Agents Intervening against Delirium in the Intensive Care Unit (AID-ICU)
A randomised, blinded, placebo-controlled trial.

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Applicable protocol registration numbers
ClinicalTrials.gov identifier NCT03392376
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In drafting of present protocol Copenhagen Trial Unit's Standard Operating Procedures were used.

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Abstract

Background: Delirium among critically ill patients in the intensive care unit (ICU) is a common condition associated with increased morbidity and mortality. No evidence-based treatment exist of this condition. Haloperidol is the most frequently used agent to treat ICU-related delirium, but according to an overview of reviews (Appendix 11) carried out at the initiative of the steering committee with no firm evidence of efficacy and safety of this intervention.

Objective: To assess benefits and harms of haloperidol in adult, critically ill patients with delirium in the ICU.

Design: An investigator-initiated, pragmatic, international, multicentre, randomised, blinded, parallel-group trial of delirium management with haloperidol versus placebo.

Inclusion and exclusion criteria: Inclusion criteria: Adult patients with acute admission to the ICU and diagnosed delirium with a validated screening tool. Exclusion criteria: contraindications of haloperidol, habitual treatment with any antipsychotic medication, permanently incompetent, delirium assessment non applicable, withdrawal from active therapy or brain death, positive urine human chorionic gonadotropin (hCG) or plasma hCG or consent according to national regulations not obtainable.

Intervention: Experimental intervention with 2.5mg haloperidol IV three times daily. Control intervention is matching placebo (saline). Further as needed doses of haloperidol/placebo to a maximum of 20mg/daily if needed. If further pharmaceutical intervention is needed the following escape medications may be chosen at the discretion of the clinician: intravenous propofol, benzodiazepines or α2-agonists. Delirium status will be evaluated twice daily with a validated screening tool.

Outcomes: Primary outcome: Days alive out of the hospital within 90 days after randomisation. Secondary outcomes: Number of days alive without delirium and coma in the ICU, serious adverse reactions to haloperidol, number of days alive without mechanical ventilation, one year mortality post-randomisation, health-related quality of life measures, cognitive function and a health economic analysis one year after randomisation.

Trial size: A total of 2 x 500 patients are required to show an 8% improvement or worsening of the mean days alive out of the hospital, assuming a 90-day baseline mortality of 27% (α=0.05, two-sided and β=0.1)

Time schedule:

September 2017 - January 2018: Governance approvals, education of trial sites and other preparations.

February-March 2018: First Danish patient enrolled

September 2018: Commencement of inclusion in other countries

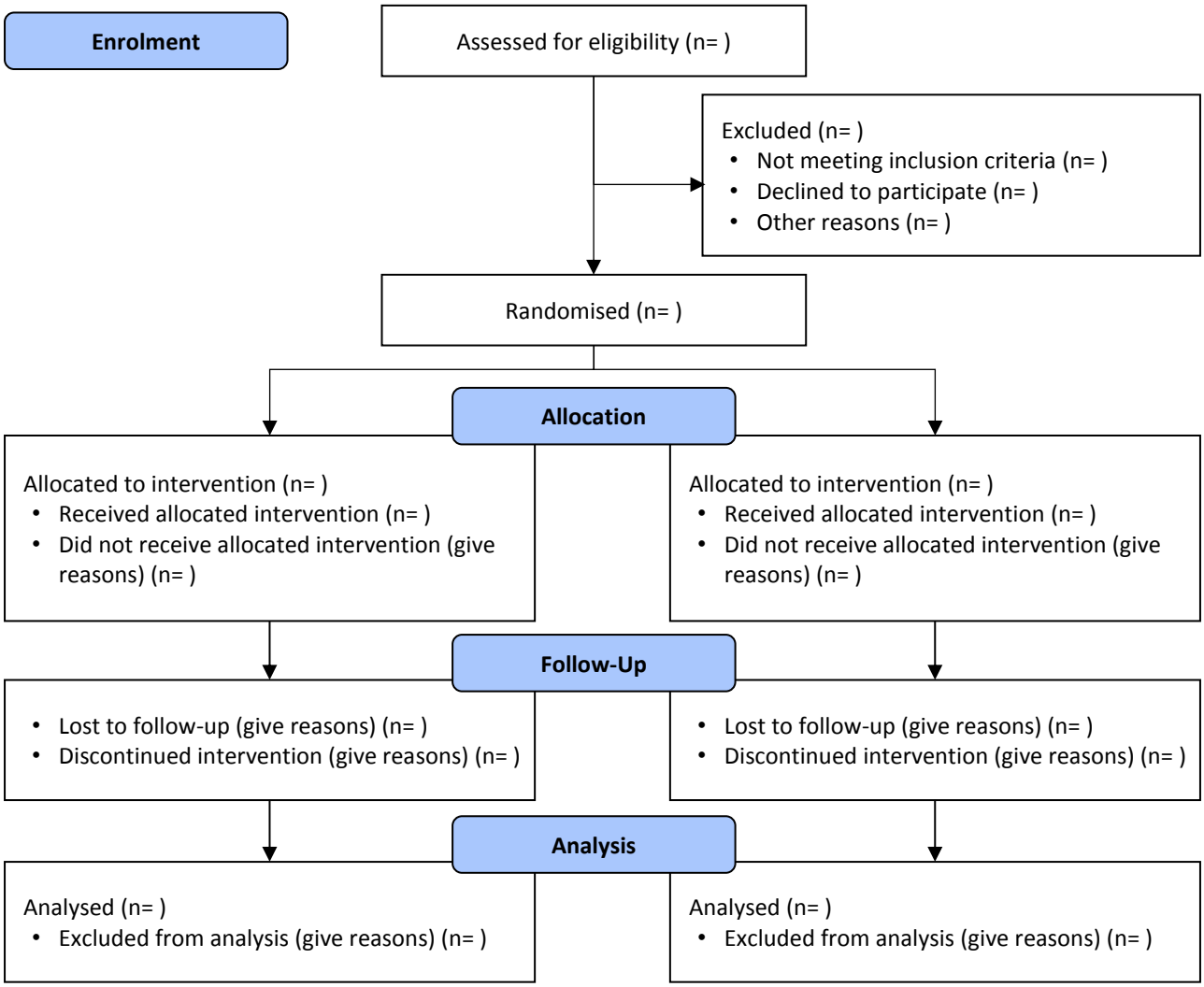
March 2020: Last patient enrolled

July 2020: Follow-up completed

August 2020: Data analysis and submission for publication of the 90-day results.

Trial flow chart

The flowchart (n=) will be filled in during or at the end of the trial.



