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BMJ Open

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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3 1 **TITLE PAGE**
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6 2 **Title:** Alpha-2-adrenergic receptor agonists for the prevention of delirium and cognitive decline after
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8 3 open heart surgery (ALPHA2PREVENT): protocol for a multicentre randomised controlled trial
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58 87 **Word count:** Abstract = 274 words. Body = 4002 words
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6 89 **Key words:** delirium, prevention, dexmedetomidine, clonidine, cardiac surgery, frailty, older,
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For peer review only

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3 93 **ABSTRACT**
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6 94 **Introduction:** Postoperative delirium is common in older cardiac surgery patients and associated with
7
8 95 negative short-term and long-term outcomes. The alpha-2-adrenergic receptor agonist
9
10 96 dexmedetomidine shows promise as prophylaxis and treatment for delirium in intensive care units
11
12 97 (ICU) and postoperative settings. Clonidine has similar pharmacological properties and can be
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14 98 administered both parenterally and orally. We aim to study whether repurposing of clonidine can
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16 99 represent a novel treatment option for delirium, and the possible effects of dexmedetomidine and
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18 100 clonidine on long-term cognitive trajectories, motor activity patterns and biomarkers of neuronal
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20 101 injury, and whether these effects are associated with frailty status.
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23
24 102 **Methods and analysis:** This five-centre, double blind randomised controlled trial will include 900
25
26 103 cardiac surgery patients aged 70+. Participants will be randomized 1:1:1 to dexmedetomidine or
27
28 104 clonidine or placebo. The study drug will be given as a continuous intravenous infusion from the start
29
30 105 of cardiopulmonary bypass, at a rate of 0.4 µg/kg/h. The infusion rate will be decreased to 0.2
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32 106 µg/kg/h postoperatively and be continued until discharge from the ICU or 24 hours postoperatively,
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34 107 whichever happens first.
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38 108 Primary endpoint is the 7-day cumulative incidence of postoperative delirium (Diagnostic and
39
40 109 Statistical Manual of Mental Disorders, 5th edition). Secondary endpoints include the composite
41
42 110 endpoint of coma, delirium or death, delirium severity and motor activity patterns, levels of
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44 111 circulating biomarkers of neuronal injury, cognitive function and frailty status 1 and 6 months after
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46 112 surgery.
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50 113 **Ethics and dissemination:** This trial is approved by the Regional Committee for Ethics in Medical
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52 114 Research in Norway (South-East Norway) and by the Norwegian Medicines Agency. Dissemination
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54 115 plans include publication in peer-reviewed medical journals and presentation at scientific meetings.
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58 116 **Trial registration number:** EudraCT: 2021-001645-12. ClinicalTrials.gov: NCT05029050
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3 117 **STRENGTHS AND LIMITATIONS OF THIS STUDY**
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- 6 118 • This multicentre trial will provide evidence for prophylactic efficacy of dexmedetomidine and
7
8 119 clonidine in reducing the incidence of postoperative delirium as well as decline in cognitive
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10 120 function 1 and 6 months postoperatively in older cardiac surgical patients
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13 121 • Inclusion of preoperative frailty assessments will provide evidence for frailty as a predictive
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15 122 marker of treatment effect
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17 123 • The analysis of biomarkers will provide insights into the neural mechanisms in postoperative
18
19 124 delirium and long-term cognitive dysfunction
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22 125 • The analysis of activity by accelerometers will provide insight into motor activity patterns in
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24 126 subtypes of delirium
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26 127 • The dose of the active drugs may potentially be too low or the duration of treatment too
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29 128 short in order to show effects
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129 BACKGROUND

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

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

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

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

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3 152 Conventionally, delirium has been separated into hyperactive and hypoactive subtypes based on
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5 153 clinical impression,¹⁹ but recent research using body-worn sensors indicates a more heterogeneous
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7 154 pattern of motor activity across the clinical delirium motor subtypes.^{20 21} Body-worn motor activity
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10 155 sensors may provide objective measures of the effectiveness of delirium treatment intervention, by
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12 156 classifying motor activity patterns in delirious patients. A small postoperative study on cardiac
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14 157 surgery patients showed the possibility of detecting the amount of movement in sedated patients.²²

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17 158 Routinely, several actions are taken in perioperative care to minimize the risk of delirium, such as
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19 159 appropriate management of pain and minimizing the use of sedative drugs like benzodiazepines.
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22 160 Further, non-pharmacological multicomponent interventions are essential,²³ but there is currently no
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24 161 compelling evidence to support the use of specific prophylactic pharmacological measures in routine
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26 162 perioperative care for patients at risk of postoperative delirium.²⁴

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29 163 However, dexmedetomidine, a parenterally administered alpha-2-adrenergic receptor agonist that
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31 164 attenuates sympathetic nervous system activity, shows promise as prophylaxis and treatment for
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34 165 delirium in ICUs and postoperative settings.^{25 26} In a recent meta-analysis, perioperative use of
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36 166 dexmedetomidine in various surgical procedures was associated with a lower incidence of
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38 167 postoperative delirium. The relative risk (RR) and 95% confidence interval (CI) was 0.52 (0.39-0.70)
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40 168 when compared with placebo.²⁵ A meta-analysis in cardiac surgery patients showed that
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42 169 dexmedetomidine could reduce the risk of postoperative delirium (Odds Ratio 0.56, 95% CI 0.36-
43
44 170 0.89)²⁷. Among newer studies, some,²⁸⁻³¹ but not all,^{32 33} have found a beneficial short time effect on
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46 171 the incidence of delirium. Effects upon long time cognitive trajectories have so far only been
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49 172 assessed in two studies, with conflicting results.^{34 35} Nevertheless, the use of dexmedetomidine in
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51 173 ICUs is rapidly increasing.²⁶

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54 174 An alternative agent is clonidine, which has similar pharmacological properties to
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56 175 dexmedetomidine,³⁶ even though it's alpha-2-adrenergic selectivity is lower.³⁷ Clonidine can be
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58 176 administered both parenterally and orally, thus potentially widening its clinical usefulness.^{36 37}
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3 177 Clonidine was originally launched as an antihypertensive agent, but it is also used as an analgesic
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5 178 drug. Further, clonidine has a long tradition as a sedative in patients with hyperactive delirium, and is
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7 179 used by several anaesthesiologists and intensivists.³⁸ This practice is based on their clinical
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10 180 experiences and knowledge on the drug's properties, but is so far not supported by placebo-
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12 181 controlled clinical trials. A pilot study indicated that clonidine infusion during the period of weaning
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14 182 from mechanical ventilation after surgery for aortic dissection may reduce the severity of delirium.³⁹
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16 183 A recent study compared clonidine with dexmedetomidine postoperatively after CABG and found
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18 184 better effect on risk and duration of delirium of dexmedetomidine. Since no placebo control group
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21 185 was included, that study could not assess potential effects of clonidine.⁴⁰
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24 186 Thus, there is a need for prospective large-scale studies on the potential prophylactic effect of alpha-
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26 187 2-adrenergic receptor agonists on delirium in susceptible patients. The aims of the present planned
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28 188 trial are to study 1) whether repurposing of clonidine can represent a novel treatment option for
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30 189 delirium, and 2) the possible effects of dexmedetomidine and clonidine on long-term cognitive
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32 190 trajectories, motor activity patterns, patient rated outcome measures and biomarkers of neuronal
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35 191 injury, and 3) whether these effects are associated with frailty status.
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3 194 **METHODS AND ANALYSIS**
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6 195 **Study design**
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9 196 ALPHA2PREVENT is a nationwide five-centre, double blind randomised controlled trial (RCT). Patients
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11 197 aged 70+ scheduled for open heart surgery will be randomized 1:1:1 to dexmedetomidine or
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13 198 clonidine or placebo. The patients will be cognitively assessed preoperatively, then assessed for any
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15 199 symptoms of delirium according to the Diagnostic and Statistical Manual of Mental Disorders, 5th
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17 200 edition (DSM-5) criteria⁴¹ or subsyndromal delirium⁴² postoperatively, and finally assessed for
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19 201 cognitive function after 1 and 6 months (figure 1).
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23 202 **Study locations**
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26 203 The trial will be carried out at Oslo University Hospital (Ullevaal and Rikshospitalet) in Oslo,
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28 204 Haukeland University Hospital in Bergen, Trondheim University Hospital in Trondheim, and the
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30 205 University Hospital of Northern Norway in Tromsø, all in Norway.
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34 206 **Participants, randomisation and blinding**
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37 207 Patients will be assessed for eligibility and asked for participation in cooperation with the responsible
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39 208 thoracic surgeons or anaesthesiologists. A full listing of trial inclusion and exclusion criteria is
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41 209 displayed in table 1. Participants must be ≥ 70 years old, accepted for cardiac surgery with CPB and
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43 210 capable of giving signed informed consent. The surgical procedures may constitute CABG, valve
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45 211 replacement, surgery on the ascending aorta, or combinations of these. Main exclusion criteria are
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47 212 bradycardia, uncontrolled hypotension, ischemic stroke the last month or acute coronary syndrome
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49 213 last 24 hours,⁴³ left ventricular ejection fraction $< 40\%$, severe renal failure or hepatic dysfunction,
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51 214 sepsis, planned deep hypothermia and circulatory arrest, as well as emergency surgery.
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56 215 **Table 1. Inclusion and exclusion criteria**
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<p>Participants are eligible to be included in the study only if all of the following criteria apply:</p>	<p>Participants are excluded from the study if any of the following criteria apply:</p>
<p>1. Participant must be ≥ 70 years old at the time of signing the informed consent.</p> <p>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.</p> <p>3. Participant must be capable of giving signed informed consent.</p>	<p>4. Preoperative delirium (present at time of potential inclusion)</p> <p>5. Known hypersensitivity to the active ingredient or components of the product</p> <p>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</p> <p>7. Uncontrolled hypotension</p> <p>8. Ischemic stroke or transitory ischemic attack the last month or critical peripheral ischemia</p> <p>9. Acute coronary syndrome last 24 hours. Acute coronary syndrome is defined according to international guidelines</p> <p>10. Left ventricular ejection fraction $< 40\%$</p> <p>11. Severe renal impairment (estimated GFR < 20 ml/min) or expected requirement for renal replacement therapy</p> <p>12. Severe hepatic dysfunction (liver enzyme three times the upper limit of normal together with a serum albumin concentration below the normal reference limit</p>

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

217 Consenting patients will be randomly assigned 1:1:1, to dexmedetomidine, clonidine or placebo.

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

223 **Data collected at study entry**

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

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

239 **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

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

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241 ProBNP, Pro B-type Natriuretic Peptide; ECG, electrocardiogram; PROM, Patient Rated Outcome

242 Measure; ASA-classification, American Society of Anesthesiologists Physical Status Classification; AE,

243 Adverse Event; SAE, Serious AE

244 ^a No delirium assessment at follow-up after 6 months

245 **Trial interventions**

246 Dexmedetomidine, clonidine or placebo (saline), will be given as a continuous intravenous infusion,

247 without a loading dose, from the start of CPB, at a rate of 0.4 µg/kg/h for the active drugs. The

248 infusion rate will be decreased to 0.2 µg/kg/h postoperatively and maintained for at least 12 hours

249 after end of surgery. The infusion will be continued until discharge from the ICU or 24 hours

250 postoperatively, whichever happens first. Clinicians are allowed to decrease, pause or stop

251 administration of study medication if clinically indicated, e.g. if the patient is difficult to wake up

252 after surgery or study drug induced hemodynamic instability is suspected.

253 **Concomitant therapy and rescue medicine**

254 Patients will not be included if they use tricyclic antidepressants, monoamine reuptake inhibitors or

255 cyclosporine. The perioperative anaesthesia will be given per routine at participating institutions. If

256 delirium develops and pharmacological intervention is needed, the study drug will be stopped, and

257 further treatment will be according to local routines and the treating physician's preferences.

258 **Primary endpoint**

259 The primary endpoint for ALPHA2PREVENT is the 7-day cumulative incidence of postoperative

260 delirium. The diagnosis of delirium will be made according to DSM-5 criteria⁴¹ by using a standardized

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3 261 procedure developed for our previous study⁴⁵ and as recommended by others⁴⁶. The methods are
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5 262 refined in order, in a stepwise approach, to assess presence or absence of the diagnostic criteria in
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7 263 DSM-5 and will be carried out by specially trained research assistants. Level of arousal will be
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9
10 264 assessed using the Norwegian versions of Richmond Agitation Sedation Scale (RASS)⁴⁷ and
11
12 265 Observational Scale of Level of Arousal (OSLA).⁴⁸ Attention and awareness will be evaluated using
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14 266 objective tests (vigilance “A”-test, months of the years backwards, days of the week backwards, and
15
16 267 counting down from 20 to 1)⁴⁹ and observations by the examiner of the patient’s distractibility,
17
18 268 comprehension and tendency to lose the thread of conversation. Presence of additional cognitive
19
20 269 disturbances will be assessed by tests for orientation and recall test of three words (different words
21
22 270 for each day), as well as information derived from nursing staff and clinical notes. Acute change in
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24 271 the patient’s mental condition, and fluctuations of any disturbance, will be ascertained through
25
26 272 informant history from nursing staff and derived from clinical notes.
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31 273 The Norwegian version of the Confusion Assessment Method for Intensive Care Units (CAM-ICU)⁵⁰
32
33 274 will be used as a delirium screening tool by the study nurses. The results from each of the CAM-ICU-
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35 275 items, as well as the total CAM-ICU score, will also be used as a source of information for making the
36
37 276 final delirium diagnosis.
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41 277 Two or more experienced delirium researchers will independently use all available information
42
43 278 (including the project assistants’ assessments) on each patient to decide if the DSM-5 criteria for
44
45 279 delirium are fulfilled. An interrater agreement for the diagnosis of delirium will be calculated and
46
47 280 disagreements will be resolved through discussion.
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51 281 Subsyndromal delirium will be defined as evidence of change, in addition to any one of these:
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53 282 altered arousal, attentional deficits, other cognitive change, delusions or hallucinations. DSM-5
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55 283 delirium criteria D and E must be met.
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58 284 Postoperative delirium assessment will start as soon as possible after admission to the ICU, and will
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60 285 continue daily until the seventh postoperative day or until discharge from the university hospital,

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3 286 whichever happens first. Tests for delirium will also be repeated at the 1-month follow-up, to pick up
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5 287 signs of persistent delirium.
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8 288 **Secondary endpoints**
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11 289 Secondary endpoints include the composite endpoint of coma, delirium or death, number of delirium
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13 290 days, delirium severity and motor activity patterns, comparison to inclusion of serum concentrations
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15 291 of neurofilament light (NFL) and p-tau181 1, 3 and 5 days postoperatively, as well as change between
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17 292 inclusion and after 1 and 6 months in cognitive function, patient rated health status, frailty status,
18
19 293 and comparison of change in frailty status between patients with or without postoperative delirium.
20
21 294 We will also assess preoperative frailty status as a predictive marker of effect of dexmedetomidine
22
23 295 and clonidine treatment, by studying the interaction between preoperative frailty and treatment on
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25 296 delirium and the other mentioned endpoints.
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30 297 All endpoints will be assessed using Norwegian versions of validated instruments: Delirium severity
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32 298 will be measured using CAM-ICU-7,⁵¹ OSLA⁴⁸ and RASS;⁴⁷ motor activity patterns using body worn
33
34 299 accelerometers; cognitive function using Montreal Cognitive Assessment (MoCA),⁵² immediate and
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36 300 delayed recall from The Ten Words Memory Task from The Consortium to Establish a Registry for
37
38 301 Alzheimer's Disease,⁵³ Trail Making Test (TMT) version A and B,⁵⁴ semantic and phonemic verbal
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40 302 fluency,⁵⁵ digit span forwards and backwards (by Wechsler Adult Intelligence Scale);⁵⁶ frailty using a
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42 303 comprehensive geriatric assessment-based Frailty Index⁵⁷ and Essential Frailty Toolset;⁵⁸ and patient
43
44 304 rated health status using the EQ-5D-5L questionnaire.⁴⁴
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49 305 For assessment of cognitive trajectories, the same cognitive test battery will be performed in a stable
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51 306 phase preoperatively as well as after 1 and 6 months. Information regarding functional status will be
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53 307 obtained from the patient preoperatively and from either the patient or their proxy at follow-up,
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55 308 depending on the patient's ability to provide detailed information.
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3 309 For a sub-sample of one hundred patients from the Trondheim cohort, motor activity will be
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5 310 measured by 3D accelerometer inertial sensors (AX3 sensors) (Axivity Ltd., Newcastle, UK) sampled at
6
7 311 100 Hz and processed using custom made software. Accelerometers will be attached to the
8
9 312 abdomen, the dominant thigh (ventrally, midhigh), and on the dominant wrist pre surgery. Motor
10
11 313 activity patterns will be monitored continuously (day and nights) before and the five first days after
12
13 314 surgery or until discharge from hospital, and over one week after 1 and 6 months. Sensor data will be
14
15 315 analyzed regarding both quantity and quality of movements and compared with the clinical delirium
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17 316 assessments.

