing major non-cardiac surgery. *The British journal of surgery* 2020;107(2):e123-e32. doi: 10.1002/bjs.11354 [published Online First: 2020/01/07]

30. Likhvantsev VV, Landoni G, Grebenchikov OA, et al. Perioperative Dexmedetomidine Supplement Decreases Delirium Incidence After Adult Cardiac Surgery: A Randomized, Double-Blind, Controlled Study. *Journal of cardiothoracic and vascular anesthesia* 2020 doi: 10.1053/j.jvca.2020.02.035 [published Online First: 2020/04/09]

31. van Norden J, Spies CD, Borchers F, et al. The effect of peri-operative dexmedetomidine on the incidence of postoperative delirium in cardiac and non-cardiac surgical patients: a randomised, double-blind placebo-controlled trial. *Anaesthesia* 2021 doi: 10.1111/anae.15469 [published Online First: 2021/05/08]

32. Peng K, Shen YP, Ying YY, et al. Perioperative dexmedetomidine and 5-year survival in patients undergoing cardiac surgery. *British journal of anaesthesia* 2021 doi: 10.1016/j.bja.2021.03.040 [published Online First: 2021/06/05]

33. Subramaniam B, Shankar P, Shaefi S, et al. Effect of Intravenous Acetaminophen vs Placebo Combined With Propofol or Dexmedetomidine on Postoperative Delirium Among Older Patients Following Cardiac Surgery: The DEXACET Randomized Clinical Trial. *JAMA* 2019;321(7):686-96. doi: 10.1001/jama.2019.0234 [published Online First: 2019/02/20]

34. 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]

35. Li P, Li LX, Zhao ZZ, et al. Dexmedetomidine reduces the incidence of postoperative delirium after cardiac surgery: a meta-analysis of randomized controlled trials. BMC anesthesiology 2021;21(1):153. doi: 10.1186/s12871-021-01370-1 [published Online First: 2021/05/20]

36. Pichot C, Ghignone M, Quintin L. Dexmedetomidine and clonidine: from second- to first-line sedative agents in the critical care setting? *Journal of intensive care medicine* 2012;27(4):219-37. doi: 10.1177/0885066610396815 [published Online First: 2011/04/29]

37. Khan ZP, Ferguson CN, Jones RM. alpha-2 and imidazoline receptor agonists. Their pharmacology and therapeutic role. *Anaesthesia* 1999;54(2):146-65.

38. Wang JG, Belley-Cote E, Burry L, et al. Clonidine for sedation in the critically ill: a systematic review and meta-analysis. *Crit Care* 2017;21(1):75. doi: 10.1186/s13054-017-1610-8 [published Online First: 2017/03/24]

39. Rubino AS, Onorati F, Caroleo S, et al. Impact of clonidine administration on delirium and related respiratory weaning after surgical correction of acute type-A aortic dissection: results of a pilot study. *InteractCardiovascThoracSurg* 2010;10(1):58-62. doi: icvts.2009.217562 [pii];10.1510/icvts.2009.217562 [doi]

40. Shokri H, Ali I. A randomized control trial comparing prophylactic dexmedetomidine versus clonidine on rates and duration of delirium in older adult patients undergoing coronary

artery bypass grafting. *Journal of clinical anesthesia* 2020;61:109622. doi: 10.1016/j.jclinane.2019.09.016 [published Online First: 2019/11/02]

41. AmericanPsychiatricAssociation. Diagnostic and Statistical Manual of Mental Disorders: DSM-5 (5th ed.). Washington DC: American Psychiatric Association 2013.

42. Cole MG, Ciampi A, Belzile E, et al. Subsyndromal delirium in older people: a systematic review of frequency, risk factors, course and outcomes. *Int J Geriatr Psychiatry* 2013;28(8):771-80. doi: 10.1002/gps.3891

43. Collet JP, Thiele H, Barbato E, et al. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *European heart journal* 2021;42(14):1289-367. doi: 10.1093/eurheartj/ehaa575 [published Online First: 2020/08/30]

44. EuroQol G. EuroQol--a new facility for the measurement of health-related quality of life. *Health policy (Amsterdam, Netherlands)* 1990;16(3):199-208. doi: 10.1016/0168-8510(90)90421-9 [published Online First: 1990/11/05]

45. Neerland BE, Hov KR, Bruun Wyller V, et al. The protocol of the Oslo Study of Clonidine in Elderly Patients with Delirium; LUCID: a randomised placebo-controlled trial. *BMC geriatrics* 2015;15(1):7. doi: 10.1186/s12877-015-0006-3 [published Online First: 2015/04/19]