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- Spain
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List of abbreviations and definitions

AE	Adverse events
AID ICU	Agents Intervening against Delirium in the Intensive Care Unit
AR	Adverse reactions
ARR	Absolute risk reduction
CAM-ICU	Confusion Assessment Method
CI	Confidence interval
CRIC	Centre for Research in Intensive Care
CT	Computed Tomography
CTC	Computed Tomography of Cerebrum
CTU	Copenhagen Trial Unit
DMSC	Data Monitoring and Safety Committee
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, 4th Edition
eCRF	Electronic case report form
EPS	Extrapyramidal symptoms
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FDA	U.S. Food and drug administration
GCP	Good Clinical Practice
GDP	Good Distribution Practice
GMP	Good Manufacturing Practice
hCG	Human Chorionic Gonadotropin
HP	Hospital Pharmacy of the Capital Region of Denmark
ICDSC	Intensive Care Delirium Screening Checklist
ICMJE	International Committee of Medical Journal Editors
ICU	Intensive care unit
IM	Intramuscularly
IV	Intravenously
MNAR	Missing not at random
MRI	Magnetic Resonance Imaging
NMS	Neuroleptic Malignant Syndrome
PO	Orally
PVC	Premature ventricular contractions
QTc	Rate corrected QT
QTp	Rate corrected QT prolongation
RCT	Randomised clinical trial
RBANS	Repeatable Battery for Assessment of Neuropsychological Status
SMS-ICU	Simplified mortality score in the ICU
SPC	Summary of Products Characteristics
TD	Tardive Dyskinesia
VIVE	Danish institute for Local and Regional Government Research (former KORA)

1 Introduction and background

1.1 The patient population

Delirium is the clinical term of an acute brain dysfunction, which often occurs in the course of severe illness. Delirium derives from the Latin *deliro-delirare* meaning 'going off track'[1]. It is known as a complex neuropsychiatric syndrome, characterized as an acutely changing or fluctuating mental status, which includes inattention, disorganized thinking, hallucinations, changes in mood and an altered level of consciousness with or without agitation [2, 3]. The pathophysiology of delirium is poorly understood [4, 5]. Several theories have been proposed including neurotransmitter imbalances (decreased acetylcholine and increased dopamine), hypoxia, neuroinflammation and stress responses, which eventually result in encephalopathy [5, 6].

Delirium is typically divided into 3 clinical subclasses; hyperactive, hypoactive and mixed delirium. The classification is based on the predominant psychomotor activity. The hypoactive patient has slowed mentation, lethargy, and decreased movements, and the hyperactive patient has increased number of spontaneous movements that are purposeless, uncontrollable and inefficient. A delirious patient may fluctuate between a hypoactive and hyperactive state and the delirium is then termed mixed form [7]. The hypoactive and mixed forms of delirium are most common in Intensive Care Unit (ICU) patients [8, 9]. The hypoactive is frequently overlooked and associated with higher mortality [10-12].

In a recent meta-analysis the prevalence of delirium in the ICU was reported to 32% [13], but prevalence up to 84% have been observed in mechanically ventilated patients [14]. Furthermore, delirium in ICU patients is associated with increased days on mechanical ventilation, longer hospital admittances, higher costs of care, long-term disability, continuous cognitive impairments, and increased mortality [15-17].

Several risk factors are known for the development of delirium, and may be divided into predisposing and precipitating factors. Predisposing factors are non-modifiable and include advanced age, baseline cognitive impairment, co-morbidity and frailty [18-20]. Theoretically patients with lower cognitive and physical reserves are less able to adapt and maintain normal brain function during stress (e.g. critical illness) and are thereby at higher risk of developing delirium [21]. Precipitating factors of delirium are prolonged mechanical ventilation, major surgery, poor pain control, sepsis, hypotension, sleep disturbances and certain analgesic and sedative medications (benzodiazepines and opioids) [18, 19, 22, 23].

Various tools have been validated for screening of delirium [24] e.g. the Confusion Assessment Method for ICU (CAM-ICU) [25] and the Intensive Care Delirium Screening Checklist (ICDSC)[26]. Both tools have been adopted for use in ICUs around the world, and have demonstrated to identify a diagnosis of delirium as reliably as the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) criteria used by psychiatrists. These diagnostic tools have therefore significantly improved diagnosis of delirium [27].

1.2 Current treatment

Various pharmacologic agents including antipsychotics, statins, steroids, benzodiazepines and dexmedetomidine are used against delirium in the clinical setting despite the fact that it is unclear if these drugs are in fact effective [28-30]. A recent unpublished, multicentre, 14-day inception cohort study investigating pharmacological interventions for delirium in ICU patients, found on the basis of data from 99 ICUs, that haloperidol was the most frequently used agent in delirium treatment followed by benzodiazepines and dexmedetomidine [31].

Haloperidol is a so-called first generation antipsychotic compound and the main mechanisms of action is by blocking dopamine (D2) receptors in the basal ganglia. Furthermore, haloperidol may increase the signalling of acetylcholine [32].

Haloperidol may be administered orally (PO), intramuscularly (IM) or intravenously (IV) and has a high level of bioavailability. The mean half-life of haloperidol following PO or IV administration is 14-21h, due to metabolization in the liver by CYP-enzymes [33, 34]. The pharmacokinetics of haloperidol have never been studied in critically ill patients, but it has been predicted that haloperidol may have large intra-individual bioavailability because of fluctuating health status, presence of multiple therapeutic interventions and drug interactions [34].

Various dosing regimens of haloperidol exist, and daily dose ranges vary extensively. Escalating doses to extreme levels of IV haloperidol daily (3-400mg/daily) has been reported, although data on dosage regimes in critically ill patients consist of case reports or descriptive studies of small populations [34]. A study on D2 receptor occupancy in relation to plasma levels of haloperidol in a small patient population (n=12) with schizophrenia revealed that a daily oral dose of 2-5mg was sufficient to occupy between 50-80% of D2 receptors [35]. In psychotic patients, a D2 receptor occupancy of 65-80 % is considered optimal for obtaining an antipsychotic response [36]. Higher D2-occupancy increases the risk of extrapyramidal

symptoms (EPS). This indicates that low-dose haloperidol may be sufficient to achieve an adequate antipsychotic response [35].

Current guidelines recommend initial doses of haloperidol between 0.5-10 mg PO or IV depending on patient age and level of agitation. Dosage may be repeated after 20-30 min until therapeutic effect is reached [37-39].

1.3 Trial interventions

Haloperidol gained popularity for use in ICUs in the 1990's, when Riker et al. in a case series showed that haloperidol infusion reduced agitation and requirements of sedatives in ICU patients [40]. The treatment gained popularity in 2005 where Milbrandt et al. in a retrospective study of 989 patients found that mechanically ventilated patients, who received haloperidol, had lower hospital mortality compared with those who never received haloperidol [41]. Kallisvaart et al. showed that prophylactic treatment with haloperidol of elderly patients undergoing hip surgery reduced the duration and severity of delirium. However, the authors were not able to show any difference in incidence of delirium between the haloperidol and placebo groups [42]. In 2013 Page et al. conducted a randomized, placebo-controlled trial in mechanically ventilated ICU patients. Patients were randomized irrespective of their CAM-ICU status to receive haloperidol or placebo. However, no differences in days alive without delirium and coma between the two study groups was reported, making the effect of haloperidol on delirium duration questionable [43].

In the past decade treatment with atypical antipsychotics have increased as these are regarded to be as efficient in treating delirium, but with less extrapyramidal symptoms and fewer adverse reactions as compared to haloperidol [28, 29]. In 2004 Skrobik et al. showed in a prospective randomized trial but with unconcealed allocation, that olanzapine was a safe alternative to haloperidol in delirious patients in the ICU with equal improvement in ICU Delirium Index scores and less extra pyramidal symptoms [44]. A RCT by Girard et al. randomly assigned 103 mechanically ventilated ICU patients with a positive CAM-ICU to receive haloperidol or ziprasidone or placebo every 6 hours during 14 days. No differences were observed in days alive without delirium or coma between the three treatment groups [45].

A systematic review from 2010 by Cochrane Library based on three studies with small patients cohorts, found that antipsychotics (haloperidol, chlorpromazine, risperidone, and olanzapine) significantly reduced established delirium when comparing delirium scores at baseline and during treatment. The study found no difference between haloperidol and atypical antipsychotics (i.e. risperidone and olanzapine) in the management of delirium [29]. These

conclusions should be interpreted with caution since the meta-analysis of antipsychotics effect on delirium was applied on only two studies with small patient cohorts. A systematic review by Rodrigo et al. from 2015 found no single pharmacological intervention to reduce delirium duration or hospital LOS or mortality. The studied agents included antipsychotics (haloperidol, ziprasidone, quetiapine, olanzapine), and other agents (rivastigmin and dexmedetomidine). The authors concluded that large randomized placebo-controlled trials are needed to assess the role of antipsychotics in the treatment of delirium and long-term outcomes such as cognitive function and mortality [46].