317 **Biomarkers**

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

326 **Standardised training**

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

332 **Data management and monitoring**

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3 333 Participant data will be collected by authorized trained personnel, be recorded on electronic Case
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5 334 Report Forms (CRF) and stored on a password protected database. Paper files will be stored in locked
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7 335 cabinets accessible to team members only. Study monitors will perform ongoing source data
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10 336 verification to confirm that data entered into the CRFs are accurate, complete, and verifiable from
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12 337 source documents; that the safety and rights of participants are being protected; and that the study
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14 338 is being conducted in accordance with the currently approved protocol, International Conference on
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16 339 Harmonization Good Clinical Practice, and all applicable regulatory requirements. Records and
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18 340 documents, including signed Informed Consent Forms, pertaining to the conduct of this study will be
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21 341 retained by the investigators for 15 years after study completion.
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24 25 343 **Safety and adverse events management**

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28 344 Immediate safety concerns will be handled by the treating anaesthesiologist, who will determine if
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30 345 the participant should continue or discontinue study intervention. Since patients are closely
31
32 346 monitored in the perioperative phase of cardiac surgery, potential adverse circulatory effects will be
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34 347 rapidly revealed and corrected;

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38 348 • Temporal epicardial pacing wires are placed routinely during cardiac surgery, and
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40 349 bradycardia will be treated with atropine and/or pacemaker as per routine.
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42 350 • Hypotension will be treated at discretion of the treating anaesthesiologists, who are
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44 351 permitted to reduce dose of the study drug as necessary to preserve haemodynamic stability,
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46 352 following guidelines and local routines. A Mean Arterial Pressure (MAP) >55-60mmHg is
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48 353 recommended.
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50 354 • If not rapid and satisfactory response on other measures is achieved, the treating
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52 355 anaesthesiologist will consider to turn off the infusion/unblind the study.

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57 356 Planned time points for safety assessments are provided in table 2.
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3 357 The following safety indicators will be compared between the three treatment groups with
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5 358 appropriate statistical methods: Highest and lowest heart rate, systolic, diastolic and mean arterial
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7 359 blood pressure, oxygen saturation, PaO₂/FiO₂ ratio, number of units for blood transfusion, volume of
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9 360 postoperative blood loss, use of pressor substances, use of rescue medication, number of episodes of
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11 361 bradycardia, hypotension or hypoxemia in need of intervention, perioperative myocardial infarction
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13 362 and stroke, postoperative serum concentrations of troponin and Pro B-type Natriuretic Peptide
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15 363 (proBNP), mortality.

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19 364 An independent Data Monitoring Committee will have unblinded access to all data and meet
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21 365 whenever the members find it necessary.⁶⁸ Meetings are pre-planned after inclusion of 20, 50, 100
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23 366 and 400 participants, to assess safety indicators and to advise on continuation or termination of the
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25 367 study.

26 27 28 29 368 **Current sample size justification**

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32 369 The proportion of patients experiencing postoperative delirium after open heart surgery for all ages
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34 370 has been reported to be 24%,³ and higher in the elderly.⁴ Since the lower age limit in our trial is 70
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36 371 years, we estimate that the proportion in the control group will be at least 30%. The most recent
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38 372 meta-analysis of the effect of dexmedetomidine estimates the delirium risk to be reduced to
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40 373 approximately half of the untreated group (*i.e.*, 15%).²⁵ The effect of clonidine may be weaker but
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42 374 still worth finding. We have thus powered the study based on an estimated delirium incidence of
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44 375 20% in the clonidine group. A sample size of 290 in each group (870 altogether) will give a power of
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46 376 80% with a significance level of 5% to detect such a difference between the clonidine and the
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48 377 placebo group. To account for dropouts, we aim at including 900 patients.

49 50 51 52 53 378 **Statistical analysis**

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56 379 The primary analysis population will be the intention-to-treat population, and all tests will be two-
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58 380 sided. The primary objective in this study is to prevent postoperative delirium. The primary endpoint

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3 381 is the cumulative incidence of postoperative delirium. The endpoint will be registered when the
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5 382 patient is diagnosed with delirium or receives rescue medication for delirium. The postoperative
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7 383 observation time will vary between patients, as time to discharge or transfer to other hospitals will
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10 384 be different. We will thus estimate cumulative incidence by the Kaplan Meier estimator with time to
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12 385 first delirium as the dependent variable and compare time to event curves between treatments by
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14 386 the logrank test. Patients who are discharged from the university hospital during the observation
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16 387 period or reach the end of the observation period (7 days) without having developed delirium, are
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18 388 regarded as censored. We consider that there is no risk that allocation to treatment group will
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21 389 influence the risk of being censored. Those who die, will also be regarded as censored in the primary
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23 390 analysis, but we will carry out a secondary analysis with the combined endpoint *death or delirium*.
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25 391 The same approach will be applied for those who are comatose, and thus impossible to evaluate for
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27 392 delirium. Additional analyses may also include estimating the incidence of delirium treating deaths as
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29 393 a competing risk by the Fine and Gray method.
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33 394 All analyses will be adjusted for variables applied in the stratified randomization.
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36 395 Sensitivity analyses will be carried out by estimating hazard ratios using Cox' proportional hazards
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38 396 model to adjust for potential imbalance of prognostic factors between treatment groups.
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41 397 Secondary endpoints as the cumulative incidence of death, coma or postoperative delirium will be
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43 398 analysed using the Kaplan Meier estimator and the logrank test as above. Additional analyses by Cox'
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45 399 proportional hazards model may also be performed. Mean duration of delirium; severity of delirium;
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47 400 combination of duration and severity of delirium; cognitive tests after 1 and 6 months; EQ-5D-5L
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49 401 scores after 1 and 6 months; and postoperative plasma concentrations of NFL and p-tau181 will be
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51 402 compared between treatments by linear mixed models with time, treatment group, and strata as
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53 403 fixed factors and constraining the means to be equal in all groups at baseline.
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58 404 Frailty as risk factor for delirium and for adverse effects of the study medication, will be analysed by
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60 405 linear or logistic regression (as appropriate), adjusted for other known risk factors. The association

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3 406 between frailty and delirium will be analysed by adding frailty as a covariate in a Cox'proportional
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5 407 hazards model on time to delirium (as above). Any interaction between frailty and treatment will also
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7 408 be assessed. The association between frailty and occurrence of adverse events (AE) will be estimated
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10 409 by logistic regression models including covariates as above.

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13 410 A detailed statistical analysis plan will be finalized prior to un-blinding.

14 15 16 411 **Ethics and dissemination**

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19 412 This trial is approved by the Regional Committee for Ethics in Medical Research in Norway (South-
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21 413 East Norway) and by the Norwegian Medicines Agency, and will be conducted in accordance with
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23 414 consensus ethical principles derived from international guidelines including the Declaration of
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25 415 Helsinki. The results of this study will be published in peer-reviewed medical journals, as well as
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28 416 presented at scientific meetings

29 30 31 417 **Discussion**

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34 418 To our knowledge, ALPHA2PREVENT will be the first large randomised controlled multicentre trial to
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36 419 study the prophylactic efficacy of dexmedetomidine and clonidine to reduce the incidence of
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38 420 postoperative delirium in older cardiac surgical patients, as well as reducing cognitive decline 1 and 6
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41 421 months postoperatively.

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44 422 One should expect that treatment options that can prevent delirium in a short-term perspective,
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46 423 would also improve the long-term cognitive prognosis. Evidence for such an effect is slowly emerging
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48 424 for non-pharmacological interventions,⁶⁹ but is lacking regarding drug treatment.

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51 425 Published studies of dexmedetomidine for prevention of delirium in ICU vary largely with respect to
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53 426 dosing regimens, from 0.1⁷⁰ to 1.4 µg/kg/h.³² Many of the authors also administered an initial
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55 427 bolus. In the cardiac surgery context, Turan et al started dexmedetomidine infusion already before
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58 428 start of CPB, gave 0.4 µg/kg/h postoperatively,³³ and found more side effects in the actively treated
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3 429 than in the placebo group. We have chosen a careful dosage of 0.4 µg/kg/h peroperatively and 0.2
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5 430 µg/kg/h postoperatively, with no bolus, to reduce the risk of AE, but not so low that we cannot
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7 431 expect an effect on delirium.
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10 432 Regarding clonidine, the recommended dosage varies greatly between sources, but is mainly in the
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12 433 range 1-1.5 µg/kg/h.⁷² We will dose the drug considerably lower, to avoid side effects. A recent meta-
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14 434 analysis indicates that clonidine and dexmedetomidine are approximately equipotent in similar
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16 435 doses.⁷³ We have thus chosen the same dosage for clonidine as for dexmedetomidine.
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20 436 To further reduce the risk of hemodynamic instability due to the combination of anaesthesiological
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22 437 procedures and study drug at the start of surgery, we will postpone infusion of study drug until the
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24 438 CPB is established.
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28 439 Strengths of this trial are the prospective and randomised placebo controlled design, the use of two
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30 440 relevant and much used drugs, inclusion of a high number of patients from multiple sites, adequate
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32 441 statistic strength, repeated cognitive and frailty assessments, use of body-worn accelerometers, and
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34 442 repeated samples of biomarkers. The analyses of biomarkers reflecting neural injury will give us
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36 443 increased understanding of the pathophysiological mechanisms of delirium. Inclusion of preoperative
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38 444 frailty assessments will provide evidence for frailty as a predictive marker of treatment effect and
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40 445 allow for interaction analyses. The use of body-worn accelerometers will provide insight into motor
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42 446 activity patterns in subtypes of delirium.
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46 447 This trial has, however, some limitations to consider. The exclusion criteria might limit the
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48 448 generalisability of our findings to other patient populations. There might be a problem with statistical
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50 449 power if the incidence of delirium is lower than expected. The dose of the active drugs might be too
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52 450 low or the duration of treatment be too short in order to show effects. As many patients live far
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54 451 away from the study site, there is a potential for missing long-term data.
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3 452 Should the treatment have a positive effect, it would have important beneficial implications for
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5 453 patients, cares and society, such as alleviating acute patient distress and carer burden. If this
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7 454 treatment could reduce longer-term negative effects of delirium, it might have significant
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9 455 consequences for financial and human resource use in health care.
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16 457 **DECLARATIONS**

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19 458 **Patient and public involvement:** Panellists from the user panel established by the Norwegian
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21 459 National Advisory Unit on Ageing and Health, participate in the Trial Advisory Board. They have
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23 460 experience as relatives to patients with dementia or delirium, have given valuable input to the
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25 461 project plans and will follow up during the project period.
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29 462 **Ethics approval:** The trial is approved by the Regional Committee for Ethics in Medical Research in
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31 463 Norway (South-east Norway) (REK 262384), June 9th 2021, and by the Norwegian Medicines Agency
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33 464 June 17th 2021.
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36 465 **Availability of data and materials:** Materials can be available upon reasonable request to the
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38 466 corresponding author. However, availability is dependent on approval from the Regional Ethics
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40 467 Committee and the local data protection officer.
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44 468 **Competing interest:** HZ has served at scientific advisory boards and/or as a consultant for Alector,
45
46 469 Eisai, Denali, Roche Diagnostics, Wave, Samumed, Siemens Healthineers, Pinteon Therapeutics,
47
48 470 Nervgen, AZTherapies, CogRx and Red Abbey Labs, has given lectures in symposia sponsored by
49
50 471 Celectricon, Fujirebio, Alzecure and Biogen, and is a co-founder of Brain Biomarker Solutions in
51
52 472 Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program (outside submitted
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54 473 work).
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3 474 AJCS is advisor for Prolira, a start-up company that develops an EEG-based delirium monitor. Any
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5 475 (future) profits from EEG-based delirium monitoring will be used for future scientific research only.
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7

8 476 GS has participated in one advisory meeting for Biogen. HMN has received lecture fees from Vifor
9
10 477 Pharma and Orion Pharma.
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12

13
14 478 The other authors declare that they have no competing interests.
15

16
17 479 **Consent for publication:** Not required
18

19
20 480 **Funding:** The trial is funded by KLINBEFORSK, The National Programme for Clinical Therapy Research
21
22 481 in the Specialist Health Service in Norway, grant number 2020204. HZ is a Wallenberg Scholar.
23
24

25 482 **Disclaimer:** Funders have no role in the trial design, data collection, management, analysis, writing of
26
27 483 the manuscript or decision to publish.
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29

30 484 **Author contributions:**
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32
33 485 Drafting of the manuscript: BEN
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35

36 486 Critical revision of the manuscript for important intellectual content: BEN, RB, RH, JLH, AKK, SAL, IM,
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39 487 HMN, JR, GS, ES, NKS, ES, AS, ØSS, TT, AW, HZ, TBW
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41

42 488 Obtained funding: TBW
43
44

45 489 All authors contributed to the writing of the manuscript and approved the final version.
46
47

48 490 **Acknowledgements:** The trial is investigator-initiated and investigator-led, and is conducted
49
50 491 independently of the pharmaceutical industry. We are thankful to the staff of the participating
51
52 492 departments for their compliance with the project directives and their caring for the patients.
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58 494 **Abbreviations:**
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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

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TMT	Trail Making Test
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3 497 **LEGENDS**
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6 498 **Figure 1:**
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9 499 Study schema. MoCA, Montreal Cognitive Assessment; TMT, Trail Making Test; EQ-5D-5L, EuroQol 5

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11 500 Dimension 5 Level; POD, Postoperative Day
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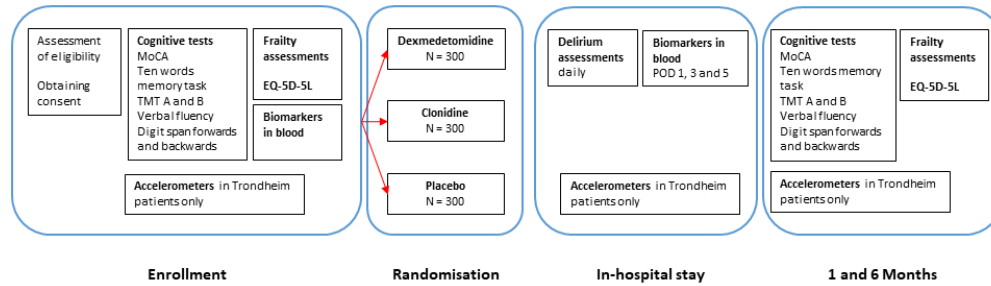


Figure 1:
Study schema. MoCA, Montreal Cognitive Assessment; TMT, Trail Making Test; EQ-5D-5L, EuroQol 5 Dimension 5 Level; POD, Postoperative Day