46. Oh ES, Akeju O, Avidan MS, et al. A roadmap to advance delirium research: Recommendations from the NIDUS Scientific Think Tank. *Alzheimer's & dementia : the journal of the Alzheimer's Association* 2020;16(5):726-33. doi: 10.1002/alz.12076 [published Online First: 2020/04/16]

47. Sessler CN, Gosnell MS, Grap MJ, et al. The Richmond Agitation-Sedation Scale: validity and reliability in adult intensive care unit patients. *AmJRespirCrit Care Med* 2002;166(10):1338-44. doi: 10.1164/rccm.2107138 [doi];166/10/1338 [pii]

48. Tieges Z, McGrath A, Hall RJ, et al. Abnormal level of arousal as a predictor of delirium and inattention: an exploratory study. *The American journal of geriatric psychiatry : official*

journal of the American Association for Geriatric Psychiatry 2013;21(12):1244-53. doi: 10.1016/j.jagp.2013.05.003

49. Hall RJ, Meagher DJ, Maclullich AM. Delirium detection and monitoring outside the ICU. *BestPractResClinAnaesthesiol* 2012;26(3):367-83. doi: S1521-6896(12)00035-3 [pii];10.1016/j.bpa.2012.07.002 [doi]

50. Ely EW, Inouye SK, Bernard GR, et al. Delirium in mechanically ventilated patients: validity and reliability of the confusion assessment method for the intensive care unit (CAM-ICU). *JAMA* 2001;286(21):2703-10. doi: 10.1001/jama.286.21.2703 [published Online First: 2001/12/26]

51. Khan BA, Perkins AJ, Gao S, et al. The Confusion Assessment Method for the ICU-7 Delirium Severity Scale: A Novel Delirium Severity Instrument for Use in the ICU. *Crit Care Med* 2017;45(5):851-57. doi: 10.1097/CCM.0000000000002368

52. Nasreddine ZS, Phillips NA, Bedirian V, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *Journal of the American Geriatrics Society* 2005;53(4):695-9. doi: 10.1111/j.1532-5415.2005.53221.x [published Online First: 2005/04/09]

53. Morris JC, Heyman A, Mohs RC, et al. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part I. Clinical and neuropsychological assessment of Alzheimer's disease. *Neurology* 1989;39(9):1159-65. [published Online First: 1989/09/01]

54. Tombaugh TN. Trail Making Test A and B: normative data stratified by age and education. *Archives of clinical neuropsychology : the official journal of the National Academy of Neuropsychologists* 2004;19(2):203-14. doi: 10.1016/S0887-6177(03)00039-8 [published Online First: 2004/03/11]

55. Tombaugh TN, Kozak J, Rees L. Normative data stratified by age and education for two measures of verbal fluency: FAS and animal naming. *Archives of clinical neuropsychology : the official journal of the National Academy of Neuropsychologists* 1999;14(2):167-77. [published Online First: 2003/11/01]

56. Wechsler D NH, Nordvik H. Wais-III Wechsler Adult Intelligence Scale : manual. 3. Ed. Stockholm: Psykologiförlaget 2003.

57. 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]

58. Kim DH, Afilalo J, Shi SM, et al. Evaluation of Changes in Functional Status in the Year After Aortic Valve Replacement. *JAMA Intern Med* 2019;179(3):383-91. doi: 10.1001/jamainternmed.2018.6738 [published Online First: 2019/02/05]

59. Afilalo J, Lauck S, Kim DH, et al. Frailty in Older Adults Undergoing Aortic Valve Replacement: The FRAILTY-AVR Study. *J Am Coll Cardiol* 2017;70(6):689-700. doi: 10.1016/j.jacc.2017.06.024 [published Online First: 2017/07/12]

60. Halaas NB, Blennow K, Idland AV, et al. Neurofilament Light in Serum and Cerebrospinal Fluid of Hip Fracture Patients with Delirium. *Dementia and geriatric cognitive disorders* 2018;46(5-6):346-57. doi: 10.1159/000494754 [published Online First: 2018/12/07]

61. Karikari TK, Pascoal TA, Ashton NJ, et al. Blood phosphorylated tau 181 as a biomarker for Alzheimer's disease: a diagnostic performance and prediction modelling study using data from four prospective cohorts. *The Lancet Neurology* 2020;19(5):422-33. doi: 10.1016/S1474-4422(20)30071-5 [published Online First: 2020/04/26]