A recent unpublished overview of reviews (Appendix 11) on pharmacological interventions for the treatment and prevention of delirium in ICU patients, found only one review of moderate quality (GRADE-assessment) and high risk of bias (ROBIS tool), addressing the effect of haloperidol on prevention and treatment of delirium. The review indicated no difference in delirium incidence or duration between the haloperidol and control groups. The systematic review emphasizes the need of conducting a large pragmatic trial with overall low risk of bias for treatment of delirium with haloperidol and dexmedetomidine (Appendix 11).

In conclusion, the literature so far, provides no definitive answer of neither beneficial nor harmful effects of haloperidol in the treatment of delirium and the long-term outcomes hereof.

However, various international guidelines continues to recommend haloperidol for the treatment of delirium [38, 48-50], although no blinded, randomized, placebo-controlled trials with adequate power have established efficacy or safety of haloperidol in the management of delirium in ICU patients [51]. In contrast, the most recent guidelines from the American College of Critical Care Medicine and the Society of Critical Care Medicine in the US did not recommend haloperidol for the management of delirium due to lack of evidence and emphasized the need of a well-designed RCT to assess the role of haloperidol in the management of delirium [51].

With the current protocol, we will conduct an international, multicentre, prospective, randomized, placebo-controlled trial to investigate the effect of haloperidol in treating delirium in ICU patients. Before testing other drugs (e.g. atypical antipsychotics) compared with haloperidol, we need to establish firm evidence that haloperidol is superior to placebo in treating delirium in ICU patients. The control intervention is therefore chosen to be placebo.

1.4 Risks and benefits

The use of haloperidol against delirium is a well-known and widespread used regimen in the ICU and many patients receive it every day. Haloperidol has a number of potentially harmful adverse reaction (see section 8.3) and is associated with increased mortality after long-term treatment in elderly people with dementia-related psychosis [52]. From the available evidence there is not firm evidence demonstrating that haloperidol is superior or inferior to placebo in ICU patients with delirium [47]. Many patients may thereby be exposed to the adverse reactions of haloperidol without any firm evidence of benefit.

1.5 Serious Adverse Reactions of haloperidol

Extrapyramidal symptoms

Extrapyramidal symptoms (EPS) include dystonia, akathisia, parkinsonism, bradykinesia and tremor [53]. In a meta-analysis of the safety and efficacy of haloperidol in delirium patients, the drug was proven relatively safe with regard to EPS symptoms. In six studies that used standardized methods to record adverse reactions, especially EPS symptoms, only one out of 1123 patients experienced mild akathisia [54].

Tardive dyskinesia

Tardive dyskinesia (TD) is a syndrome of potentially irreversible, involuntary, dyskinetic movements. The rate of TD after haloperidol is highest among elderly, especially elderly women. The risk of developing TD is believed to increase as the duration of drug administration and accumulated drug dose increases. However, the syndrome may develop after low doses and brief treatment with haloperidol [53].

Cardiovascular effects

Haloperidol has been associated with rate corrected QT-prolongation (QTp), Torsade de Pointes tachyarrhythmia and sudden death [53]. QTp frequently occurs in critically ill patients [55] and is thereby a well-known condition in the ICU. QTp in critically ill patients have through retrospective studies been associated to patients receiving high doses of IV haloperidol (> 20mg/d) [56, 57]. The association between QTp and low-dose IV haloperidol is less clear. A recent post-hoc analysis of a randomized, placebo-controlled trial in a mixed population of critically ill adults (n=68) showed that low dose IV haloperidol (< 20 mg/d) was not associated with QTp, suggesting no need for additional QTc monitoring after initiation of low dose IV haloperidol [58].

All ICU patients are under continuous cardiac monitoring enabling clinicians to identify patients suspicious of QTp and those with ventricular arrhythmia. The current clinical practice in the ICU does not include QTp screening before or during haloperidol use and ICU staff are experienced in handling IV haloperidol for the treatment of delirium. Furthermore, QTp is not necessarily equivalent to arrhythmogenicity and the use of QT-prolonging drugs should be based on a risk-benefit analysis in individual patients [55]. Clinicians in the ICU are experienced in this risk assessment and have the means to initiate haloperidol treatment without QTp screening due to their experience and a higher level of surveillance. According to available evidence and in line with current practice there will be no protocolized QTp screening after enrolment in the AID-ICU trial.

Neuroleptic malignant syndrome

Neuroleptic malignant syndrome (NMS) is a rare but serious adverse reaction to haloperidol. It is a complex condition recognized by hyperpyrexia, severe muscle rigidity and autonomic instability such as a labile blood pressure. Other signs may include high levels of creatinine phosphokinase, myoglobinuria and acute kidney injury. NMS is an exclusion diagnosis, since many of the symptoms may be related to co-morbid conditions in critically ill patients. The condition is extremely rare with incidence rates for all antipsychotics probably being between 0.01 and 0.02%. The incidence of NMS has decreased probably due to the use of lower doses of antipsychotics. The syndrome typically occurs in the first two weeks after drug initiation [59].

Mortality in elderly

Analyses from 17 placebo-controlled trials, largely on atypical antipsychotics including haloperidol, have revealed an increased mortality in elderly patients with dementia-related psychosis. Compared to placebo the risk of death was 1.6-1.7 times higher among patients treated with antipsychotics [60]. Furthermore, observational studies suggest that treatment with typical antipsychotics may increase mortality in elderly [61, 62]. Following these findings, the American Food and Drugs administration (FDA) issued a 'black box-warning' stating that antipsychotics are not approved for treatment of dementia-related psychosis. However, a systematic review and meta-analysis of randomized placebo-controlled trials in elderly with dementia, delirium or high risk of delirium, found no increased mortality associated with the use of haloperidol [63].

1.6 Ethical justification and trial rationale

As described above, there is no firm or reliable evidence from systematic reviews of RCTs or single RCT on the potential benefit or harm of haloperidol in the adult patients in the ICU. Haloperidol is, however, recommended in several guidelines, and regarded as a first line drug for treatment of delirium. Since it is widespread and currently the most used intervention, the patients assigned to the haloperidol group in the AID-ICU trial, will not be exposed to additional risk when enrolled in the trial. If a randomised patient experiences an adverse reaction, the trial intervention will be discontinued and the patient will be treated according to usual care other than haloperidol. For patients with severe agitated delirium, who cannot be managed with the interventional drug alone, there is a protocolized escape plan to ensure the safety of the patient. The escape plan will be in accordance with everyday practice and will not expose the patients to additional risks.

The individual patient may benefit from participating in the trial as this will lead to increased focus on delirium. The trial secures daily delirium screening enabling early diagnosis of delirium. An early diagnosis will possibly secure earlier implementation of other non-pharmacological interventions for delirium which is part of usual care in the ICU (eq. sleep- and pain control). Furthermore, the close surveillance will ensure discontinuation of trial intervention when it is no longer needed.

We find the trial justified since it is believed that it is in the interest of the individual patient, future patients and society, to establish firm evidence of the role of haloperidol in treating delirium. If the drug is not found superior to placebo, future patients will benefit from this trial by avoiding the potential harm of receiving haloperidol.