254x190mm (96 x 96 DPI)

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

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 SPIRIT reporting 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

			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

1	Funding	#4	Sources and types of financial, material, and other support	26
2				
3				
4	Roles and	#5a	Names, affiliations, and roles of protocol contributors	1-3,26
5	responsibilities:			
6	contributorship			
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10	Roles and	#5b	Name and contact information for the trial sponsor	25-26
11	responsibilities:			
12	sponsor contact			
13	information			
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18	Roles and	#5c	Role of study sponsor and funders, if any, in study design; collection,	26
19	responsibilities:		management, analysis, and interpretation of data; writing of the report;	
20	sponsor and funder		and the decision to submit the report for publication, including whether	
21			they will have ultimate authority over any of these activities	
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27	Roles and	#5d	Composition, roles, and responsibilities of the coordinating centre,	19-21
28	responsibilities:		steering committee, endpoint adjudication committee, data management	
29	committees		team, and other individuals or groups overseeing the trial, if applicable	
30			(see Item 21a for data monitoring committee)	
31				
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35	Introduction			
36				
37				
38	Background and	#6a	Description of research question and justification for undertaking the trial,	8-10,16,23
39	rationale		including summary of relevant studies (published and unpublished)	
40			examining benefits and harms for each intervention	
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45	Background and	#6b	Explanation for choice of comparators	11
46	rationale: choice of			
47	comparators			
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51	Objectives	#7	Specific objectives or hypotheses	10
52				
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54	Trial design	#8	Description of trial design including type of trial (eg, parallel group,	11
55			crossover, factorial, single group), allocation ratio, and framework (eg,	
56			superiority, equivalence, non-inferiority, exploratory)	
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1 **Methods: Participants,**
 2
 3 **interventions, and**
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 5 **outcomes**
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7	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
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14	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
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20	Interventions:	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	16
21	description			
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25	Interventions:	#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
26	modifications			
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31	Interventions:	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	21
32	adherence			
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38	Interventions:	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	16
39	concomitant care			
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43	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
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1	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
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10	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
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17	Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	11
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21	Methods: Assignment			
22	of interventions (for			
23	controlled trials)			
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28	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
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38	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
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46	Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	11-13
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51	Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	13
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1	Blinding (masking):	#17b	If blinded, circumstances under which unblinding is permissible, and	20-21
2				
3	emergency unblinding		procedure for revealing a participant's allocated intervention during the	
4				
5			trial	
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8	Methods: Data			
9	collection,			
10	management, and			
11	analysis			
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16	Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial	13,16-19,
17			data, including any related processes to promote data quality (eg,	Table 2
18			duplicate measurements, training of assessors) and a description of	
19			study instruments (eg, questionnaires, laboratory tests) along with their	
20			reliability and validity, if known. Reference to where data collection forms	
21			can be found, if not in the protocol	
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28	Data collection plan:	#18b	Plans to promote participant retention and complete follow-up, including	21-22
29	retention		list of any outcome data to be collected for participants who discontinue	
30			or deviate from intervention protocols	
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35	Data management	#19	Plans for data entry, coding, security, and storage, including any related	19-20
36			processes to promote data quality (eg, double data entry; range checks	
37			for data values). Reference to where details of data management	
38			procedures can be found, if not in the protocol	
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43	Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes.	21-23
44			Reference to where other details of the statistical analysis plan can be	
45			found, if not in the protocol	
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49	Statistics: additional	#20b	Methods for any additional analyses (eg, subgroup and adjusted	21-23
50	analyses		analyses)	
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54	Statistics: analysis	#20c	Definition of analysis population relating to protocol non-adherence (eg,	21-23
55	population and		as randomised analysis), and any statistical methods to handle missing	
56	missing data		data (eg, multiple imputation)	
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1	Methods: Monitoring		
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4	Data monitoring:	#21a	Composition of data monitoring committee (DMC); summary of its role 21
5			
6	formal committee		and reporting structure; statement of whether it is independent from the
7			sponsor and competing interests; and reference to where further details
8			about its charter can be found, if not in the protocol. Alternatively, an
9			explanation of why a DMC is not needed
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14	Data monitoring:	#21b	Description of any interim analyses and stopping guidelines, including 21
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16	interim analysis		who will have access to these interim results and make the final decision
17			to terminate the trial
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21	Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and 20-21
22			spontaneously reported adverse events and other unintended effects of
23			trial interventions or trial conduct
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27	Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether 21
28			the process will be independent from investigators and the sponsor
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32	Ethics and		
33	dissemination		
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36	Research ethics	#24	Plans for seeking research ethics committee / institutional review board 6,23,25
37			
38	approval		(REC / IRB) approval
39			
40			
41	Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes 23
42			to eligibility criteria, outcomes, analyses) to relevant parties (eg,
43			investigators, REC / IRBs, trial participants, trial registries, journals,
44			regulators)
45			
46			
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48			
49	Consent or assent	#26a	Who will obtain informed consent or assent from potential trial 11
50			participants or authorised surrogates, and how (see Item 32)
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54	Consent or assent:	#26b	Additional consent provisions for collection and use of participant data 11
55			
56	ancillary studies		and biological specimens in ancillary studies, if applicable
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1	Confidentiality	#27	How personal information about potential and enrolled participants will be	19,20
2			collected, shared, and maintained in order to protect confidentiality	
3			before, during, and after the trial	
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7	Declaration of	#28	Financial and other competing interests for principal investigators for the	25-26
8	interests		overall trial and each study site	
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12	Data access	#29	Statement of who will have access to the final trial dataset, and	20,25
13			disclosure of contractual agreements that limit such access for	
14			investigators	
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18	Ancillary and post trial	#30	Provisions, if any, for ancillary and post-trial care, and for compensation	20-21
19	care		to those who suffer harm from trial participation	
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23	Dissemination policy:	#31a	Plans for investigators and sponsor to communicate trial results to	6,23
24	trial results		participants, healthcare professionals, the public, and other relevant	
25			groups (eg, via publication, reporting in results databases, or other data	
26			sharing arrangements), including any publication restrictions	
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31	Dissemination policy:	#31b	Authorship eligibility guidelines and any intended use of professional	23
32	authorship		writers	
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36	Dissemination policy:	#31c	Plans, if any, for granting public access to the full protocol, participant-	25
37	reproducible research		level dataset, and statistical code	
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41	Appendices			
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43				
44	Informed consent	#32	Model consent form and other related documentation given to	11
45	materials		participants and authorised surrogates	
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48	Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological	14,19
49			specimens for genetic or molecular analysis in the current trial and for	
50			future use in ancillary studies, if applicable	
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BMJ Open

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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6 2 **Title:** Alpha-2-adrenergic receptor agonists for the prevention of delirium and cognitive decline after
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8 3 open heart surgery (ALPHA2PREVENT): protocol for a multicentre randomised controlled trial
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12 91 **Key words:** delirium, prevention, dexmedetomidine, clonidine, cardiac surgery, frailty, older,
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14 92 cognitive decline
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95 **ABSTRACT**

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

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

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

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

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

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3 119 **STRENGTHS AND LIMITATIONS OF THIS STUDY**
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- 6 120 • This multicentre trial will provide evidence for prophylactic efficacy of dexmedetomidine and
7
8 121 clonidine in reducing the incidence of postoperative delirium as well as decline in cognitive
9
10 122 function 1 and 6 months postoperatively in older cardiac surgical patients
11
12
13 123 • Inclusion of preoperative frailty assessments will provide evidence for frailty as a predictive
14
15 124 marker of treatment effect
16
17 125 • The analysis of biomarkers will provide insights into the neural mechanisms in postoperative
18
19 126 delirium and long-term cognitive dysfunction
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21
22 127 • The analysis of activity by accelerometers will provide insight into motor activity patterns in
23
24 128 subtypes of delirium
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26 129 • The dose of the active drugs may potentially be too low or the duration of treatment too
27
28 130 short in order to show effects
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131 **BACKGROUND**

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

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

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

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

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3 154 Conventionally, delirium has been separated into hyperactive and hypoactive subtypes based on
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5 155 clinical impression,¹⁹ but recent research using body-worn sensors indicates a more heterogeneous
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7 156 pattern of motor activity across the clinical delirium motor subtypes.^{20 21} Small light-weight body-
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10 157 worn accelerometers may provide objective measures of the effectiveness of delirium treatment
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12 158 intervention on motor activity level and types of patterns. A small postoperative study on cardiac
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14 159 surgery patients showed the possibility of detecting the amount of movement in sedated patients.²²

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

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

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3 178 cognitive trajectories have so far not been assessed in this patient population. Nevertheless, the use
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5 179 of dexmedetomidine in ICUs is rapidly increasing.²⁶
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8 180 An alternative agent is clonidine, which has similar pharmacological properties to
9
10 181 dexmedetomidine,³⁶ even though it's alpha-2-adrenergic selectivity is lower.³⁷ Clonidine can be
11
12 182 administered both parenterally and orally, thus potentially widening its clinical usefulness.^{36 37}
13
14 183 Clonidine was originally launched as an antihypertensive agent, but it is also used as an analgesic
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16 184 drug. Further, clonidine has a long tradition as a sedative in patients with hyperactive delirium, and is
17
18 185 used by several anaesthesiologists and intensivists.³⁸ This practice is based on their clinical
19
20 186 experiences and knowledge on the drug's properties, but is so far not supported by placebo-
21
22 187 controlled clinical trials. A pilot study indicated that clonidine infusion during the period of weaning
23
24 188 from mechanical ventilation after surgery for aortic dissection may reduce the severity of delirium.³⁹
25
26 189 A recent study compared clonidine with dexmedetomidine postoperatively after CABG and found
27
28 190 better effect on risk and duration of delirium of dexmedetomidine. Since no placebo control group
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30 191 was included, that study could not assess potential effects of clonidine.⁴⁰
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36 192 Thus, there is a need for prospective large-scale studies on the potential prophylactic effect of alpha-
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38 193 2-adrenergic receptor agonists on delirium in susceptible patients. The aims of the present planned
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40 194 trial are to study 1) whether repurposing of clonidine can represent a novel treatment option for
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42 195 delirium, and 2) the possible effects of dexmedetomidine and clonidine on long-term cognitive
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44 196 trajectories, motor activity patterns, patient rated outcome measures and biomarkers of neuronal
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46 197 injury, and 3) whether these effects are associated with frailty status.
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3 200 **METHODS AND ANALYSIS**
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6 201 **Study design**
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9 202 ALPHA2PREVENT is a nationwide five-centre, double blind randomised controlled trial (RCT). Patients
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11 203 aged 70+ scheduled for open heart surgery will be randomized 1:1:1 to dexmedetomidine or
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13 204 clonidine or placebo. The patients will be cognitively assessed preoperatively, then assessed for any
14
15 205 symptoms of delirium according to the Diagnostic and Statistical Manual of Mental Disorders, 5th
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17 206 edition (DSM-5) criteria⁴¹ or subsyndromal delirium⁴² postoperatively, and finally assessed for
18
19 207 cognitive function after 1 and 6 months (figure 1).
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23 208 **Study locations**
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25

26 209 The trial will be carried out at Oslo University Hospital (Ullevaal and Rikshospitalet) in Oslo,
27
28 210 Haukeland University Hospital in Bergen, Trondheim University Hospital in Trondheim, and the
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30 211 University Hospital of Northern Norway in Tromsø, all in Norway.
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34 212 **Participants, randomisation and blinding**
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37 213 Patients will be assessed for eligibility and asked for participation in cooperation with the responsible
38
39 214 thoracic surgeons or anaesthesiologists. A full listing of trial inclusion and exclusion criteria is
40
41 215 displayed in table 1. Participants must be ≥ 70 years old, accepted for cardiac surgery with CPB and
42
43 216 capable of giving signed informed consent. The surgical procedures may constitute CABG, valve
44
45 217 replacement, surgery on the ascending aorta, or combinations of these. Main exclusion criteria are
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47 218 bradycardia, uncontrolled hypotension, ischemic stroke the last month or acute coronary syndrome
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49 219 last 24 hours,⁴³ left ventricular ejection fraction $< 40\%$, severe renal failure or hepatic dysfunction,
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51 220 sepsis, planned deep hypothermia and circulatory arrest, as well as emergency surgery.
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56 221 **Table 1. Inclusion and exclusion criteria**
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<p>Participants are eligible to be included in the study only if all of the following criteria apply:</p>	<p>Participants are excluded from the study if any of the following criteria apply:</p>
<p>1. Participant must be ≥ 70 years old at the time of signing the informed consent.</p> <p>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.</p> <p>3. Participant must be capable of giving signed informed consent.</p>	<p>4. Preoperative delirium (present at time of potential inclusion)</p> <p>5. Known hypersensitivity to the active ingredient or components of the product</p> <p>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</p> <p>7. Uncontrolled hypotension</p> <p>8. Ischemic stroke or transitory ischemic attack the last month or critical peripheral ischemia</p> <p>9. Acute coronary syndrome last 24 hours. Acute coronary syndrome is defined according to international guidelines</p> <p>10. Left ventricular ejection fraction $< 40\%$</p> <p>11. Severe renal impairment (estimated GFR < 20 ml/min) or expected requirement for renal replacement therapy</p> <p>12. Severe hepatic dysfunction (liver enzyme three times the upper limit of normal together with a serum albumin concentration below the normal reference limit</p>

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

223 Consenting patients will be randomly assigned 1:1:1, to dexmedetomidine, clonidine or placebo.

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

229 **Data collected at study entry**

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

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

245 **Table 2. Study procedures**

Procedure	Screening	Baseline	Surgery	Postoperative day number:							Hospital discharge	1 and 6 months	
	≤30 days before Day 0	-3 to -1 days before Day 0	Day 0	1	2	3	4	5	6	7			
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												

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3 265 delirium develops and pharmacological intervention is needed, the study drug will be stopped, and
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5 266 further treatment will be according to local routines and the treating physician's preferences.
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8 267 **Primary endpoint**
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11 268 The primary endpoint for ALPHA2PREVENT is the cumulative incidence of postoperative delirium
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13 269 within 7 days. Postoperative delirium assessment will start as soon as possible after admission to the
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15 270 ICU, and will continue daily until the seventh postoperative day or until discharge from the university
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17 271 hospital, whichever happens first. To allow for differences in the duration of the postoperative
18
19 272 observation period, time until delirium diagnosis will be recorded and the cumulative incidence will
20
21 273 be assessed using Kaplan Meier estimates and compared between groups with the log-rank test as
22
23 274 described below. A clinical assessment for delirium will also be repeated at the 1-month follow-up, to
24
25 275 pick up signs of persistent delirium.
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30 276 The diagnosis of delirium will be ascertained using all available information, and will be determined
31
32 277 to be present if participants meet all DSM-5 criteria⁴¹ by using a standardized procedure developed
33
34 278 for our previous study⁴⁵ and as recommended by others⁴⁶, table 3. The methods are refined in order,
35
36 279 in a stepwise approach, to assess presence or absence of the diagnostic criteria in DSM-5 and will be
37
38 280 carried out once daily by specially trained research assistants. Level of arousal will be assessed using
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40 281 the Norwegian versions of Richmond Agitation Sedation Scale (RASS)⁴⁷ and Observational Scale of
41
42 282 Level of Arousal (OSLA).⁴⁸ Attention and awareness will be evaluated using objective tests (vigilance
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44 283 "A"-test, months of the years backwards, days of the week backwards, and counting down from 20 to
45
46 284 1)⁴⁹ and observations by the examiner of the patient's distractibility, comprehension and tendency to
47
48 285 lose the thread of conversation. Presence of additional cognitive disturbances will be assessed by
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50 286 tests for orientation and recall test of three words (different words for each day), as well as
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52 287 information derived from nursing staff and clinical notes. Acute change in the patient's mental
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54 288 condition, and fluctuations of any disturbance, will be ascertained through informant history from
55
56 289 nursing staff and derived from clinical notes. Nurses will, as part of their routine and for each shift
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290 (i.e., three times daily), actively register symptoms of delirium in the case notes, as well as screen for
 291 delirium using the Norwegian version of the Confusion Assessment Method for Intensive Care Units
 292 (CAM-ICU)⁵⁰ and RASS. The same delirium assessment tools will be used for the ICU, step-down and
 293 bed wards. The results from each of the CAM-ICU-items, as well as the total CAM-ICU score, will also
 294 be used as a source of information for making the final delirium diagnosis.