62. Ballweg T, White M, Parker M, et al. Association between plasma tau and postoperative delirium incidence and severity: a prospective observational study. *British journal of anaesthesia* 2021;126(2):458-66. doi: 10.1016/j.bja.2020.08.061 [published Online First: 2020/11/25]

63. Yu L, Wen G, Zhu S, et al. Abnormal phosphorylation of tau protein and neuroinflammation induced by laparotomy in an animal model of postoperative delirium. *Experimental brain research* 2021 doi: 10.1007/s00221-020-06007-2 [published Online First: 2021/01/08]

64. Sajjad MU, Blennow K, Knapskog AB, et al. Cerebrospinal Fluid Levels of Interleukin-8 in Delirium, Dementia, and Cognitively Healthy Patients. *Journal of Alzheimer's disease : JAD* 2020;73(4):1363-72. doi: 10.3233/JAD-190941 [published Online First: 2020/01/14]

65. Hov KR, Bolstad N, Idland AV, et al. Cerebrospinal Fluid S100B and Alzheimer's Disease Biomarkers in Hip Fracture Patients with Delirium. *Dementia and geriatric cognitive disorders extra* 2017;7(3):374-85. doi: 10.1159/000481853 [published Online First: 2017/12/29]

66. Neerland BE, Hall RJ, Seljeflot I, et al. Associations Between Delirium and Preoperative Cerebrospinal Fluid C-Reactive Protein, Interleukin-6, and Interleukin-6 Receptor in Individuals with Acute Hip Fracture. *Journal of the American Geriatrics Society* 2016;64(7):1456-63. doi: 10.1111/jgs.14238 [published Online First: 2016/06/25]

67. Balaganapathy P, Baik SH, Mallilankaraman K, et al. Interplay between Notch and p53 promotes neuronal cell death in ischemic stroke. *Journal of cerebral blood flow and metabolism : official journal of the International Society of Cerebral Blood Flow and Metabolism* 2018;38(10):1781-95. doi: 10.1177/0271678X17715956

68. Wedervang-Resell K, Ueland T, Aukrust P, et al. Reduced levels of circulating adhesion molecules in adolescents with early-onset psychosis. *NPJ Schizophr* 2020;6(1):20. doi: 10.1038/s41537-020-00112-5

69. Fleming TR, DeMets DL, Roe MT, et al. Data monitoring committees: Promoting best practices to address emerging challenges. *Clin Trials* 2017;14(2):115-23. doi: 10.1177/1740774516688915

70. Wang YY, Yue JR, Xie DM, et al. Effect of the Tailored, Family-Involved Hospital Elder Life Program on Postoperative Delirium and Function in Older Adults A Randomized Clinical Trial. *Jama Internal Medicine* 2020;180(1):17-25. doi: 10.1001/jamainternmed.2019.4446

71. Su X, Meng ZT, Wu XH, et al. Dexmedetomidine for prevention of delirium in elderly patients after non-cardiac surgery: a randomised, double-blind, placebo-controlled trial. *Lancet* 2016 doi: 10.1016/S0140-6736(16)30580-3

72. Shehabi Y, Grant P, Wolfenden H, et al. Prevalence of delirium with dexmedetomidine compared with morphine based therapy after cardiac surgery: a randomized controlled trial (DEXmedetomidine COmpared to Morphine-DEXCOM Study). *Anesthesiology* 2009;111(5):1075-84. doi: 10.1097/ALN.0b013e3181b6a783 [doi]

73. Jamadarkhana S, Gopal S. Clonidine in adults as a sedative agent in the intensive care unit. *Journal of anaesthesiology, clinical pharmacology* 2010;26(4):439-45. [published Online First: 2011/05/07]

74. 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]

75. 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]

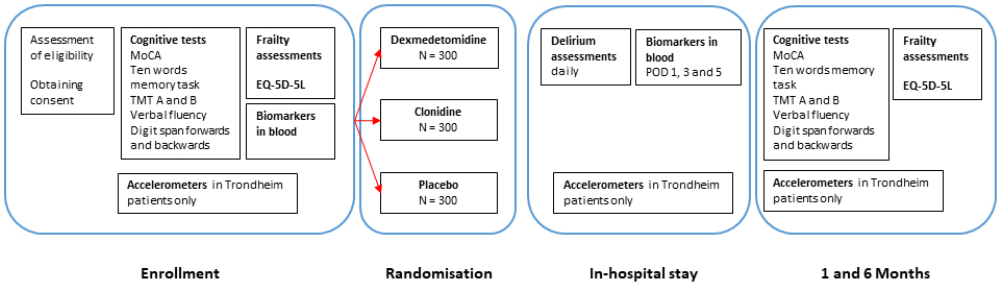

Figure 1:
Study schema. MoCA, Montreal Cognitive Assessment; TMT, Trail Making Test; EQ-5D-5L, EuroQol 5 Dimension 5 Level; POD, Postoperative Day