All ICU patients with delirium are mentally incompetent by definition (it is the hallmark of delirium). We cannot conduct the trial in less sick patients neither in- nor outside the ICU since such patient populations are not representative for ICU patients with delirium. Delirium in the ICU is prevalent and associated with a high degree of morbidity and mortality [23, 64, 65]. Patients requiring an intervention for ICU delirium cannot have the intervention withheld for them to regain competence so that informed consent can be obtained. To make a clinical trial with the goal of improving the outcome of delirious patients in the ICU, it is necessary to randomise and enrol patients before obtaining informed consent from the patient. Consent will be obtained according to national law. In Denmark, temporarily incompetent patients will be enrolled after informed consent from one physician, who is independent of the trial (first trial guardian). As soon as possible after enrolment, consent will be obtained from the

patient's next of kin and a second physician (second trial guardian). The second trial guardian must be different from the first trial guardian, but also independent of the trial. Patients, who regain competence, will be asked for informed consent as soon as possible (*appendix 5*). The process leading to the achievement of informed consent will be in compliance with all applicable regulations. The consenting party will be provided with written and oral information about the trial so he/she is able to make an informed decision about participation in the trial. Written information and the consent form will be subject to review and approval by the ethical committee system according to national law in all participating countries. The consenting party can at any time, without further explanation, withdraw consent. The process leading to the achievement of consent may differ in the participating countries, but will be described and be in compliance with all applicable regulations in the country.

1.7 Trial conduct

The trial will be conducted in compliance with the published trial protocol, the Helsinki Declaration in its latest version [66], the good clinical practice (GCP) guidelines [67], and national laws in the participating countries. The protocol is written in accordance with the SPIRIT 2013 Statement [68] and will be registered on www.clinicaltrials.gov and at the European Union Drug Regulating Authorities Clinical Trials (EudraCT) before trial start. No substantial deviation from the protocol will be implemented without prior review and approval of the regulatory authorities except where it may be necessary to eliminate an immediate hazard to the trial participants. In such case, the deviation will be reported to the authorities as soon as possible. Enrolment will start after approval by the ethical committees, medicines agencies, data protection agencies and health authorities in the participating countries. A manuscript with main points of the protocol including description of design, rationale and analysis plan will be submitted to a peer-reviewed journal in English language.

2 Trial objectives and purpose

To assess the benefits and harms of haloperidol in adult ICU patients with delirium.

2.1 Trial hypotheses

- In adult ICU patients with delirium, haloperidol as compared with placebo, will have an effect on the number of days alive out of the hospital within 90-days.
- Haloperidol as compared with placebo will reduce the duration of delirium in these patients.

- Haloperidol as compared with placebo will increase the total number of serious adverse reactions and number of serious adverse reactions per patient.

2.2 Primary objective

To determine, if haloperidol treatment in ICU patients with delirium will increase the number of days alive out of the hospital within 90 days. This primary objective includes 90 days mortality and length of hospital stay within 90 days after randomisation.

2.3 Secondary objectives

To investigate if haloperidol as compared with placebo in ICU patients with delirium will change the:

- Number of days alive without delirium or coma in the ICU
- Number of patients with one or more adverse reactions and/or the total number of adverse reactions to haloperidol compared with placebo.
- Number of patients needing one or more doses of escape medicine and or the dosages of escape medicine per patient in the haloperidol group compared with the placebo group
- Number of days alive without mechanical ventilation in the 90-day trial period
- One-year mortality after inclusion
- Measurement of cognitive function at inclusion and 1-year after inclusion at selected trial sites.
- A health economic analysis will be performed. The analytic details will be based on the result of the trial and specified (cost-effectiveness vs. cost-minimisation analyses). Outcomes will be one-year mortality and Quality adjusted Life Years (QALYs). The latter will be conducted on the basis of EQ-5D-5L. The inclusion of QALYs generates a cost-utility analysis.

3 Trial design

3.1 Trial design

The AID-ICU trial is an investigator-initiated, international, multicentre, randomised, blinded, parallel-group trial of haloperidol versus placebo in adult ICU patients with delirium.

3.2 Randomisation

Patients with a positive delirium score will be screened for enrolment in the participating ICUs. This will be ensured through implementation of trial methodology at trial sites. The 1:1 randomisation will be centralised and web-based according to the computer-generated allocation sequence list, stratification variables, and varying block size at Copenhagen Trial Unit (CTU). The allocation sequence list will exclusively be known to the data manager at CTU and will be unknown to the investigators to allow immediate and concealed allocation to intervention with haloperidol or placebo. Each patient will be allocated a unique patient-screening number.

3.3 Blinding

Haloperidol is contained in liquid form in an ampule. Our placebo drug will be isotonic saline and will be contained in an identical ampule. The solution of haloperidol is colourless and cannot be visually distinguished from isotonic saline. Each vial will contain the same volume, corresponding to 5 mg (1ml) haloperidol in the intervention group. The trial medication will be labelled with a white label, which is identical on placebo and active drug. The label will contain the required information of the trial drugs including date of expire. The top of the placebo ampule will be identical with the ampule of the active drug.

The allocated trial medication will be blinded to the clinical staff caring for the patient, to the patient, investigators, outcome assessors, and only the data manager has the possibility to unblind the allocated intervention. The statistical analysis of the trial will be blinded with the intervention groups coded as, e.g., X and Y. Based on this blinded analysis two conclusions will be drawn: one assuming X is the experimental group and Y is the control group, and one conclusion assuming the opposite. Two abstracts will be written and accepted by the author group. After this, the blinding will be demasked.

The members of the Data Monitoring and Safety Committee (DMSC) will remain blinded unless 1) they request otherwise or 2) the interim analysis has provided strong indications of one intervention being beneficial or harmful compared to the other.

3.3.1 Unblinding

The intervention may be unblinded for individual patients if deemed necessary by the clinician or investigator for the treatment and safety of the patient. In case of a suspected unexpected serious adverse reaction (SUSAR) the sponsor (or delegated party) shall break the blinding in order to judge the 'expectedness' and therefore the occurrence of a SUSAR (according to the

summary of product characteristics), and report it to the authorities accordingly. See section 8 for more information.

If the intervention for an individual patient needs to be unblinded during the trial, the treating physician shall contact the Coordinating investigator who will be available around the clock: The Coordinating investigator will establish contact to Copenhagen Trial Unit (CTU) if needed, from where information of allocated trial intervention (haloperidol or placebo) is available. This can be done by telephone at all hours, any day of the week.

For the entire trial

Unblinding the entire trial will be performed confidentially via the data manager to the steering committee at the end of the statistical analysis and after two approved abstracts are written, one assuming X is the intervention while the other assuming Y is the intervention. The author will be blinded to the allocation until the abstracts are approved by the steering committee. If the interim analysis gives strong indications of one intervention is beneficial or harmful, the trial will be unblinded before planned.

3.4 Participant timeline

We will strive to enrol patients as soon as they fulfil the inclusion criteria. Patients admitted to a clinical trial site will be screened with a validated screening tool (CAM-ICU or ICDSC) of delirium morning and evening. When a patient is diagnosed with delirium the patient is screened for enrolment. Upon enrolment the patients will be randomized to receive either intravenous 2.5mg haloperidol or placebo three times daily. The patients will continue the allocated intervention until they fulfil the pausing criteria (see section 6.4), discharge from the ICU or death in the ICU with a maximum of 90 days after randomization.