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

299 Subsyndromal delirium (table 3) will be defined as evidence of change, in addition to any one of
 300 these: altered arousal, attentional deficits, other cognitive change, delusions or hallucinations. DSM-
 301 5 delirium criteria D and E must be met.

303 **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		

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	<table border="1"> <tr> <td data-bbox="689 197 986 340">Months of the year backwards</td> <td data-bbox="986 197 1251 340">unable to pass June</td> </tr> <tr> <td data-bbox="689 340 986 483">Count backwards from 20 to 1</td> <td data-bbox="986 340 1251 483">any error</td> </tr> <tr> <td data-bbox="689 483 986 564">Digit span backwards</td> <td data-bbox="986 483 1251 564"><5 digits</td> </tr> </table>	Months of the year backwards	unable to pass June	Count backwards from 20 to 1	any error	Digit span backwards	<5 digits		
Months of the year backwards	unable to pass June								
Count backwards from 20 to 1	any error								
Digit span backwards	<5 digits								
<p>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.</p>	<p><u>Observation (by the examiner during the interview):</u></p> <p>Distractibility. Comprehension. Tendency to lose the tread of conversation</p> <p>Level of arousal measured using RASS and OSLA</p> <p>Acute onset and/or fluctuation obtained from informant history from nursing staff and clinical notes</p> <p><u>Questions to carer/ nursing staff or derived from clinical notes:</u></p> <p>Has there been a sudden change in the patient’s mental state?</p> <p>Does the patient seem to be better at any period in the day compared to other times?</p> <p>Has the level of consciousness been altered (drowsy/ not interacting or agitated)?</p> <p>Sleep-wake cycle disturbances?</p>								

<p>C. An additional disturbance in cognition (e.g., memory deficit, disorientation, language, visuospatial ability, or perception).</p>	<p><u>Questions to the patient:</u></p> <p>Orientation to time, place and person</p> <p>3 item recall at three minutes</p> <p>Questions from CAM-ICU: Why are you in hospital? Will a stone float in water? Are there fish in the sea?</p> <p><u>Questions to carer/ nursing staff or derived from clinical notes:</u></p> <p>Any evidence of perceptual disturbances as illusions or hallucinations? Memory disturbances? Psychotic symptoms? Psychomotor abnormalities?</p>		
<p>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.</p>	<p>Information from history/chart/clinical assessment</p>		
<p>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</p>	<p>By virtue of the surgery, all participants are considered to fulfil this criterion.</p>		

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.		

304 DSM-5, Diagnostic and Statistical Manual of Mental Disorders, 5th edition; RASS, Richmond Agitation

305 Sedation Scale; OSLA, Observational Scale of Level of Arousal; CAM-ICU, Confusion Assessment

306 Method for Intensive Care Units

307

308 **Secondary endpoints**

309 Secondary endpoints include the composite endpoint of coma, delirium or death, in addition to
 310 number of delirium days, delirium severity and motor activity patterns, comparison to inclusion of
 311 serum concentrations of neurofilament light (NFL) and p-tau181 1, 3 and 5 days postoperatively, as
 312 well as change from inclusion to 1 and 6 months after the operation in different cognitive tests,
 313 patient rated health status, frailty status, and comparison of change in frailty status. In explorative
 314 analyses, the secondary outcomes will also be assessed between patients with or without
 315 postoperative delirium. We will also assess if preoperative frailty status modifies the effect of
 316 dexmedetomidine and clonidine treatment, by studying the interaction between preoperative frailty
 317 and treatment on delirium and the other mentioned endpoints.

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3 318 All endpoints will be assessed using Norwegian versions of validated instruments: Delirium severity
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5 319 will be measured using CAM-ICU-7,⁵¹ OSLA⁴⁸ and RASS;⁴⁷ motor activity patterns using body worn
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7 320 accelerometers; cognitive function using Montreal Cognitive Assessment (MoCA),⁵² immediate and
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9 321 delayed recall from The Ten Words Memory Task from The Consortium to Establish a Registry for
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11 322 Alzheimer's Disease,⁵³ Trail Making Test (TMT) version A and B,⁵⁴ semantic and phonemic verbal
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13 323 fluency,⁵⁵ digit span forwards and backwards (by Wechsler Adult Intelligence Scale);⁵⁶ frailty will be
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15 324 measured by a comprehensive geriatric assessment (including medical history, number of prescribed
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17 325 drugs, sensory impairment, activity of daily living, gait speed, handgrip strength, chair stand and
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19 326 nutritional status) calculating a frailty-index (range, 0-1; higher values indicate greater frailty) based
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21 327 on the accumulation of deficits model of frailty^{57 58} and by the shorter Essential Frailty Toolset;⁵⁹ and
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23 328 patient rated health status using the EQ-5D-5L questionnaire.⁴⁴

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28 329 For assessment of cognitive trajectories, the same cognitive tests will be performed in a stable phase
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30 330 preoperatively as well as after 1 and 6 months. Information regarding functional status will be
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32 331 obtained from the patient preoperatively and from either the patient or their proxy at follow-up,
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34 332 depending on the patient's ability to provide detailed information.

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38 333 For a sub-sample of one hundred patients from the Trondheim cohort, motor activity will be
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40 334 measured by 3D accelerometer inertial sensors (AX3 sensors) (Axivity Ltd., Newcastle, UK) sampled at
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42 335 100 Hz and processed using custom made software. Accelerometers will be attached to the frontal
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44 336 part of the waist, the dominant thigh (ventrally, midthigh), and on the dominant wrist pre surgery.
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46 337 Motor activity patterns will be monitored continuously (day and nights) before and the five first days
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48 338 after surgery or until discharge from hospital, and over one week after 1 and 6 months. Sensor data
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50 339 will be analyzed regarding both quantity and quality of movements and compared with the clinical
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52 340 delirium assessments.

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57 341 **Biomarkers**
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3 342 In addition to routine blood tests, blood will be taken in the morning for specific study analyses
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5 343 (serum, plasma and wholeblood) before surgery, and at postoperative day 1, 3 and 5 (or earlier if
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7 344 discharged before day 5) and frozen at -80°C locally. Frozen samples will then be shipped to the
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9 345 coordinating centre (Oslo) to be stored in a biobank at -80°C for future analyses. The stored blood
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11 346 samples will be analysed for promising markers such as NFL already known to be associated with
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13 347 delirium,⁶⁰⁹ p-tau181 associated with dementia and delirium,⁶¹⁻⁶³ and possibly other biomarkers of
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15 348 neuronal degeneration, neuroinflammation and neurotransmitters,⁶⁴⁻⁶⁸ using state-of-the-art
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17 349 ultrasensitive assays to evaluate their association with observed clinical responses to the study drugs.
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22 350 **Standardised training**

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25 351 The research assistants across all sites will receive standardized training for all study measures prior
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27 352 to study initiation, including cognitive tests, delirium assessments and measurements of frailty
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29 353 indicators. Retraining will be provided as necessary. Detailed instructions and operation manuals in
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31 354 Norwegian language, including an instruction video for the MoCA, will be made available to all
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33 355 assessors.
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36 356 **Data management and monitoring**

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40 357 Participant data will be collected by authorized trained personnel, be recorded on electronic Case
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42 358 Report Forms (CRF) and stored on a password protected database. Paper files will be stored in locked
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44 359 cabinets accessible to team members only. Study monitors will perform ongoing source data
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46 360 verification to confirm that data entered into the CRFs are accurate, complete, and verifiable from
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48 361 source documents; that the safety and rights of participants are being protected; and that the study
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50 362 is being conducted in accordance with the currently approved protocol, International Conference on
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52 363 Harmonization Good Clinical Practice, and all applicable regulatory requirements. Records and
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54 364 documents, including signed Informed Consent Forms, pertaining to the conduct of this study will be
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56 365 retained by the investigators for 15 years after study completion.
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3 367 **Safety and adverse events management**
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6 368 Immediate safety concerns will be handled by the treating anaesthesiologist, who will determine if
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8 369 the participant should continue or discontinue study intervention. If the patient is hemodynamically
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10 370 unstable at any time during infusion of the study medication or difficult to wake up after surgery, the
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12 371 infusion can be temporarily stopped, as decided by the treating physician. In such a case the patient
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14 372 will continue in the study. The reason for temporary discontinuation will be recorded. Since patients
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16 373 are closely monitored in the perioperative phase of cardiac surgery, potential adverse circulatory
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18 374 effects will be rapidly revealed and corrected;

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23 375 • Temporal epicardial pacing wires are placed routinely during cardiac surgery, and
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25 376 bradycardia will be treated with atropine and/or pacemaker as per routine.
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27 377 • Hypotension will be treated at discretion of the treating anaesthesiologists, who are
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29 378 permitted to reduce dose of the study drug as necessary to preserve haemodynamic stability,
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31 379 following guidelines and local routines. A Mean Arterial Pressure (MAP) >55-60mmHg is
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33 380 recommended.
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35 381 • If not rapid and satisfactory response on other measures is achieved, the treating
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37 382 anaesthesiologist will consider to turn off the infusion/unblind the study.

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41 383 Planned time points for safety assessments are provided in table 2.
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44 384 The following safety indicators will be compared between the three treatment groups with
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46 385 appropriate statistical methods: Highest and lowest heart rate and mean arterial blood pressure,
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48 386 oxygen saturation, number of units for blood transfusion, volume of postoperative blood loss, use of
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50 387 pressor substances, use of rescue medication, number of episodes of bradycardia, hypotension or
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52 388 hypoxemia in need of intervention, perioperative myocardial infarction and stroke, postoperative
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54 389 serum concentrations of troponin and Pro B-type Natriuretic Peptide (proBNP), mortality.
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3 390 An independent Data Monitoring Committee will have unblinded access to all data and meet at pre-
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5 391 planned inclusion milestones and whenever the members find it necessary.⁶⁹ Meetings are pre-
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7 392 planned after inclusion of 20, 50, 100 and 400 participants, to assess safety indicators and to advise
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9 393 on continuation or termination of the study. All safety data collected will be summarized and
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11 394 reviewed by the DMC for agreement of next steps. In particular, data will be reviewed by for
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13 395 identification of the following events that would potentially contribute to a requirement to pause or
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15 396 stop the study: Any deaths, regardless of causality; cerebral infarctions; haemodynamic variables
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17 397 (time during surgery with MAP<50 mmHg, highest/lowest MAP and HR, lowest SpO₂); need for
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19 398 vasopressor, non-invasive ventilation, active pacing, respiratory support or extracorporeal
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21 399 membrane oxygenation (ECMO); postoperative troponin values. If a pausing/stopping rule is met, a
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23 400 decision will be made, based on the review, as to whether enrolment in the study will be allowed to
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25 401 resume. Case unblinding will be performed for above reviews if necessary.
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34 403 **Current sample size justification**

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37 404 The proportion of patients experiencing postoperative delirium after open heart surgery for all ages
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39 405 has been reported to be 24%,³ and higher in older adults.⁴ Since the lower age limit in our trial is 70
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41 406 years, we estimate that the proportion in the control group will be at least 30%. The most recent
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43 407 meta-analysis of the effect of dexmedetomidine estimates the delirium risk to be reduced to
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45 408 approximately half of the untreated group (*i.e.*, 15%).²⁵ We anticipate that the effect of clonidine
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47 409 may be weaker, but still clinically relevant. We have thus powered the study based on an estimated
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49 410 delirium incidence of 20% in the clonidine group. An initial, conservative sample size calculation
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51 411 based on comparison of two proportions indicated that a sample size of 290 in each group (870
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53 412 altogether) will give a power of 80% with a significance level of 5% to detect such a difference
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55 413 between the clonidine and the placebo group in the proportion developing delirium within 7 days
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57 414 postoperatively. To account for dropouts, we aim at including 900 patients. This sample size
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3 415 calculation approach was conservative considering the use of time-to-delirium analysis strategy,
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5 416 accommodating for both a higher drop-out rate and that this trial has three-arms. We have further
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7 417 confirmed the adequacy of this sample size estimate for the logrank test with differing rates of drop-
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9 418 out and considering the three-arms (Supplementary file 1).
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13 419 **Statistical analysis**

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16 420 The primary analysis population will be the intention-to-treat population, and all tests will be two-
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18 421 sided. The primary objective in this study is to prevent postoperative delirium. The primary endpoint
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20 422 is the cumulative incidence of postoperative delirium. In the analysis of this endpoint, time to
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22 423 diagnosis of delirium will be used to account for the varying postoperative observation time due to
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24 424 difference in time to discharge or transfer to other hospitals will be different. The cumulative
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26 425 incidence will therefore be estimated using the Kaplan Meier estimator with time to first delirium as
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28 426 the dependent variable and compare time to event curves between treatments by the logrank test.
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30 427 Patients who are discharged from the university hospital during the observation period or reach the
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32 428 end of the observation period (7 days) without having developed delirium, are regarded as censored.
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34 429 We consider that treatment group allocation will not influence the risk of being censored. Those who
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36 430 die prior to 7 days, will also be regarded as censored in the primary analysis, but we will carry out a
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38 431 secondary analysis with the combined endpoint *death or delirium*. The same approach will be applied
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40 432 for those who are comatose, and thus impossible to evaluate for delirium. Additional analyses may
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42 433 also include estimating the incidence of delirium treating deaths as a competing risk by the Fine and
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44 434 Gray method.
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50 435 All analyses will be adjusted for study centre which was used to as a stratification variable in the
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52 436 randomisation process.
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55 437 Sensitivity analyses will be carried out by estimating hazard ratios using Cox' proportional hazards
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57 438 model to adjust for potential imbalance of prognostic factors between treatment groups.
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3 439 Secondary endpoints as the cumulative incidence of death, coma or postoperative delirium will be
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5 440 analysed using the Kaplan Meier estimator and the logrank test as above. Additional analyses by Cox'
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7 441 proportional hazards model may also be performed. Mean duration of delirium; severity of delirium;
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9 442 combination of duration and severity of delirium; cognitive tests after 1 and 6 months; EQ-5D-5L
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11 443 scores after 1 and 6 months; and postoperative plasma concentrations of NFL and p-tau181 will be
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13 444 compared between treatments with appropriate regression models which will be defined in a
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15 445 Statistical Analysis Plan prior to analysis.

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19 446 Frailty as risk factor for delirium and for adverse effects of the study medication, will be analysed by
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21 447 linear or logistic regression (as appropriate), adjusted for other known risk factors. The association
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23 448 between frailty and delirium will be analysed by adding frailty as a covariate in a Cox'proportional
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25 449 hazards model on time to delirium (as above). Additionally, we will assess if the presence of frailty
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27 450 modifies the effect of the treatment by including an interaction term between frailty and treatment
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29 451 allocation in the Cox proportional hazards model. The association between frailty and occurrence of
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31 452 adverse events (AE) will be estimated by logistic regression models including covariates as above.

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36 453 No interim analyses of the efficacy of the treatments are planned. A detailed statistical analysis plan
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38 454 will be finalized prior to unblinding.