254x190mm (96 x 96 DPI)

Supplementary File 1

Detailed explanation of sample size calculations

The following parameters were considered in the samples size calculation strategy and confirmations:

Parameter		Explanation / justification
Proportions	**% delirium within 7 days**	
Placebo	30 %	Proportion of patients experiencing postoperative delirium after open heart surgery for all ages has been reported to be 24%,[1] and higher in the elderly.[2] With participants over 70 years in this trial, we expect the proportion to be at least 30%.
Dexmedetomidine (DEX)	15 %	Recent meta-analysis indicated dexmedetomidine approximately halves the risk of delirium[3]
Clonidine	20 %	Clonidine is anticipated to have similar effect to DEX, however 10 percentage point reduction would also be clinically significant
Power	80 %	
Significance level	5 %	
Duration of follow-up	7-days	
Accrual period	0-days*	

*Observation period starts with operation for all participants

Conservative sample size: As described the initial, conservative samples 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 of 20 % delirium in the clonidine and 30 % in 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 a higher drop-out rate. Furthermore, the study will be more than adequately powered to find the greater expected reduction in delirium in the dexmedetomidine group.

Since we intend to use the logrank test to account for difference in the observation period, we confirmed that the calculated sample size was adequate using the more flexible calculation options in PASS Sample size software (version 20, NCSS, Kaysville, Utah, USA).

Logrank test: A two-sided logrank test with an overall sample size of 498 subjects (249 in the control group and 249 in the treatment group) achieves 80 % power at a 5 % significance level to a reduction in the proportion with delirium from 30 % in the control arm to 20 % in the clonidine arm (equivalent to a hazard ratio of 1.34). By including 300 participants in each group, we will still achieve 80 % power with up to 7 % drop-out rate over the first seven postoperative days. Drop out rates lower than 7 % will result in a higher power. Even with 10 % drop out rate, we will still achieve 80 % to detect a slightly larger difference between the groups (10.4 percentage point reduction, rather than 10 percentage points) (Figure S1).

Multiplicity: The planned comparisons for this trial are between dexmedetomidine versus placebo and clonidine versus placebo. Any comparison between dexmedetomidine and clonidine groups will be explorative and clearly stated as such. The extension of the CONSORT 2010 Statement for multi-arm parallel-group randomised trials recommend that adjustments for multiple comparisons are generally not necessary in trials comparing two or more independent treatments to placebo as we are here.[4] This has therefore not been factored into the sample size calculation. However, even with the very conservative Bonferroni adjustment for two comparisons a sample size of 300 participants per arm will be sufficient if there were no drop-outs and only minimally affect the difference in proportions which we can hope to identify with 80 % power if there is up to 10 % drop-out (Figure S1). For example, with 5 % dropout we can detect a 10.6 percentage point reduction in delirium cumulative incidence with 80 % and 2.5 % significance level (to account for multiplicity), or 11.3 percentage points if there was 10 % dropout (Figure S1).