If the patient meets pausing criteria (see section 6.4), the intervention will be discontinued. However, if the patient again turns delirious, the patient shall resume the allocated treatment. If the patient is readmitted to the ICU within 90 days after randomisation and still meet inclusion criteria, the patient should continue the allocated treatment. If a patient has received haloperidol or other antipsychotics in the department against delirium, the treatment should be discontinued and the patient should continue the allocated treatment.

The trial site will be responsible for registration of 90-day mortality and length of stay in the ICU within 90 days. The national investigator will be responsible for registration of 1-year mortality.

4 Selection of participants

All patients admitted to a clinical trial site are considered for inclusion. Patients will be eligible if they comply with inclusion criteria and not any of the exclusion criteria listed below.

4.1 Inclusion criteria

- Acute admission to the ICU AND
- Age ≥ 18 years AND
- Diagnosed delirium with a validated screening tool as either CAM-ICU or ICDSC.

4.2 Exclusion criteria

- Contraindications to haloperidol (intolerance to haloperidol or additives, known Parkinson's disease or other extrapyramidal symptoms, known QTc prolongation, history of tardive dyskinesia or comatose (non-pharmacological) patients, previous ventricular arrhythmia or torsades de pointes, uncorrected hypokalaemia)
- Habitual treatment with any antipsychotic medication or treatment with antipsychotics in the ICU prior to inclusion
- Permanently incompetent (e.g. dementia, mental retardation)
- Delirium assessment non-applicable (coma or language barriers)
- Withdrawal from active therapy or brain death
- Fertile women (women < 50 years) with positive urine human chorionic gonadotropin (hCG) or plasma-hCG
- Consent according to national regulations not obtainable
- Patients under coercive measures by regulatory authorities
- Patients with alcohol-induced delirium (delirium tremens)

4.3 Participant discontinuation and withdrawal

4.3.1 Discontinuation and withdrawal at the choice of the participant

The procedure of handling withdrawal of consent from a patient will follow national regulations and will be described by each participating country.

The Danish procedure:

A patient, who no longer wishes to participate in the trial, can withdraw his/her consent at any time without need of further explanation, and without consequences for further treatment. For incompetent patient's consent can be withdrawn at any time by the person(s),

who has given proxy-consent. In order to limit the amount of missing data, we plan to collect as much data from each patient as possible. Therefore, if possible, the investigator will ask the patient or the proxy to which extent the withdrawal includes:

- receiving the trial intervention only (allowing for all data registration and follow-up)
  OR
- receiving the trial intervention AND further registration of daily data and/or follow-up

Only the patient can demand deletion of already registered data and only if the patient did not consent previously. If so, data will be deleted and enrolment of a new patient will be ensured to obtain the full sample size.

4.3.2 Discontinuation and withdrawal at the choice of the treating clinician or the investigator

The intervention of a particular patient can be discontinued by the clinician or investigator at any time, if:

- The patient experiences intolerable adverse reactions (including SAR and SUSAR) suspected to be related to the trial intervention.
- Clinicians discretion in conjunction with the coordinating investigator decide it to be in the patient's interest
- The patient after inclusion is subject to involuntary hospitalization (coercive measures), the intervention will stop.
- The patient after inclusion experiences QTc prolongation.
- The patient after inclusion becomes comatose and the coma is suspected to be caused by the intervention medication. All other causes should be considered and abolished before the intervention is paused.

In these cases, the collection of data will continue and the follow-up will be conducted. The patient will remain in the intention-to-treat population if the allocated trial intervention has been given.

4.3.3 Discontinuation due to wrong inclusion of an ineligible patient

If an ineligible patient is randomised by mistake and the trial intervention has not been given, data will be deleted (logged as a flawed randomisation) and a new patient will be randomised.

If the intervention has been given, the patient will continue in the trial and in the intention-to-treat population. If the patient experiences a serious adverse reaction (SAR) or a suspected unexpected serious adverse reaction (SUSAR) the trial intervention will be stopped; data registration will continue.

4.3.4 Transferral between ICUs

Patients who are transferred to another ICU will be regarded as discharged from the ICU unless the receiving ICU is an active AID-ICU trial site. The patient will then continue the allocated intervention at the new trial site until discharge from ICU, achievement of pausing criteria or death. The trial site with the final discharge or death of the patient is responsible for follow-up of primary and secondary outcome measures.

5 Selection of trial sites and personnel

5.1 Trial sites and setting

Trial sites will be ICUs in Europe. Trial sites are listed in the section 'Administrative information'. This section will be updated during the trial.

5.2 Trial personnel

All clinicians caring for patients in participating ICUs will be eligible to screen patients and perform the interventions. All participating ICUs will receive written and oral instructions about the trial procedures. A 24-hour hotline will be available for questions.

6 Trial interventions

6.1 Experimental intervention

All patients randomised to the experimental group will be given intravenous haloperidol 2.5 mg three times daily. If necessary, administration of trial medication can be repeated to a maximum dose of 20 mg haloperidol/placebo a day (corresponding to 8 administrations of trial medication). The intervention period will be from randomisation until discharge or death in the ICU, or 90 days post-randomisation (maximum length of the intervention period) or a patient meets the pausing criteria. When a patient meets pausing criteria, the intervention will be discontinued but daily assessment and data registration will continue. If the patient again turns delirious, the patient shall resume the allocated intervention. If the patient is readmitted to the ICU within the 90-day trial period and has delirium, the allocated

intervention should be resumed until final discharge from the ICU, the patient meets pausing criteria, the end of the 90-day trial period or death.

6.2 Control intervention

The control intervention will be placebo in the form of isotonic saline, which will be administered intravenously three times daily or in the same algorithm described above. The intervention period will be identical to the intervention period of the experimental intervention.

6.3 Delirium assessment

All patients included in the trial are assessed twice daily with a diagnostic tool for delirium (CAM-ICU or ICDSC, appendix 8 and 9). The test results can be positive or negative for delirium (positive CAM-ICU or ≥ 4) and is registered daily in the eCRF from source data.

6.4 Pausing criteria

When a patient has two consecutive negative CAM-ICU or ICDSC (< 4) scores in the same day (morning assessment and evening assessment) the patient will be classified as 'delirium-free' and the intervention will be paused. Data registration and follow-up will continue. If a patient is termed 'delirium-free' and discontinued from the trial intervention, but after some time again has delirium (positive CAM-ICU or ≥ 4 ICDSC), the patient will resume the allocated treatment.

6.5 Co-interventions

The only protocolized co-intervention in the trial will be our escape protocol, see section 6.8 for more details. The patients will in any other sense be subject to standard care in the ICU during the whole trial period.

6.6 Concomitant interventions

Haloperidol or other antipsychotics cannot be prescribed in the ICU during the intervention period. If a patient develops uncontrollable agitation there will be an escape plan (*see section 6.8*) to ensure safety of the patient. If an included patient receives open-label haloperidol or other antipsychotics it will be considered a major protocol violation. This will be registered and the allocated trial intervention and data collection will continue.

Patients readmitted to the ICU within the 90-day intervention period:

- If the patient has received haloperidol or other antipsychotics in the ward, the drug will be discontinued when the patient is admitted to the ICU. If the patient has a positive delirium score, the patient will resume the allocated trial medication.

All other interventions will be allowed since they are expected to be distributed evenly in the two groups.

6.6.1 Treatment with benzodiazepines and α2 agonists prior to inclusion

Patients receiving benzodiazepines or α2-agonists on a regular daily basis prior to ICU admittance may continue their habitual treatment during the trial. Patients who have prescriptions on benzodiazepines or α2 agonists in an as needed formula (not habitual/pro necessitate) prior to ICU admittance should have their medication discontinued upon inclusion in the trial.