41 455 **Ethics and dissemination**

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44 456 This trial is approved by the Regional Committee for Ethics in Medical Research in Norway (South-
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46 457 East Norway) and by the Norwegian Medicines Agency, and will be conducted in accordance with
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48 458 consensus ethical principles derived from international guidelines including the Declaration of
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50 459 Helsinki. The results of this study will be published in peer-reviewed medical journals, as well as
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52 460 presented at scientific meetings

53 54 55 56 461 **Discussion**

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3 462 To our knowledge, ALPHA2PREVENT will be the first large randomised controlled multicentre trial to
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5 463 study the prophylactic efficacy of dexmedetomidine as well as clonidine on the incidence of
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7 464 postoperative delirium in older cardiac surgical patients, and also including long-term cognitive
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9 465 trajectories.

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13 466 One should expect that treatment options that can prevent delirium in a short-term perspective,
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15 467 would also improve the long-term cognitive prognosis. Evidence for such an effect is slowly emerging
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17 468 for non-pharmacological interventions,⁷⁰ but is lacking regarding drug treatment.

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20 469 Published studies of dexmedetomidine for prevention of delirium in ICU vary largely with respect to
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22 470 dosing regimens, from 0.1^{71 72} to 1.4 µg/kg/h.³³ Many of the authors also administered an initial
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24 471 bolus. In the cardiac surgery context, Turan et al started dexmedetomidine infusion already before
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26 472 start of CPB, gave 0.4 µg/kg/h postoperatively,³⁴ and found more side effects in the actively treated
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28 473 than in the placebo group. We have chosen a careful dosage of 0.4 µg/kg/h peroperatively and 0.2
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30 474 µg/kg/h postoperatively, with no bolus, to reduce the risk of AE, but not so low that we cannot
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32 475 expect an effect on delirium.

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37 476 Regarding clonidine, the recommended dosage varies greatly between sources, but is mainly in the
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39 477 range 1-1.5 µg/kg/h.⁷³ We will dose the drug considerably lower, to avoid side effects. There is a
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41 478 shortage of studies comparing i.v. dexmedetomidine and i.v. clonidine in ICU or postoperative
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43 479 settings.⁷⁴ To our knowledge, a widely agreed evidence-based i.v. dosage regimen has not been
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45 480 developed for i.v. clonidine. A study by Grest in critically ill patients after cardiac surgery⁷⁴ and a
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47 481 recent meta-analysis favour equipotency mg per mg.⁷⁵ Thus, our choice is fairly pragmatic, but the
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49 482 doses are similar to that currently used in many ICUs as part of routine practice.

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53 483 To further reduce the risk of hemodynamic instability due to the combination of anaesthesiological
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55 484 procedures and study drug at the start of surgery, we will postpone infusion of study drug until the
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57 485 CPB is established. If clonidine is both effective and safe to administer, then it may be relevant to
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59 486 conduct more studies on per oral treatment with clonidine in other patient groups later on.

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3 487 Strengths of this trial are the prospective and randomised placebo controlled design, the use of two
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5 488 relevant and much used drugs, inclusion of a high number of patients from multiple sites, adequate
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7 489 statistic strength, repeated cognitive and frailty assessments, use of body-worn accelerometers, and
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10 490 repeated samples of biomarkers. The analyses of biomarkers reflecting neural injury will give us
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12 491 increased understanding of the pathophysiological mechanisms of delirium. Inclusion of preoperative
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14 492 frailty assessments will provide evidence for frailty as a predictive marker of treatment effect and
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16 493 allow for interaction analyses. The use of body-worn accelerometers will provide insight into motor
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18 494 activity patterns in subtypes of delirium.

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22 495 This trial has, however, some limitations to consider. The exclusion criteria might limit the
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24 496 generalisability of our findings to other patient populations. If the incidence of delirium in the
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26 497 placebo group is lower than expected, or if the anticipated effect of the treatment is smaller, the
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28 498 study may be underpowered. The dose of the active drugs might be too low or the duration of
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30 499 treatment be too short in order to show effects. As many patients live far away from the study site,
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33 500 there is a potential for missing long-term data.

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36 501 Should the treatment have a positive effect, it would have important beneficial implications for
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38 502 patients, carers and society, such as alleviating acute patient distress and carer burden. If this
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40 503 treatment could reduce longer-term negative effects of delirium, it might have significant
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42 504 consequences for financial and human resource use in health care.

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47 48 49 506 **DECLARATIONS**

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52 507 **Patient and public involvement:** Panellists from the user panel established by the Norwegian
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54 508 National Advisory Unit on Ageing and Health, participate in the Trial Advisory Board. They have
55
56 509 experience as relatives to patients with dementia or delirium, have given valuable input to the
57
58 510 project plans and will follow up during the project period.

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3 511 **Ethics approval:** The trial is approved by the Regional Committee for Ethics in Medical Research in
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5 512 Norway (South-east Norway) (REK 262384), June 9th 2021, and by the Norwegian Medicines Agency
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7 513 June 17th 2021.
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10 514 **Availability of data and materials:** Materials can be available upon reasonable request to the
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12 515 corresponding author. However, availability is dependent on approval from the Regional Ethics
13
14 516 Committee and the local data protection officer.
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18 517 **Competing interest:** HZ has served at scientific advisory boards and/or as a consultant for Alector,
19
20 518 Eisai, Denali, Roche Diagnostics, Wave, Samumed, Siemens Healthineers, Pinteon Therapeutics,
21
22 519 Nervgen, AZTherapies, CogRx and Red Abbey Labs, has given lectures in symposia sponsored by
23
24 520 Cellectricon, Fujirebio, Alzecure and Biogen, and is a co-founder of Brain Biomarker Solutions in
25
26 521 Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program (outside submitted
27
28 522 work).
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32 523 AJCS is advisor for Prolira, a start-up company that develops an EEG-based delirium monitor. Any
33
34 524 (future) profits from EEG-based delirium monitoring will be used for future scientific research only.
35
36
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38 525 GS has participated in one advisory meeting for Biogen. HMN has received lecture fees from Vifor
39
40 526 Pharma and Orion Pharma.
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42

43 527 The other authors declare that they have no competing interests.
44
45

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48

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52
53

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55
56 532 the manuscript or decision to publish.
57
58

59 533 **Author contributions:**
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3 534 Drafting of the manuscript: BEN
4
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7

8 536 HMN, JR, GS, ES, NKS, ES, AS, ØSS, TT, AW, HZ, TBW, MRS
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12
13

14 538 All authors contributed to the writing of the manuscript and approved the final version.
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16

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18

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28 543 **Abbreviations:**
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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

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546 **LEGENDS**

547 **Figure 1:**

548 Study schema. MoCA, Montreal Cognitive Assessment; TMT, Trail Making Test; EQ-5D-5L, EuroQol 5

549 Dimension 5 Level; POD, Postoperative Day

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For peer review only

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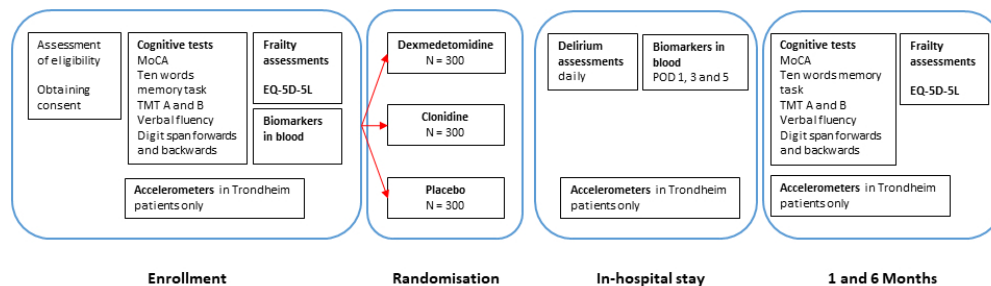


Figure 1:
Study schema. MoCA, Montreal Cognitive Assessment; TMT, Trail Making Test; EQ-5D-5L, EuroQol 5 Dimension 5 Level; POD, Postoperative Day

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.

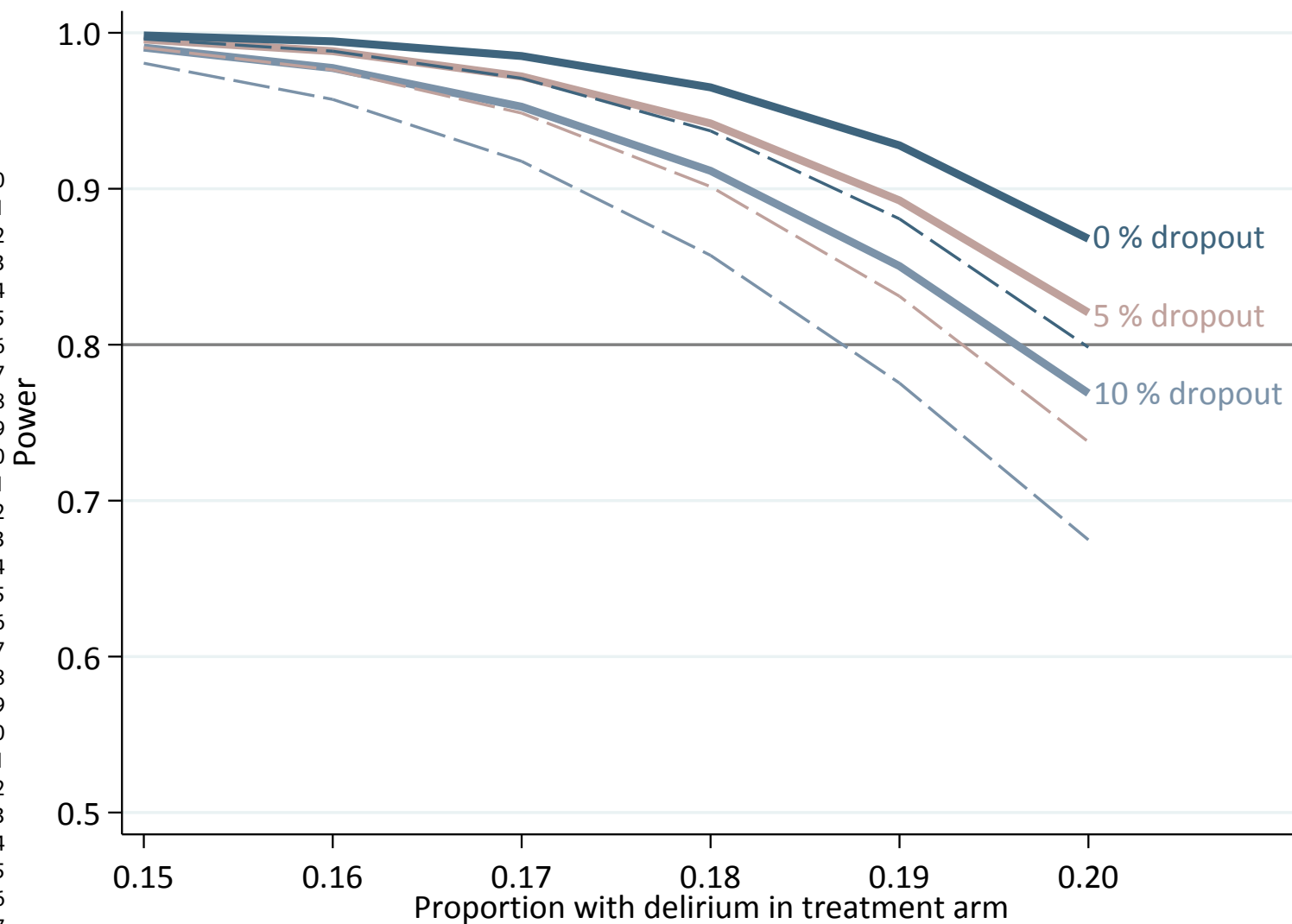
Since we intend to use the logrank test to account for difference in the observation period, we confirmed that the calculated sample size was adequate using the more flexible calculation options in PASS Sample size software (version 20, NCSS, Kaysville, Utah, USA).

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

1
2
3 80 % power with up to 7 % drop-out rate over the first seven postoperative days. Drop out rates
4 lower than 7 % will result in a higher power. Even with 10 % drop out rate, we will still achieve 80 %
5 to detect a slightly larger difference between the groups (10.4 percentage point reduction, rather
6 than 10 percentage points) (Figure S1).
7

8
9 **Multiplicity:** The planned comparisons for this trial are between dexmedetomidine versus
10 placebo and clonidine versus placebo. Any comparison between dexmedetomidine and clonidine
11 groups will be explorative and clearly stated as such. The extension of the CONSORT 2010 Statement
12 for multi-arm parallel-group randomised trials recommend that adjustments for multiple
13 comparisons are generally not necessary in trials comparing two or more independent treatments to
14 placebo as we are here.⁴ This has therefore not been factored into the sample size calculation.
15 However, even with the very conservative Bonferroni adjustment for two comparisons a sample size
16 of 300 participants per arm will be sufficient if there were no drop-outs and only minimally affect the
17 difference in proportions which we can hope to identify with 80 % power if there is up to 10 % drop-
18 out (Figure S1). For example, with 5 % dropout we can detect a 10.6 percentage point reduction in
19 delirium cumulative incidence with 80 % and 2.5 % significance level (to account for multiplicity), or
20 11.3 percentage points if there was 10 % dropout (Figure S1).
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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.



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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

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For peer review only

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 SPIRIT reporting 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

			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

1	Funding	#4	Sources and types of financial, material, and other support	26
2				
3				
4	Roles and	#5a	Names, affiliations, and roles of protocol contributors	1-3,26
5	responsibilities:			
6	contributorship			
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10	Roles and	#5b	Name and contact information for the trial sponsor	25-26
11	responsibilities:			
12	sponsor contact			
13	information			
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18	Roles and	#5c	Role of study sponsor and funders, if any, in study design; collection,	26
19	responsibilities:		management, analysis, and interpretation of data; writing of the report;	
20	sponsor and funder		and the decision to submit the report for publication, including whether	
21			they will have ultimate authority over any of these activities	
22				
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27	Roles and	#5d	Composition, roles, and responsibilities of the coordinating centre,	19-21
28	responsibilities:		steering committee, endpoint adjudication committee, data management	
29	committees		team, and other individuals or groups overseeing the trial, if applicable	
30			(see Item 21a for data monitoring committee)	
31				
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35	Introduction			
36				
37				
38	Background and	#6a	Description of research question and justification for undertaking the trial,	8-10,16,23
39	rationale		including summary of relevant studies (published and unpublished)	
40			examining benefits and harms for each intervention	
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45	Background and	#6b	Explanation for choice of comparators	11
46	rationale: choice of			
47	comparators			
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51	Objectives	#7	Specific objectives or hypotheses	10
52				
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54	Trial design	#8	Description of trial design including type of trial (eg, parallel group,	11
55			crossover, factorial, single group), allocation ratio, and framework (eg,	
56			superiority, equivalence, non-inferiority, exploratory)	
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1 **Methods: Participants,**
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 3 **interventions, and**
 4
 5 **outcomes**

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8	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
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14	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
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21	Interventions:	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	16
22	description			
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25	Interventions:	#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
26	modifications			
27				
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32	Interventions:	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	21
33	adherence			
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38	Interventions:	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	16
39	concomitant care			
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43	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
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1	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
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10	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
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17	Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	11
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21	Methods: Assignment			
22	of interventions (for			
23	controlled trials)			
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28	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
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38	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
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46	Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	11-13
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51	Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	13
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1	Blinding (masking):	#17b	If blinded, circumstances under which unblinding is permissible, and	20-21
2				
3	emergency unblinding		procedure for revealing a participant's allocated intervention during the	
4				
5			trial	
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7	Methods: Data			
8				
9	collection,			
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11	management, and			
12				
13	analysis			
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16	Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial	13,16-19,
17			data, including any related processes to promote data quality (eg,	Table 2
18			duplicate measurements, training of assessors) and a description of	
19			study instruments (eg, questionnaires, laboratory tests) along with their	
20			reliability and validity, if known. Reference to where data collection forms	
21			can be found, if not in the protocol	
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28	Data collection plan:	#18b	Plans to promote participant retention and complete follow-up, including	21-22
29	retention		list of any outcome data to be collected for participants who discontinue	
30			or deviate from intervention protocols	
31				
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35	Data management	#19	Plans for data entry, coding, security, and storage, including any related	19-20
36			processes to promote data quality (eg, double data entry; range checks	
37			for data values). Reference to where details of data management	
38			procedures can be found, if not in the protocol	
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43	Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes.	21-23
44			Reference to where other details of the statistical analysis plan can be	
45			found, if not in the protocol	
46				
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48				
49	Statistics: additional	#20b	Methods for any additional analyses (eg, subgroup and adjusted	21-23
50	analyses		analyses)	
51				
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53				
54	Statistics: analysis	#20c	Definition of analysis population relating to protocol non-adherence (eg,	21-23
55	population and		as randomised analysis), and any statistical methods to handle missing	
56	missing data		data (eg, multiple imputation)	
57				
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1 **Methods: Monitoring**