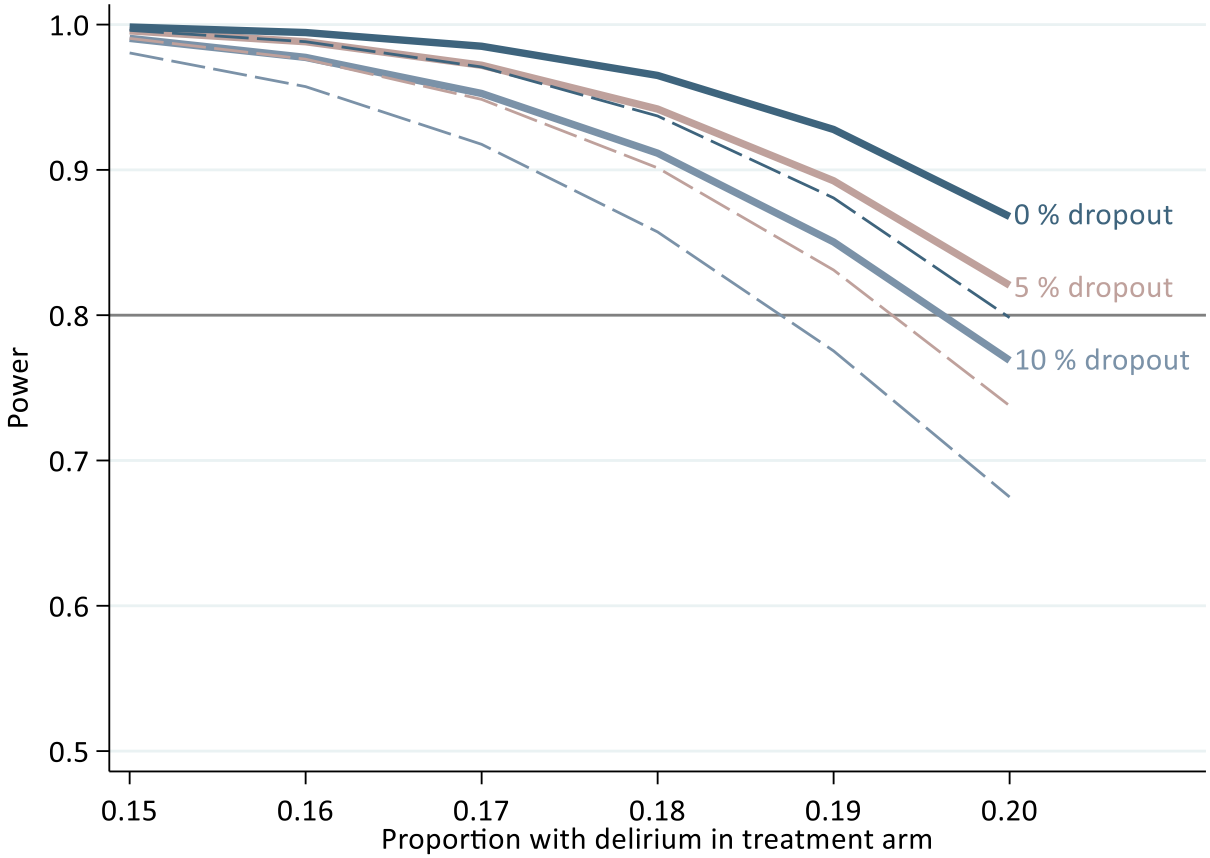

Figure S1: Power depending differing drop-out rates over the proportion with delirium in the treatment arm and where the proportion in the control arm is 30 %. The solid lines indicate the power with 5 % significance level for studies with no dropout (dark blue), 5 % dropout (pink) or 10 % dropout (medium blue). The corresponding broken lines indicate the power with 2.5 % significance level, a Bonferroni adjustment for the two planned comparisons.

1. Greaves D, Psaltis PJ, Ross TJ, et al. Cognitive outcomes following coronary artery bypass grafting: A systematic review and meta-analysis of 91,829 patients. *International journal of cardiology* 2019;289:43-49. doi: 10.1016/j.ijcard.2019.04.065 [published Online First: 2019/05/13]
2. Eide LS, Ranhoff AH, Fridlund B, et al. Comparison of frequency, risk factors, and time course of postoperative delirium in octogenarians after transcatheter aortic valve implantation versus surgical aortic valve replacement. *The American journal of cardiology* 2015;115(6):802-9. doi: 10.1016/j.amjcard.2014.12.043 [published Online First: 2015/02/04]
3. Flukiger J, Hollinger A, Speich B, et al. Dexmedetomidine in prevention and treatment of postoperative and intensive care unit delirium: a systematic review and meta-analysis. *Annals of intensive care* 2018;8(1):92. doi: 10.1186/s13613-018-0437-z [published Online First: 2018/09/22]
4. Juszczak E, Altman DG, Hopewell S, et al. Reporting of Multi-Arm Parallel-Group Randomized Trials: Extension of the CONSORT 2010 Statement. *JAMA* 2019;321(16):1610-20. doi: 10.1001/jama.2019.3087

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	6
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	11
Protocol version	#3	Date and version identifier	NA

Funding	#4	Sources and types of financial, material, and other support	26
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1-3,26
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	25-26
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	26
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	19-21
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	8-10,16,23
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	11
Objectives	#7	Specific objectives or hypotheses	10
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	11

Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	11
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	11-13
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	16
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	16, 20-21
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	21
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	16
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	16-19

Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	11-16, Table 2, Figure 1
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	21
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	11
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	13
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	13
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	11-13
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	13

Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	20-21
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	13,16-19, Table 2
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	21-22
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	19-20
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	21-23
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	21-23
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	21-23

Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	21
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	21
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	20-21
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	21
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	6,23,25
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	23
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	11
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	11

Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	19,20
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	25-26
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	20,25
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	20-21
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	6,23
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	23
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	25
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	11
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	14,19