6.7 Criteria for modification of interventions for a given trial participant

The intervention can only be modified if the patient is subject to intolerable adverse reactions or if the clinician in conjunction with coordinating investigator finds it necessary, see section 4.3.2. If the patient experiences uncontrollable delirium and the intervention protocol is not found sufficient, the intervention may be modified according to our escape protocol (see section 6.8).

6.7.1 Special circumstances: Comatose patients post-inclusion

Comatose patients whether intended or unintended are not assessable for delirium, but should generally continue to receive trial medication. If the coma is intended and easing the level of sedation is not possible, the patient will be registered as 'unable to assess' in the eCRF dayform and the intervention will continue. The clinician should on a daily basis, if appropriate, ease the level of sedation to ensure sufficient level of consciousness so delirium screening may be performed.

Unintended coma should be relieved by initially removing all sedative medication but the trial medication. If the coma is unexplained and at the clinician discretion suspected to be caused by the trial medication, all other causes should be considered and abolished (e.g. level of sedatives, analgesics etc.) before the trial medication is paused. This judgement is made by the treating physician.

6.8 Escape protocol

If the patient develops uncontrollable delirium that cannot be sufficiently treated with the trial medication including additional as needed doses of trial medication up to 20mg/daily, the patient may receive one of the following escape medications chosen at the discretion of the clinician: benzodiazepines, propofol-sedation or α2-agonists. The chosen agent should be titrated until the delirium is sufficiently managed according to usual clinical practice. Patients who are managed with one of the escape agents will continue to receive the intervention medication and as needed doses of haloperidol up to 20mg on a daily basis.

6.9 Management of patients with uncontrollable delirium before inclusion

If a patient presents with an uncontrollable delirium before inclusion and there is an immediate need to act, the clinicians are allowed to choose between one of the mentioned escape drugs in 6.8 before inclusion. Patients who have received the escape protocol before inclusion are still eligible for inclusion and this should be done as soon as possible.

6.10 Intervention accountability

Trial medication:

Active drug: Haloperidol, solution for intravenous injection, 5mg/ml.

Each glass ampule contains 1ml corresponding to 5 mg haloperidol. The content is colourless. The drug is produced by Jannsen-Cilag A/S, Bregnerødvej 133, 3460 Birkeroed, Denmark.

Placebo drug: Isotonic saline, solution for intravenous injection, 9mg/ml

Each glass ampule contains 1 ml corresponding to 9mg saline in sterile water. Content of electrolytes/l: 154mmol chlorid, 154mmol natrium. Isotonic. Osmolarity 308mmol/l.

The placebo-drug is produced by the Hospital Pharmacy of the Capital Region of Denmark.

Haloperidol for intravenous injection will be bought and delivered from Janssen-Cilag to the Hospital Pharmacy of the Capital Region of Denmark (HP). The haloperidol will be part of the regular production and hence not made especially for the AID-ICU trial. The HP will be responsible for relabelling of haloperidol (making them identical to placebo), storage and packaging.

HP will produce the sterile ampules with isotonic saline used for placebo. The production will follow all regulations and according to Good Manufacturing Practice (GMP) and Good Distribution Practice (GDP). HP will be responsible for production, labelling, storage and

packaging of placebo medication (ampules containing 1ml of isotonic saline). All services will be performed by qualified and trained personnel and according to GMP and GDP.

A computer program (from CTU) will generate a coding list with numbers for the ampules**.** At randomisation, the computer program will allocate a package with 3 ampules each labelled with an unique ampule ID. In this way the trial participant number (CPR or national identification number) is linked to the unique ampule number on the trial medication. The procedure is repeated when more medication is needed. This procedure enables the investigator to trace all trial medication. CRIC will be responsible for having a sufficient number of ampules to be allocated to patients enrolled at each trial site. At each trial site, trial products will be stored in a secure place. Combined with the unique packaging and labelling number this will ensure that trial medications will not be mixed up with other medications. Used and unused products will be registered.

Distribution in Denmark will be handled by HP (distribution within and between regions). Distribution out-side Denmark will be handled by World Courier or other delivery companies that provide transfer temperature logs.

7 Outcomes

7.1 Primary outcome

- Days alive out of the hospital within 90 days post-randomisation

7.2 Secondary outcomes

1. Number of days alive without delirium and coma in the ICU
2. Number of patients with one or more serious adverse reactions to haloperidol and total number of serious adverse reactions to haloperidol
3. Usage of escape medicine and dosage of escape medicine per patient
4. Number of days alive without mechanical ventilation in the 90-day period
5. 1-year mortality post-randomisation
6. EQ-5D-5L and EQ-VAS one year after randomisation. Patients who have died will be assigned the lowest possible EQ-5D-5L and EQ-VAS score.
7. Cognitive function at inclusion using IQCODE and 1-year after randomisation assessed with RBANS score and Trail Making Test A&B at selected sites.
8. A health economic analysis will be performed. The analytic details will be based on the result of the trial and specified (cost-effectiveness vs. cost-minimisation analyses). Outcomes will be one-year mortality and Quality adjusted Life Years (QALYs). The

latter will be conducted on the basis of Eq-5D-5L. The inclusion of QALYs generates a cost-utility analysis.

7.3 Exploratory outcomes

No exploratory outcomes or sub-studies are planned. However, sub-studies will be encouraged as long as they do not hamper the completion of the main protocol and can be conducted after approval of the protocol by the Steering Committee (SC).

8 Safety

8.1 Definitions

Adverse Event (AE): any undesirable medical event occurring to a participant during a clinical trial, which does not necessarily have a causal relationship with the intervention.

Adverse Reaction (AR): any undesirable and unintended medical response related to the intervention occurring to a participant during a clinical trial.

Serious Adverse Event (SAE): any adverse event that results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect.

Serious Adverse Reaction (SAR): any adverse reaction that results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect.

Suspected Unexpected Serious Adverse Reaction (SUSAR): any suspected adverse reaction which is both serious and unexpected (the nature or severity of which is not consistent with the information available to date).

8.2 Risk and safety issues in the current trial

See summary of Product Characteristics in appendix 3.

8.3 Assessment of adverse reactions and events

8.3.1 Serious adverse reactions

SARs to Haloperidol.

- Anaphylactic reaction
- Agranulocytosis
- Pancytopenia
- Ventricular arrhythmia
- Extrapyramidal symptoms (EPS)
- Tardive dyskinesia
- Malignant neuroleptic syndrome
- Acute hepatic failure

Registered SARs are defined in appendix 2 in accordance with the Summary of Products Characteristics (SPC).

SARs to 7,5ml isotonic saline

No SARs are associated with a small volume of intravenous isotonic saline.

8.3.2 Recording of serious adverse reaction and events

SARs will be recorded daily in the eCRF from the time of the first administration of trial medication and until last administration of trial medication. If the patient is readmitted to the ICU and trial medication is re-introduced, SARs will be recorded. If a patient experience a SAR, the local investigator must report this without undue delay to the sponsor (or delegated party). Furthermore, when a SAR is registered in the eCRF, the coordinating investigator and sponsor will be informed directly, which will secure fast reporting of SAR. If a patient experiences a SAR he or she will be withdrawn from the trial medication. Daily registration will be continued and the follow-up will be conducted. SARs in the two groups will be compared as an outcome measure in the interim and final analyses.

If a patient experiences a SUSAR, the local investigator must report this without undue delay to the sponsor (or delegated party). The patient will be withdrawn from the trial and the trial medication will be demasked. If a SUSAR is still reasonable after demasking, a report will be conducted describing onset and end of event, severity, the relation to the intervention, the actions taken and the outcome.