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4 Data monitoring: [#21a](#) Composition of data monitoring committee (DMC); summary of its role 21

5 formal committee

6 and reporting structure; statement of whether it is independent from the

7 sponsor and competing interests; and reference to where further details

8 about its charter can be found, if not in the protocol. Alternatively, an

9 explanation of why a DMC is not needed

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14 Data monitoring: [#21b](#) Description of any interim analyses and stopping guidelines, including 21

15 interim analysis

16 who will have access to these interim results and make the final decision

17 to terminate the trial

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21 Harms [#22](#) Plans for collecting, assessing, reporting, and managing solicited and 20-21

22 spontaneously reported adverse events and other unintended effects of

23 trial interventions or trial conduct

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27 Auditing [#23](#) Frequency and procedures for auditing trial conduct, if any, and whether 21

28 the process will be independent from investigators and the sponsor

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32 **Ethics and**

33 **dissemination**

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36 Research ethics [#24](#) Plans for seeking research ethics committee / institutional review board 6,23,25

37 approval (REC / IRB) approval

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39

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41 Protocol amendments [#25](#) Plans for communicating important protocol modifications (eg, changes 23

42 to eligibility criteria, outcomes, analyses) to relevant parties (eg,

43 investigators, REC / IRBs, trial participants, trial registries, journals,

44 regulators)

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49 Consent or assent [#26a](#) Who will obtain informed consent or assent from potential trial 11

50 participants or authorised surrogates, and how (see Item 32)

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54 Consent or assent: [#26b](#) Additional consent provisions for collection and use of participant data 11

55 ancillary studies and biological specimens in ancillary studies, if applicable

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1	Confidentiality	#27	How personal information about potential and enrolled participants will be	19,20
2			collected, shared, and maintained in order to protect confidentiality	
3			before, during, and after the trial	
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7	Declaration of	#28	Financial and other competing interests for principal investigators for the	25-26
8	interests		overall trial and each study site	
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12	Data access	#29	Statement of who will have access to the final trial dataset, and	20,25
13			disclosure of contractual agreements that limit such access for	
14			investigators	
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18	Ancillary and post trial	#30	Provisions, if any, for ancillary and post-trial care, and for compensation	20-21
19	care		to those who suffer harm from trial participation	
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22				
23	Dissemination policy:	#31a	Plans for investigators and sponsor to communicate trial results to	6,23
24	trial results		participants, healthcare professionals, the public, and other relevant	
25			groups (eg, via publication, reporting in results databases, or other data	
26			sharing arrangements), including any publication restrictions	
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31	Dissemination policy:	#31b	Authorship eligibility guidelines and any intended use of professional	23
32	authorship		writers	
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36	Dissemination policy:	#31c	Plans, if any, for granting public access to the full protocol, participant-	25
37	reproducible research		level dataset, and statistical code	
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41	Appendices			
42				
43	Informed consent	#32	Model consent form and other related documentation given to	11
44	materials		participants and authorised surrogates	
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48	Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological	14,19
49			specimens for genetic or molecular analysis in the current trial and for	
50			future use in ancillary studies, if applicable	
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None The SPIRIT Explanation and Elaboration paper is distributed under the terms of the Creative Commons Attribution License CC-BY-NC. This checklist can be completed online using <https://www.goodreports.org/>, a tool made by the EQUATOR Network in collaboration with [Penelope.ai](#)

For peer review only - <http://bmjopen.bmj.com/site/about/guidelines.xhtml>

BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2021-057460.R2
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3 1 **TITLE PAGE**
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6 2 **Title:** Alpha-2-adrenergic receptor agonists for the prevention of delirium and cognitive decline after
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8 3 open heart surgery (ALPHA2PREVENT): protocol for a multicentre randomised controlled trial
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95 **ABSTRACT**

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

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

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

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

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

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3 119 **STRENGTHS AND LIMITATIONS OF THIS STUDY**
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- 6 120 • This multicentre trial will provide evidence for prophylactic efficacy of dexmedetomidine and
7
8 121 clonidine in reducing the incidence of postoperative delirium as well as decline in cognitive
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10 122 function 1 and 6 months postoperatively in older cardiac surgical patients
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13 123 • Inclusion of preoperative frailty assessments will provide evidence for frailty as a predictive
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15 124 marker of treatment effect
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17 125 • The analysis of biomarkers will provide insights into the neural mechanisms in postoperative
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19 126 delirium and long-term cognitive dysfunction
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22 127 • The analysis of activity by accelerometers will provide insight into motor activity patterns in
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24 128 subtypes of delirium
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26 129 • The dose of the active drugs may potentially be too low or the duration of treatment too
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28 130 short in order to show effects
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131 **BACKGROUND**

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

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

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

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

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3 154 Conventionally, delirium has been separated into hyperactive and hypoactive subtypes based on
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5 155 clinical impression,¹⁹ but recent research using body-worn sensors indicates a more heterogeneous
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7 156 pattern of motor activity across the clinical delirium motor subtypes.^{20 21} Small light-weight body-
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10 157 worn accelerometers may provide objective measures of the effectiveness of delirium treatment
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12 158 intervention on motor activity level and types of patterns. A small postoperative study on cardiac
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14 159 surgery patients showed the possibility of detecting the amount of movement in sedated patients.²²

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

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

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3 178 cognitive trajectories have so far not been assessed in this patient population. Nevertheless, the use
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5 179 of dexmedetomidine in ICUs is rapidly increasing.²⁶
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8 180 An alternative agent is clonidine, which has similar pharmacological properties to
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10 181 dexmedetomidine,³⁶ even though it's alpha-2-adrenergic selectivity is lower.³⁷ Clonidine can be
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12 182 administered both parenterally and orally, thus potentially widening its clinical usefulness.^{36 37}
13
14 183 Clonidine was originally launched as an antihypertensive agent, but it is also used as an analgesic
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16 184 drug. Further, clonidine has a long tradition as a sedative in patients with hyperactive delirium, and is
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18 185 used by several anaesthesiologists and intensivists.³⁸ This practice is based on their clinical
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20 186 experiences and knowledge on the drug's properties, but is so far not supported by placebo-
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22 187 controlled clinical trials. A pilot study indicated that clonidine infusion during the period of weaning
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24 188 from mechanical ventilation after surgery for aortic dissection may reduce the severity of delirium.³⁹
25
26 189 A recent study compared clonidine with dexmedetomidine postoperatively after CABG and found
27
28 190 better effect on risk and duration of delirium of dexmedetomidine. Since no placebo control group
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30 191 was included, that study could not assess potential effects of clonidine.⁴⁰
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36 192 Thus, there is a need for prospective large-scale studies on the potential prophylactic effect of alpha-
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38 193 2-adrenergic receptor agonists on delirium in susceptible patients. The aims of the present planned
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40 194 trial are to study 1) whether repurposing of clonidine can represent a novel treatment option for
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42 195 delirium, and 2) the possible effects of dexmedetomidine and clonidine on long-term cognitive
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44 196 trajectories, motor activity patterns, patient rated outcome measures and biomarkers of neuronal
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46 197 injury, and 3) whether these effects are associated with frailty status.
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200 **METHODS AND ANALYSIS**

201 **Study design**

202 ALPHA2PREVENT is a nationwide five-centre, double blind randomised controlled trial (RCT). Patients
203 aged 70+ scheduled for open heart surgery will be randomized 1:1:1 to dexmedetomidine or
204 clonidine or placebo. The patients will be cognitively assessed preoperatively, then assessed for any
205 symptoms of delirium according to the Diagnostic and Statistical Manual of Mental Disorders, 5th
206 edition (DSM-5) criteria⁴¹ or subsyndromal delirium⁴² postoperatively, and finally assessed for
207 cognitive function after 1 and 6 months (figure 1).

208 **Study locations**

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

212 **Participants, randomisation and blinding**

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

221 **Table 1. Inclusion and exclusion criteria**

<p>Participants are eligible to be included in the study only if all of the following criteria apply:</p>	<p>Participants are excluded from the study if any of the following criteria apply:</p>
<p>1. Participant must be ≥ 70 years old at the time of signing the informed consent.</p> <p>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.</p> <p>3. Participant must be capable of giving signed informed consent.</p>	<p>4. Preoperative delirium (present at time of potential inclusion)</p> <p>5. Known hypersensitivity to the active ingredient or components of the product</p> <p>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</p> <p>7. Uncontrolled hypotension</p> <p>8. Ischemic stroke or transitory ischemic attack the last month or critical peripheral ischemia</p> <p>9. Acute coronary syndrome last 24 hours. Acute coronary syndrome is defined according to international guidelines</p> <p>10. Left ventricular ejection fraction $< 40\%$</p> <p>11. Severe renal impairment (estimated GFR < 20 ml/min) or expected requirement for renal replacement therapy</p> <p>12. Severe hepatic dysfunction (liver enzyme three times the upper limit of normal together with a serum albumin concentration below the normal reference limit</p>

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

223 Consenting patients will be randomly assigned 1:1:1, to dexmedetomidine, clonidine or placebo.

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

229 **Data collected at study entry**

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

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

245 **Table 2. Study procedures**

Procedure	Screening	Baseline	Surgery	Postoperative day number:							Hospital discharge	1 and 6 months	
	≤30 days before Day 0	-3 to -1 days before Day 0	Day 0	1	2	3	4	5	6	7			
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												

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3 265 delirium develops and pharmacological intervention is needed, the study drug will be stopped, and
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5 266 further treatment will be according to local routines and the treating physician's preferences.
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8 267 **Primary endpoint**
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11 268 The primary endpoint for ALPHA2PREVENT is the cumulative incidence of postoperative delirium
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13 269 within 7 days. Postoperative delirium assessment will start as soon as possible after admission to the
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15 270 ICU, and will continue daily until the seventh postoperative day or until discharge from the university
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17 271 hospital, whichever happens first. To allow for differences in the duration of the postoperative
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19 272 observation period, time until delirium diagnosis will be recorded and the cumulative incidence will
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21 273 be assessed using Kaplan Meier estimates and compared between groups with the log-rank test as
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23 274 described below. A clinical assessment for delirium will also be repeated at the 1-month follow-up, to
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25 275 pick up signs of persistent delirium.
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30 276 The diagnosis of delirium will be ascertained using all available information, and will be determined
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32 277 to be present if participants meet all DSM-5 criteria⁴¹ by using a standardized procedure developed
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34 278 for our previous study⁴⁵ and as recommended by others⁴⁶, table 3. The methods are refined in order,
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36 279 in a stepwise approach, to assess presence or absence of the diagnostic criteria in DSM-5 and will be
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38 280 carried out once daily by specially trained research assistants. Level of arousal will be assessed using
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40 281 the Norwegian versions of Richmond Agitation Sedation Scale (RASS)⁴⁷ and Observational Scale of
41
42 282 Level of Arousal (OSLA).⁴⁸ Attention and awareness will be evaluated using objective tests (vigilance
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44 283 "A"-test, months of the years backwards, days of the week backwards, and counting down from 20 to
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46 284 1)⁴⁹ and observations by the examiner of the patient's distractibility, comprehension and tendency to
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48 285 lose the thread of conversation. Presence of additional cognitive disturbances will be assessed by
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50 286 tests for orientation and recall test of three words (different words for each day), as well as
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52 287 information derived from nursing staff and clinical notes. Acute change in the patient's mental
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54 288 condition, and fluctuations of any disturbance, will be ascertained through informant history from
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56 289 nursing staff and derived from clinical notes. Nurses will, as part of their routine and for each shift
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290 (i.e., three times daily), actively register symptoms of delirium in the case notes, as well as screen for
 291 delirium using the Norwegian version of the Confusion Assessment Method for Intensive Care Units
 292 (CAM-ICU)⁵⁰ and RASS. The same delirium assessment tools will be used for the ICU, step-down and
 293 bed wards. The results from each of the CAM-ICU-items, as well as the total CAM-ICU score, will also
 294 be used as a source of information for making the final delirium diagnosis.

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

299 Subsyndromal delirium (table 3) will be defined as evidence of change, in addition to any one of
 300 these: altered arousal, attentional deficits, other cognitive change, delusions or hallucinations. DSM-
 301 5 delirium criteria D and E must be met.

303 **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		

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	<table border="1"> <tr> <td data-bbox="687 190 986 338">Months of the year backwards</td> <td data-bbox="986 190 1252 338">unable to pass June</td> </tr> <tr> <td data-bbox="687 338 986 486">Count backwards from 20 to 1</td> <td data-bbox="986 338 1252 486">any error</td> </tr> <tr> <td data-bbox="687 486 986 573">Digit span backwards</td> <td data-bbox="986 486 1252 573"><5 digits</td> </tr> </table>	Months of the year backwards	unable to pass June	Count backwards from 20 to 1	any error	Digit span backwards	<5 digits	
Months of the year backwards	unable to pass June							
Count backwards from 20 to 1	any error							
Digit span backwards	<5 digits							
<p>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.</p>	<p><u>Observation (by the examiner during the interview):</u></p> <p>Distractibility. Comprehension. Tendency to lose the tread of conversation</p> <p>Level of arousal measured using RASS and OSLA</p> <hr/> <p>Acute onset and/or fluctuation obtained from informant history from nursing staff and clinical notes</p> <p><u>Questions to carer/ nursing staff or derived from clinical notes:</u></p> <p>Has there been a sudden change in the patient’s mental state?</p> <p>Does the patient seem to be better at any period in the day compared to other times?</p> <p>Has the level of consciousness been altered (drowsy/ not interacting or agitated)?</p> <p>Sleep-wake cycle disturbances?</p>							

<p>C. An additional disturbance in cognition (e.g., memory deficit, disorientation, language, visuospatial ability, or perception).</p>	<p><u>Questions to the patient:</u></p> <p>Orientation to time, place and person</p> <p>3 item recall at three minutes</p> <p>Questions from CAM-ICU: Why are you in hospital? Will a stone float in water? Are there fish in the sea?</p> <p><u>Questions to carer/ nursing staff or derived from clinical notes:</u></p> <p>Any evidence of perceptual disturbances as illusions or hallucinations? Memory disturbances? Psychotic symptoms? Psychomotor abnormalities?</p>		
<p>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.</p>	<p>Information from history/chart/clinical assessment</p>		
<p>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</p>	<p>By virtue of the surgery, all participants are considered to fulfil this criterion.</p>		

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.		

304 DSM-5, Diagnostic and Statistical Manual of Mental Disorders, 5th edition; RASS, Richmond Agitation

305 Sedation Scale; OSLA, Observational Scale of Level of Arousal; CAM-ICU, Confusion Assessment

306 Method for Intensive Care Units

307

308 **Secondary endpoints**

309 Secondary endpoints include the composite endpoint of coma, delirium or death, in addition to
 310 number of delirium days, delirium severity and motor activity patterns, comparison to inclusion of
 311 serum concentrations of neurofilament light (NFL) and p-tau181 1, 3 and 5 days postoperatively, as
 312 well as change from inclusion to 1 and 6 months after the operation in different cognitive tests,
 313 patient rated health status, frailty status, and comparison of change in frailty status. In explorative
 314 analyses, the secondary outcomes will also be assessed between patients with or without
 315 postoperative delirium. We will also assess if preoperative frailty status modifies the effect of
 316 dexmedetomidine and clonidine treatment, by studying the interaction between preoperative frailty
 317 and treatment on delirium and the other mentioned endpoints.