SAEs will not be recorded as an entity, because the majority of ICU patients will experience several SAEs during their critical illness in the ICU. These will be registered by the clinician in

the patient files. The most important SAEs will be captured in the primary outcome measure; days alive out of the hospital (includes mortality and length of hospital stay) and secondary outcome measures (days alive without mechanical ventilation). Patient charts, notes and lab reports will contain detailed daily registrations of a wide range of clinical data (ICU setting), which can be obtained on request from the medical authorities.

8.3.3 Reporting

Trial investigators are obliged to report SUSARs without any delay to the sponsor, which in turn will report these to the Danish Medicine Agency no later than 7 days after the report has been received for life-threatening and fatal SUSARs. No later than 8 days after the reporting, the sponsor must inform the Danish Medicines Agency of relevant follow-up information on the sponsor's and the investigator's follow-up action to the reporting. Any other SUSARs must be reported to the Danish Medicines Agency no later than 15 days from the time when the sponsor is informed.

Once a year the sponsor will submit a list of all SARs that have occurred in the entire trial (Danish and international sites) during the trial period as well as a report on safety of the trial subjects to the Danish Medicines Agency.

The sponsor must notify the Danish Medicines Agency when the trial has been completed (no later than 90 days thereafter) or if earlier than planned, the reasons for stopping the trial must be given.

The results from the trial must be recorded on EudraCT.

9 Procedures, assessments and data collection

9.1 Inclusion procedure

9.1.1 Screening

All patients admitted to a participating ICU and having a positive delirium score (positive CAM-ICU, ≥ 4 ICDSC) will be eligible for screening. In women younger than 50 years a pregnancy test must be performed at the investigational site prior to inclusion, thus a negative urine-hCG or plasma-hCG must be present before enrolment in the trial.

9.1.2 Procedures for informed consent

Patients will be enrolled after consent by proxy is obtained according to national regulations. Each participating country will describe this procedure according to national regulations. The procedure for Danish patients is described in appendix 5.

9.2 Data collection

9.2.1 Method

Data will be obtained from patient files and national registers and registered in an eCRF. For patients transferred from a trial ICU to a non-trial ICU, data related to the outcomes of interest will post transferral be collected according to national practice e.g. national registers in Denmark.

9.2.2 Timing

All variables are defined in appendix 2.

Baseline variables:

- Sex
- Date of birth
- Date of admission to hospital
- Date and time of admission to ICU
- Elective or emergency surgery during current hospitalization (y/n)
- Risk factors for delirium:
    - Recent traumatic brain injury (y/n)
    - Recent stroke (y/n)
    - History of mental illness (y/n)
    - History of neurodegenerative disease (y/n)
    - Previous treatment with haloperidol (y/n)
    - Smoking (y/n)
    - Alcohol abuse (y/n)
    - Substance abuse (y/n)
    - Benzodiazepine use (Y/n)
- Other co-morbidities:
    - Active hematologic cancer
    - Metastatic carcinoma
- Values for Simplified Mortality Score (SMS score) at ICU admission not covered by the above:
    - Lowest measured systolic blood pressure in the last 24h prior randomisation
    - Use of vasopressors or inotropes, respiratory support and renal replacement therapy within the last 24h prior to randomisation (appendix 2 and 7).

Daily during ICU admission (day form):

- Use of mechanical ventilation on this day
- Coma on this day
- Delirium assessment
    - Morning assessment
        - Coma (y/n)
        - Delirium (y/n)
        - Motor subtype (hypo- or hyperactive)
    - Evening assessment
        - Coma (y/n)
        - Delirium (y/n)
        - Motor subtype (hypo- or hyperactive)
- Delirium treatment
    - Delivery of trial medication
        - Morning (y/n)
        - Midday (y/n)
        - Evening (y/n)
    - Additional as needed doses of trial medication (y/n), if yes:
        - Total dose of additional trial medication
    - Use of escape protocol (y/n for everyone), if yes:
        - Propofol sedation
        - Benzodiazepines
        - A2 agonist infusion
- Open label haloperidol administration (y/n)
- Serious adverse reactions (y/n for everyone)
    - Anaphylactic reaction
    - Agranulocytosis
    - Pancytopenia
    - Ventricular arrhythmia
    - Extrapyramidal symptoms (EPS)
    - Tardive dyskinesia
    - Malignant neuroleptic syndrome
    - Acute hepatic failure

Follow-up 90 days after randomisation

- Death (y/n, if yes date of death)
- Date of discharge from ICU
- Date of discharge from hospital
- Additional hospital admissions

Follow-up 1 year after randomisation

- Death (y/n, if yes date of death)
- EQ-5D-5L and EQ-VAS scores at selected sites
- RBANS scores and Trail Making Test A&B at selected sites

10 Data handling and record keeping

10.1 Data management

Data will be entered into an electronically, web-based eCRF and obtained from the source data as defined per site and country (medical files and national registers) by trial personnel.

10.2 Confidentiality

Each patient will receive a unique trial identification number. Trial investigators will receive a personal username and passwords to access the randomisation system and the eCRF. Each site will only have access to site specific patient data. Data will be handled according to the National Data Protection Agency and protected by the Danish national laws 'Loven om behandling af personoplysninger' and 'Sundhedsloven'.

10.3 Access to data

All original records (incl. consent forms, eCRFs, and relevant correspondences) will be archived for 15 years. The electronic trial database file will be delivered to a depository and maintained anonymized if requested by the authorities.

De-identified data will be made publicly available 9 months after the publication of the outcome data according to the recent ICMJE recommendations [69]. As it is for all CRIC trials, all trial-related documents will be public available at www.CRIC.nu including those of the site master file, the eCRF template, instructions, educational material etc.

11 Statistical plan and data analysis

11.1 Sample size and power

11.1.1 Sample size estimation for primary outcome

Our primary outcome is 'days alive out of the hospital within 90 days', which include 90-day mortality and days alive out of the hospital. For 90-day mortality the result will be given as a relative risk reduction or increase in mortality between the intervention and placebo group. For days alive out of the hospital the result will be given as an estimate of improvement or worsening of the mean. Both results will be stratified for delirium motor subtype and trial site. The results will be given with 95-confidence intervals.

Based on observational data [31], data on 'days alive out of the hospital within 90 days' shows a non-normal distribution. For power calculations, a Wilcoxon rank sum test was applied. Assuming that the treatment will lower mortality by 15% and shift the distribution of 'days alive outside the hospital at day 90' to the right by an amount that a combined effect on the mean is an improvement of 8%, the power calculation show that with 500 patients randomized to each arm we will have 90% power at the 5% significance level to show such a difference.

Power analysis of 90-day mortality is also based on observational data [31], which yield a 90-day mortality of 27%. With 500 patients in each arm the study will have 90% power to detect a relative risk reduction or increase in 90-day mortality of 31%.

11.1.2 Power estimations for secondary outcomes

Due to lack of previous data we have not been able to estimate the statistical power for the secondary outcomes.

11.2 Statistical methods

Our primary analyses will be based on the intention-to-treat population being all randomized patients consenting to use their data. Secondary analyses will be performed on a per protocol population defined as all patients randomized and consenting to use their data except for patients having a major protocol violation during the intervention period. We will consider the following violations of the protocol to be major:

1) Patients not receiving the allocated intervention for two days despite having delirium at these days.