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3 318 All endpoints will be assessed using Norwegian versions of validated instruments: Delirium severity
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5 319 will be measured using CAM-ICU-7,⁵¹ OSLA⁴⁸ and RASS;⁴⁷ motor activity patterns using body worn
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7 320 accelerometers; cognitive function using Montreal Cognitive Assessment (MoCA),⁵² immediate and
8
9 321 delayed recall from The Ten Words Memory Task from The Consortium to Establish a Registry for
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11 322 Alzheimer's Disease,⁵³ Trail Making Test (TMT) version A and B,⁵⁴ semantic and phonemic verbal
12
13 323 fluency,⁵⁵ digit span forwards and backwards (by Wechsler Adult Intelligence Scale);⁵⁶ frailty will be
14
15 324 measured by a comprehensive geriatric assessment (including medical history, number of prescribed
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17 325 drugs, sensory impairment, activity of daily living, gait speed, handgrip strength, chair stand and
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19 326 nutritional status) calculating a frailty-index (range, 0-1; higher values indicate greater frailty) based
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21 327 on the accumulation of deficits model of frailty^{57 58} and by the shorter Essential Frailty Toolset;⁵⁹ and
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23 328 patient rated health status using the EQ-5D-5L questionnaire.⁴⁴

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28 329 For assessment of cognitive trajectories, the same cognitive tests will be performed in a stable phase
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30 330 preoperatively as well as after 1 and 6 months. Information regarding functional status will be
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32 331 obtained from the patient preoperatively and from either the patient or their proxy at follow-up,
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34 332 depending on the patient's ability to provide detailed information.

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38 333 For a sub-sample of one hundred patients from the Trondheim cohort, motor activity will be
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40 334 measured by 3D accelerometer inertial sensors (AX3 sensors) (Axivity Ltd., Newcastle, UK) sampled at
41
42 335 100 Hz and processed using custom made software. Accelerometers will be attached to the frontal
43
44 336 part of the waist, the dominant thigh (ventrally, midthigh), and on the dominant wrist pre surgery.
45
46 337 Motor activity patterns will be monitored continuously (day and nights) before and the five first days
47
48 338 after surgery or until discharge from hospital, and over one week after 1 and 6 months. Sensor data
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50 339 will be analyzed regarding both quantity and quality of movements and compared with the clinical
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52 340 delirium assessments.

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57 341 **Biomarkers**
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3 342 In addition to routine blood tests, blood will be taken in the morning for specific study analyses
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5 343 (serum, plasma and wholeblood) before surgery, and at postoperative day 1, 3 and 5 (or earlier if
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7 344 discharged before day 5) and frozen at -80°C locally. Frozen samples will then be shipped to the
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9 345 coordinating centre (Oslo) to be stored in a biobank at -80°C for future analyses. The stored blood
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11 346 samples will be analysed for promising markers such as NFL already known to be associated with
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13 347 delirium,⁶⁰ p-tau181 associated with dementia and delirium,⁶¹⁻⁶³ and possibly other biomarkers of
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15 348 neuronal degeneration, neuroinflammation and neurotransmitters,⁶⁴⁻⁶⁸ using state-of-the-art
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17 349 ultrasensitive assays to evaluate their association with observed clinical responses to the study drugs.
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22 350 **Standardised training**

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25 351 The research assistants across all sites will receive standardized training for all study measures prior
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27 352 to study initiation, including cognitive tests, delirium assessments and measurements of frailty
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29 353 indicators. Retraining will be provided as necessary. Detailed instructions and operation manuals in
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31 354 Norwegian language, including an instruction video for the MoCA, will be made available to all
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33 355 assessors.
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36 356 **Data management and monitoring**

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40 357 Participant data will be collected by authorized trained personnel, be recorded on electronic Case
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42 358 Report Forms (CRF) and stored on a password protected database. Paper files will be stored in locked
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44 359 cabinets accessible to team members only. Study monitors will perform ongoing source data
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46 360 verification to confirm that data entered into the CRFs are accurate, complete, and verifiable from
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48 361 source documents; that the safety and rights of participants are being protected; and that the study
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50 362 is being conducted in accordance with the currently approved protocol, International Conference on
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52 363 Harmonization Good Clinical Practice, and all applicable regulatory requirements. Records and
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54 364 documents, including signed Informed Consent Forms, pertaining to the conduct of this study will be
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56 365 retained by the investigators for 15 years after study completion.
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3 367 **Safety and adverse events management**
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6 368 Immediate safety concerns will be handled by the treating anaesthesiologist, who will determine if
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8 369 the participant should continue or discontinue study intervention. If the patient is hemodynamically
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10 370 unstable at any time during infusion of the study medication or difficult to wake up after surgery, the
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12 371 infusion can be temporarily stopped, as decided by the treating physician. In such a case the patient
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14 372 will continue in the study. The reason for temporary discontinuation will be recorded. Since patients
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16 373 are closely monitored in the perioperative phase of cardiac surgery, potential adverse circulatory
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18 374 effects will be rapidly revealed and corrected;

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23 375 • Temporal epicardial pacing wires are placed routinely during cardiac surgery, and
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25 376 bradycardia will be treated with atropine and/or pacemaker as per routine.
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27 377 • Hypotension will be treated at discretion of the treating anaesthesiologists, who are
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29 378 permitted to reduce dose of the study drug as necessary to preserve haemodynamic stability,
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31 379 following guidelines and local routines. A Mean Arterial Pressure (MAP) >55-60mmHg is
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33 380 recommended.
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35 381 • If not rapid and satisfactory response on other measures is achieved, the treating
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37 382 anaesthesiologist will consider to turn off the infusion/unblind the study.

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41 383 Planned time points for safety assessments are provided in table 2.
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44 384 The following safety indicators will be compared between the three treatment groups with
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46 385 appropriate statistical methods: Highest and lowest heart rate and mean arterial blood pressure,
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48 386 oxygen saturation, number of units for blood transfusion, volume of postoperative blood loss, use of
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50 387 pressor substances, use of rescue medication, number of episodes of bradycardia, hypotension or
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52 388 hypoxemia in need of intervention, perioperative myocardial infarction and stroke, postoperative
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54 389 serum concentrations of troponin and Pro B-type Natriuretic Peptide (proBNP), mortality.
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3 390 An independent Data Monitoring Committee will have unblinded access to all data and meet at pre-
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5 391 planned inclusion milestones and whenever the members find it necessary.⁶⁹ Meetings are pre-
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7 392 planned after inclusion of 20, 50, 100 and 400 participants, to assess safety indicators and to advise
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9 393 on continuation or termination of the study. All safety data collected will be summarized and
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11 394 reviewed by the DMC for agreement of next steps. In particular, data will be reviewed by for
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13 395 identification of the following events that would potentially contribute to a requirement to pause or
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15 396 stop the study: Any deaths, regardless of causality; cerebral infarctions; haemodynamic variables
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17 397 (time during surgery with MAP<50 mmHg, highest/lowest MAP and HR, lowest SpO₂); need for
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19 398 vasopressor, non-invasive ventilation, active pacing, respiratory support or extracorporeal
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21 399 membrane oxygenation (ECMO); postoperative troponin values. If a pausing/stopping rule is met, a
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23 400 decision will be made, based on the review, as to whether enrolment in the study will be allowed to
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25 401 resume. Case unblinding will be performed for above reviews if necessary.
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34 403 **Current sample size justification**

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37 404 The proportion of patients experiencing postoperative delirium after open heart surgery for all ages
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39 405 has been reported to be 24%,³ and higher in older adults.⁴ Since the lower age limit in our trial is 70
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41 406 years, we estimate that the proportion in the control group will be at least 30%. The most recent
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43 407 meta-analysis of the effect of dexmedetomidine estimates the delirium risk to be reduced to
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45 408 approximately half of the untreated group (*i.e.*, 15%).²⁵ We anticipate that the effect of clonidine
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47 409 may be weaker, but still clinically relevant. We have thus powered the study based on an estimated
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49 410 delirium incidence of 20% in the clonidine group. An initial, conservative sample size calculation
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51 411 based on comparison of two proportions indicated that a sample size of 290 in each group (870
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53 412 altogether) will give a power of 80% with a significance level of 5% to detect such a difference
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55 413 between the clonidine and the placebo group in the proportion developing delirium within 7 days
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57 414 postoperatively. To account for dropouts, we aim at including 900 patients. This sample size
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3 415 calculation approach was conservative considering the use of time-to-delirium analysis strategy,
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5 416 accommodating for both a higher drop-out rate and that this trial has three-arms. We have further
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7 417 confirmed the adequacy of this sample size estimate for the logrank test with differing rates of drop-
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9 418 out and considering the three-arms (Figure S1, Supplementary file 1).
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13 419 **Statistical analysis**

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16 420 The primary analysis population will be the intention-to-treat population, and all tests will be two-
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18 421 sided. The primary objective in this study is to prevent postoperative delirium. The primary endpoint
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20 422 is the cumulative incidence of postoperative delirium. In the analysis of this endpoint, time to
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22 423 diagnosis of delirium will be used to account for the varying postoperative observation time due to
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24 424 difference in time to discharge or transfer to other hospitals will be different. The cumulative
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26 425 incidence will therefore be estimated using the Kaplan Meier estimator with time to first delirium as
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28 426 the dependent variable and compare time to event curves between treatments by the logrank test.
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30 427 Patients who are discharged from the university hospital during the observation period or reach the
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32 428 end of the observation period (7 days) without having developed delirium, are regarded as censored.
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34 429 We consider that treatment group allocation will not influence the risk of being censored. Those who
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36 430 die prior to 7 days, will also be regarded as censored in the primary analysis, but we will carry out a
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38 431 secondary analysis with the combined endpoint *death or delirium*. The same approach will be applied
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40 432 for those who are comatose, and thus impossible to evaluate for delirium. Additional analyses may
41
42 433 also include estimating the incidence of delirium treating deaths as a competing risk by the Fine and
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44 434 Gray method.
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50 435 All analyses will be adjusted for study centre which was used to as a stratification variable in the
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52 436 randomisation process.
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55 437 Sensitivity analyses will be carried out by estimating hazard ratios using Cox' proportional hazards
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57 438 model to adjust for potential imbalance of prognostic factors between treatment groups.
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3 439 Secondary endpoints as the cumulative incidence of death, coma or postoperative delirium will be
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5 440 analysed using the Kaplan Meier estimator and the logrank test as above. Additional analyses by Cox'
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7 441 proportional hazards model may also be performed. Mean duration of delirium; severity of delirium;
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9 442 combination of duration and severity of delirium; cognitive tests after 1 and 6 months; EQ-5D-5L
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11 443 scores after 1 and 6 months; and postoperative plasma concentrations of NFL and p-tau181 will be
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13 444 compared between treatments with appropriate regression models which will be defined in a
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15 445 Statistical Analysis Plan prior to analysis.

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19 446 Frailty as risk factor for delirium and for adverse effects of the study medication, will be analysed by
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21 447 linear or logistic regression (as appropriate), adjusted for other known risk factors. The association
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23 448 between frailty and delirium will be analysed by adding frailty as a covariate in a Cox'proportional
24
25 449 hazards model on time to delirium (as above). Additionally, we will assess if the presence of frailty
26
27 450 modifies the effect of the treatment by including an interaction term between frailty and treatment
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29 451 allocation in the Cox proportional hazards model. The association between frailty and occurrence of
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31 452 adverse events (AE) will be estimated by logistic regression models including covariates as above.

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36 453 No interim analyses of the efficacy of the treatments are planned. A detailed statistical analysis plan
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38 454 will be finalized prior to unblinding.

41 455 **Ethics and dissemination**

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44 456 This trial is approved by the Regional Committee for Ethics in Medical Research in Norway (South-
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46 457 East Norway) and by the Norwegian Medicines Agency, and will be conducted in accordance with
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48 458 consensus ethical principles derived from international guidelines including the Declaration of
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50 459 Helsinki. The results of this study will be published in peer-reviewed medical journals, as well as
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52 460 presented at scientific meetings

53 54 55 56 461 **Discussion**

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3 462 To our knowledge, ALPHA2PREVENT will be the first large randomised controlled multicentre trial to
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5 463 study the prophylactic efficacy of dexmedetomidine as well as clonidine on the incidence of
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7 464 postoperative delirium in older cardiac surgical patients, and also including long-term cognitive
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9 465 trajectories.

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12 466 One should expect that treatment options that can prevent delirium in a short-term perspective,
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14 467 would also improve the long-term cognitive prognosis. Evidence for such an effect is slowly emerging
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16 468 for non-pharmacological interventions,⁷⁰ but is lacking regarding drug treatment.

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20 469 Published studies of dexmedetomidine for prevention of delirium in ICU vary largely with respect to
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22 470 dosing regimens, from 0.1^{71 72} to 1.4 µg/kg/h.³³ Many of the authors also administered an initial
23
24 471 bolus. In the cardiac surgery context, Turan et al started dexmedetomidine infusion already before
25
26 472 start of CPB, gave 0.4 µg/kg/h postoperatively,³⁴ and found more side effects in the actively treated
27
28 473 than in the placebo group. We have chosen a careful dosage of 0.4 µg/kg/h peroperatively and 0.2
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30 474 µg/kg/h postoperatively, with no bolus, to reduce the risk of AE, but not so low that we cannot
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32 475 expect an effect on delirium.

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37 476 Regarding clonidine, the recommended dosage varies greatly between sources, but is mainly in the
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39 477 range 1-1.5 µg/kg/h.⁷³ We will dose the drug considerably lower, to avoid side effects. There is a
40
41 478 shortage of studies comparing i.v. dexmedetomidine and i.v. clonidine in ICU or postoperative
42
43 479 settings.⁷⁴ To our knowledge, a widely agreed evidence-based i.v. dosage regimen has not been
44
45 480 developed for i.v. clonidine. A study by Grest in critically ill patients after cardiac surgery⁷⁴ and a
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47 481 recent meta-analysis favour equipotency mg per mg.⁷⁵ Thus, our choice is fairly pragmatic, but the
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49 482 doses are similar to that currently used in many ICUs as part of routine practice.

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53 483 To further reduce the risk of hemodynamic instability due to the combination of anaesthesiological
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55 484 procedures and study drug at the start of surgery, we will postpone infusion of study drug until the
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57 485 CPB is established. If clonidine is both effective and safe to administer, then it may be relevant to
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59 486 conduct more studies on per oral treatment with clonidine in other patient groups later on. Efficacy

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3 487 must first be demonstrated and found comparable to existing parenteral treatment before future
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5 488 trials with oral, longer use could be explored.
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8 489 Strengths of this trial are the prospective and randomised placebo controlled design, the use of two
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10 490 relevant and much used drugs, inclusion of a high number of patients from multiple sites, adequate
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12 491 statistic strength, repeated cognitive and frailty assessments, use of body-worn accelerometers, and
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14 492 repeated samples of biomarkers. The analyses of biomarkers reflecting neural injury will give us
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16 493 increased understanding of the pathophysiological mechanisms of delirium. Inclusion of preoperative
17
18 494 frailty assessments will provide evidence for frailty as a predictive marker of treatment effect and
19
20 495 allow for interaction analyses. The use of body-worn accelerometers will provide insight into motor
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22 496 activity patterns in subtypes of delirium.
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27 497 This trial has, however, some limitations to consider. The exclusion criteria might limit the
28
29 498 generalisability of our findings to other patient populations. If the incidence of delirium in the
30
31 499 placebo group is lower than expected, or if the anticipated effect of the treatment is smaller, the
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33 500 study may be underpowered. The dose of the active drugs might be too low or the duration of
34
35 501 treatment be too short to influence an ongoing pathophysiological process, in order to show effects.
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37 502 As many patients live far away from the study site, there is a potential for missing long-term data.
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41 503 Should the treatment have a positive effect, it would have important beneficial implications for
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43 504 patients, carers and society, such as alleviating acute patient distress and carer burden. If this
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45 505 treatment could reduce longer-term negative effects of delirium, it might have significant
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47 506 consequences for financial and human resource use in health care.
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508 **DECLARATIONS**

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

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3 511 experience as relatives to patients with dementia or delirium, have given valuable input to the
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5 512 project plans and will follow up during the project period.
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8 513 **Ethics approval:** The trial is approved by the Regional Committee for Ethics in Medical Research in
9
10 514 Norway (South-east Norway) (REK 262384), June 9th 2021, and by the Norwegian Medicines Agency
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13 515 June 17th 2021.
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16 516 **Availability of data and materials:** Materials can be available upon reasonable request to the
17
18 517 corresponding author. However, availability is dependent on approval from the Regional Ethics
19
20 518 Committee and the local data protection officer.
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22

23 519 **Competing interest:** HZ has served at scientific advisory boards and/or as a consultant for Alector,
24
25 520 Eisai, Denali, Roche Diagnostics, Wave, Samumed, Siemens Healthineers, Pinteon Therapeutics,
26
27 521 Nervgen, AZTherapies, CogRx and Red Abbey Labs, has given lectures in symposia sponsored by
28
29 522 Cellectricon, Fujirebio, Alzecure and Biogen, and is a co-founder of Brain Biomarker Solutions in
30
31 523 Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program (outside submitted
32
33 524 work).
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37 525 AJCS is advisor for Prolira, a start-up company that develops an EEG-based delirium monitor. Any
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39 526 (future) profits from EEG-based delirium monitoring will be used for future scientific research only.
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43 527 GS has participated in one advisory meeting for Biogen. HMN has received lecture fees from Vifor
44
45 528 Pharma and Orion Pharma.
46
47

48 529 The other authors declare that they have no competing interests.
49
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51 530 **Consent for publication:** Not required
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53

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55
56 532 in the Specialist Health Service in Norway, grant number 2020204. HZ is a Wallenberg Scholar.
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3 533 **Disclaimer:** Funders have no role in the trial design, data collection, management, analysis, writing of
4
5 534 the manuscript or decision to publish.

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7
8 535 **Author contributions:**

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11 536 Drafting of the manuscript: BEN

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14 537 Critical revision of the manuscript for important intellectual content: BEN, RB, RH, JLH, AKK, SAL, IM,

15
16 538 HMN, JR, GS, ES, NKS, ES, AS, ØSS, TT, AW, HZ, TBW, MRS

17
18
19 539 Obtained funding: TBW

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21
22 540 All authors contributed to the writing of the manuscript and approved the final version.

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24
25 541 **Acknowledgements:** The trial is investigator-initiated and investigator-led, and is conducted

26
27 542 independently of the pharmaceutical industry. We are thankful to the staff of the participating

28
29 543 departments for their compliance with the project directives and their caring for the patients.

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36 545 **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

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548 **LEGENDS**

549 **Figure 1:**

550 Study schema. MoCA, Montreal Cognitive Assessment; TMT, Trail Making Test; EQ-5D-5L, EuroQol 5

551 Dimension 5 Level; POD, Postoperative Day

552

For peer review only

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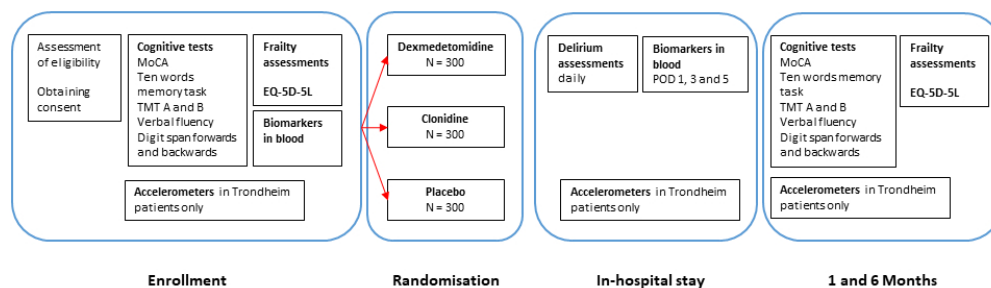


Figure 1:
Study schema. MoCA, Montreal Cognitive Assessment; TMT, Trail Making Test; EQ-5D-5L, EuroQol 5 Dimension 5 Level; POD, Postoperative Day

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, NCCS, 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).

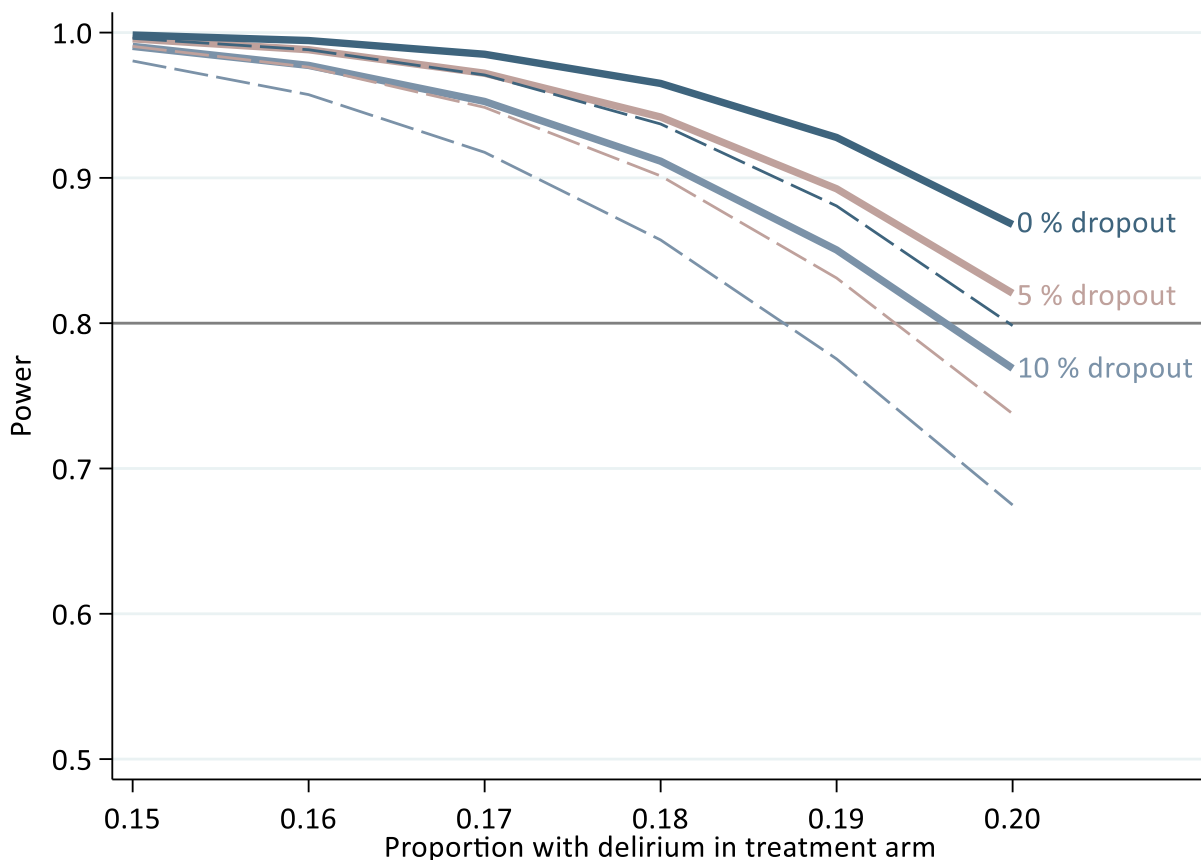


Figure S1: Power depending differing drop-out rates over the proportion with delirium in the treatment arm and where the proportion in the control arm is 30 %. The solid lines indicate the power with 5 % significance level for studies with no dropout (dark blue), 5 % dropout (pink) or 10 % dropout (medium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

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4 A systematic review and meta-analysis of 91,829 patients. *International journal of cardiology*
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- 7 2. Eide LS, Ranhoff AH, Fridlund B, et al. Comparison of frequency, risk factors, and time course of
8 postoperative delirium in octogenarians after transcatheter aortic valve implantation versus
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10 10.1016/j.amjcard.2014.12.043 [published Online First: 2015/02/04]
- 11 3. Flukiger J, Hollinger A, Speich B, et al. Dexmedetomidine in prevention and treatment of
12 postoperative and intensive care unit delirium: a systematic review and meta-analysis.
13 *Annals of intensive care* 2018;8(1):92. doi: 10.1186/s13613-018-0437-z [published Online
14 First: 2018/09/22]
- 15 4. Juszczak E, Altman DG, Hopewell S, et al. Reporting of Multi-Arm Parallel-Group Randomized Trials:
16 Extension of the CONSORT 2010 Statement. *JAMA* 2019;321(16):1610-20. doi:
17 10.1001/jama.2019.3087
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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 SPIRIT reporting 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

			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

1	Funding	#4	Sources and types of financial, material, and other support	26
2				
3				
4	Roles and	#5a	Names, affiliations, and roles of protocol contributors	1-3,26
5	responsibilities:			
6	contributorship			
7				
8				
9				
10	Roles and	#5b	Name and contact information for the trial sponsor	25-26
11	responsibilities:			
12	sponsor contact			
13	information			
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18	Roles and	#5c	Role of study sponsor and funders, if any, in study design; collection,	26
19	responsibilities:		management, analysis, and interpretation of data; writing of the report;	
20	sponsor and funder		and the decision to submit the report for publication, including whether	
21			they will have ultimate authority over any of these activities	
22				
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27	Roles and	#5d	Composition, roles, and responsibilities of the coordinating centre,	19-21
28	responsibilities:		steering committee, endpoint adjudication committee, data management	
29	committees		team, and other individuals or groups overseeing the trial, if applicable	
30			(see Item 21a for data monitoring committee)	
31				
32				
33				
34				
35	Introduction			
36				
37				
38	Background and	#6a	Description of research question and justification for undertaking the trial,	8-10,16,23
39	rationale		including summary of relevant studies (published and unpublished)	
40			examining benefits and harms for each intervention	
41				
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45	Background and	#6b	Explanation for choice of comparators	11
46	rationale: choice of			
47	comparators			
48				
49				
50				
51	Objectives	#7	Specific objectives or hypotheses	10
52				
53				
54	Trial design	#8	Description of trial design including type of trial (eg, parallel group,	11
55			crossover, factorial, single group), allocation ratio, and framework (eg,	
56			superiority, equivalence, non-inferiority, exploratory)	
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60				

1 **Methods: Participants,**
 2
 3 **interventions, and**
 4
 5 **outcomes**
 6

7	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
8				
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14	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
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16				
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19				
20	Interventions:	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	16
21	description			
22				
23				
24				
25	Interventions:	#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
26	modifications			
27				
28				
29				
30				
31	Interventions:	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	21
32	adherence			
33				
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38	Interventions:	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	16
39	concomitant care			
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42				
43	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
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1	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
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10	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
11				
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17	Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	11
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19				
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21	Methods: Assignment			
22	of interventions (for			
23	controlled trials)			
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25				
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28	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
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38	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
39				
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46	Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	11-13
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51	Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	13
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1	Blinding (masking):	#17b	If blinded, circumstances under which unblinding is permissible, and	20-21
2				
3	emergency unblinding		procedure for revealing a participant's allocated intervention during the	
4				
5			trial	
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8	Methods: Data			
9	collection,			
10	management, and			
11	analysis			
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16	Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial	13,16-19,
17			data, including any related processes to promote data quality (eg,	Table 2
18			duplicate measurements, training of assessors) and a description of	
19			study instruments (eg, questionnaires, laboratory tests) along with their	
20			reliability and validity, if known. Reference to where data collection forms	
21			can be found, if not in the protocol	
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28	Data collection plan:	#18b	Plans to promote participant retention and complete follow-up, including	21-22
29	retention		list of any outcome data to be collected for participants who discontinue	
30			or deviate from intervention protocols	
31				
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35	Data management	#19	Plans for data entry, coding, security, and storage, including any related	19-20
36			processes to promote data quality (eg, double data entry; range checks	
37			for data values). Reference to where details of data management	
38			procedures can be found, if not in the protocol	
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43	Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes.	21-23
44			Reference to where other details of the statistical analysis plan can be	
45			found, if not in the protocol	
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49	Statistics: additional	#20b	Methods for any additional analyses (eg, subgroup and adjusted	21-23
50	analyses		analyses)	
51				
52				
53				
54	Statistics: analysis	#20c	Definition of analysis population relating to protocol non-adherence (eg,	21-23
55	population and		as randomised analysis), and any statistical methods to handle missing	
56	missing data		data (eg, multiple imputation)	
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1	Methods: Monitoring		
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3			
4	Data monitoring:	#21a	Composition of data monitoring committee (DMC); summary of its role 21
5			
6	formal committee		and reporting structure; statement of whether it is independent from the
7			sponsor and competing interests; and reference to where further details
8			about its charter can be found, if not in the protocol. Alternatively, an
9			explanation of why a DMC is not needed
10			
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14	Data monitoring:	#21b	Description of any interim analyses and stopping guidelines, including 21
15			
16	interim analysis		who will have access to these interim results and make the final decision
17			to terminate the trial
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21	Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and 20-21
22			spontaneously reported adverse events and other unintended effects of
23			trial interventions or trial conduct
24			
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27	Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether 21
28			the process will be independent from investigators and the sponsor
29			
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32	Ethics and		
33	dissemination		
34			
35			
36	Research ethics	#24	Plans for seeking research ethics committee / institutional review board 6,23,25
37			
38	approval		(REC / IRB) approval
39			
40			
41	Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes 23
42			to eligibility criteria, outcomes, analyses) to relevant parties (eg,
43			investigators, REC / IRBs, trial participants, trial registries, journals,
44			regulators)
45			
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49	Consent or assent	#26a	Who will obtain informed consent or assent from potential trial 11
50			participants or authorised surrogates, and how (see Item 32)
51			
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54	Consent or assent:	#26b	Additional consent provisions for collection and use of participant data 11
55			
56	ancillary studies		and biological specimens in ancillary studies, if applicable
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1	Confidentiality	#27	How personal information about potential and enrolled participants will be	19,20
2			collected, shared, and maintained in order to protect confidentiality	
3			before, during, and after the trial	
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7	Declaration of	#28	Financial and other competing interests for principal investigators for the	25-26
8	interests		overall trial and each study site	
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12	Data access	#29	Statement of who will have access to the final trial dataset, and	20,25
13			disclosure of contractual agreements that limit such access for	
14			investigators	
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18	Ancillary and post trial	#30	Provisions, if any, for ancillary and post-trial care, and for compensation	20-21
19	care		to those who suffer harm from trial participation	
20				
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22				
23	Dissemination policy:	#31a	Plans for investigators and sponsor to communicate trial results to	6,23
24	trial results		participants, healthcare professionals, the public, and other relevant	
25			groups (eg, via publication, reporting in results databases, or other data	
26			sharing arrangements), including any publication restrictions	
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31	Dissemination policy:	#31b	Authorship eligibility guidelines and any intended use of professional	23
32	authorship		writers	
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36	Dissemination policy:	#31c	Plans, if any, for granting public access to the full protocol, participant-	25
37	reproducible research		level dataset, and statistical code	
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41	Appendices			
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43				
44	Informed consent	#32	Model consent form and other related documentation given to	11
45	materials		participants and authorised surrogates	
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48	Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological	14,19
49			specimens for genetic or molecular analysis in the current trial and for	
50			future use in ancillary studies, if applicable	
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