2) Patients receiving the intervention for two days despite fulfilling pausing criteria (two consecutive measurements of delirium free scores. If a score is not documented in source data we will consider the patient delirium free unless a core on either side (eq. +/- 12h) is positive).
3) Patients withdrawing or withdrawn from the allocated intervention despite having delirium. This includes patients discontinued from the trial by the choice of the patient or the clinician for other reasons than SARs or SUSARs.
4) Patients receiving other antipsychotics during their ICU admittance
5) Patients receiving open label haloperidol during ICU admittance

The primary analyses will be adjusted for the stratification variables being site and type of delirium at randomisation (hypoactive or hyperactive). Secondary analysis will be adjusted for the stratification variables and for other known prognostic co-variates:

1) Age
2) SMS score
3) Malignancy
4) Type of admission

To obtain maximal statistical power the primary outcome will be compared between treatment groups using a likelihood ratio test building on a logistic model for mortality and a linear regression for days alive outside hospital within 90 days for patient who are discharged alive within 90 days. Both models will be adjusted for stratification variables as described above. The likelihood ratio test will produce a single p-value. The size of the treatment effect will be quantified using raw means in the two groups along with confidence intervals for each mean and for the difference derived from the likelihood function underpinning the likelihood ratio test.

As a robustness check a linear regression including stratification variables will also be conducted, but power is expected to be lower because of the non-normality of the outcome variable.

Secondary outcomes no. 1, 4 and 6 will be analysed using the same methods as the primary outcome. Secondary outcomes no. 2 will be analysed using a Poisson regression. Secondary outcomes no. 3 and 5 will be analysed using logistic regressions. Finally, secondary outcome no. 7 will be analysed using a linear regression. All analyses of secondary outcomes will be adjusted for the covariates as described in the previous section.

The above mentioned analyses will be repeated for subgroups defined by stratification variables and other important risk factors:

1) Sites
2) Delirium type
3) Malignancy
4) Age (> 69 year, < 69years)
5) Sex
6) One or more risk factors for delirium or not
7) SMS score (> 25, < 25)

11.2.1 Significance

A two-sided P-value of less than 0.05 or a 95% confidence interval not 0 for the primary outcome will be considered statistically significant. The secondary outcomes will be given with 99% and 95% confidence intervals, corresponding to Bonferroni adjustment and no adjustment of significance for statistical multiplicity. P-values will also be provided, but 99% confidence intervals not including 1 (for RR) or 0 (for MD) will be considered as definitely statistically significant, while 95% confidence intervals not including 1 (for RR) or 0 (for MD) will be considered only possibly statistically significant.

11.2.2 Interim analysis

Interim analyses will be conducted after patient no. 500 has been followed for 90 days. Interim analyses of our primary outcome and number of patients with one or more SARs will be conducted.

The independent Data Monitoring and Safety Committee (DMSC) will recommend pausing or stopping the trial if group-difference in the primary outcome measure or mortality, SARs or SUSARs are found at the interim analyses with statistical significance levels adjusted according to the LanDeMets group sequential monitoring boundaries based on O'Brien Fleming alfa-spending function [70]. If an analysis of the interim data from 500 patients fulfils the LanDeMets stopping criterion the inclusion of further patients will be paused and an analysis including patients randomised during the analysis period will be performed. If this second analysis also fulfils the LanDeMets stopping criterion according to the group sequential monitoring boundaries the DMSC will recommend stopping the trial [71]. Furthermore, the DMSC can recommend pausing or stopping the trial if continued conduct of the trial clearly compromises patient safety. However, stopping for futility to show an intervention effect of 31% RRR in mortality or an 8% difference in means of 'days alive outside hospital' will not be

an option as intervention effects less than 31% RRR of all-cause mortality or 8% difference in means of 'days alive outside hospital' may be clinically relevant as well.
Further details are specified in appendix 4 'Charter for the independent Data Monitoring and Safety Committee (DMSC) of the AID-ICU trial'.

11.2.3 Early stopping criteria

See previous section.

11.2.4 Accountability procedure for missing data/population for analysis

If less than 5% of data are missing on any primary or secondary outcome, a complete case analysis without imputation of missing values will be performed. If missing data are more than 5%, a blinded statistician will assess whether data are 'missing completely at random' (MCAR criterion) based on a rational assessment of the pattern of missing data [72]. Little's test will be used if doubt remain [73]. If it is concluded that data are not 'missing completely at random', multiple imputation using chained equations will be performed by creating ten input data sets under the assumption that the data are missing data at random (MAR criterion) [74, 75]. We will use outcomes and the most important baseline characteristics in the multiple imputation. The exact variables to be used to estimate the missing values will be outlined in the detailed statistical analysis plan. If multiple imputation is used, then the primary result of the trial will be based on these data. The unadjusted, non-imputed analysis will also be made available. If multiple imputation is used, we will use a best-worst worst-best case scenario as a sensitivity analysis to assess the potential impact of any pattern of missingness including that the data are missing not at random (MNAR criterion) for the trial results. In the 'best-worst-case' scenario it is assumed that all patients lost to follow-up in the experimental group have had a beneficial outcome (e.g. have survived, had no serious adverse reactions etc.); and all those with missing outcomes in the control group have had a harmful outcome (e.g. have not survived; have had a serious adverse reaction etc.). Conversely, in the 'worst-best-case' scenario, it is assumed that all patients who were lost to follow up in the experimental group have had a harmful outcome; and that all those lost to follow-up in the control group have had a beneficial outcome. When continuous outcomes are used, a 'beneficial outcome' will be defined as the group mean plus two standard deviations (SD) of the group mean or highest possible value whichever is smallest, and a 'harmful outcome' will be defined as the group mean minus two SD of the group mean or lowest possible value whichever is highest.

12 Quality control and quality assurance

The coordinating investigator will be responsible for organizing the trial sites including education of local investigators, research nurses, and other trial site personnel before the initiation of the trial. This education will be continuously documented in a site file and two annual investigator meetings will be planned.

After initiation, trial site investigators will be responsible for all trial-related procedures at their site, including education of staff in trial-related procedures, recruitment and follow-up of patients and entry of data. Clinical staff at the trial sites will be responsible for the treatment of trial patients.

12.1 Monitoring of the intervention group

The trial will be externally monitored following a monitoring plan developed in collaboration with the GCP Unit in Copenhagen, which will coordinate the monitoring done by local GCP units and/or monitors in all Danish regions and participating countries. The coordinating investigator or her delegates will do a centralised day-to-day monitoring of the eCRF.

13 Legal and organisational aspects

13.1 Finance

13.1.1 Trial funding

The AID-ICU trial is funded by the Innovation Fund Denmark (4108-00011B) with 5,900,000 kr. and The Regional Medicines foundation with 1,125,000 kr. and Zealand University Hospital who has have given their consent to cover additional costs not covered by external funding (no specified amount). Other funding will be sought. The funding sources will have no influence on trial design, trial conduct, data handling, data analysis or publication.

13.1.2 Compensation

Trial sites will be given DKR 1500 (200 EUR) in case money for each completed patient follow-up at day 90 to compensate for the increased workload.

13.2 Insurance

In Denmark, the Patient Insurance Association insures all trial participants. Patient insurance will be ensured before initiating the trial in each participating countries. Costs for insurance will be sought financed by funding.

13.3 Plan for publication, authorship and dissemination

13.3.1 Publication and authorship

The trial will be registered on www.clinicaltrials.gov and EudraCT. The final protocol will be published as a design and rationale paper including the plan for analyses. Upon trial completion the main manuscript with trial results whether positive, negative or neutral will be submitted for a peer-reviewed publication, to one of the major international clinical journals. Furthermore the results will be published at the CRIC home page (www.cric.nu).

The listing of authors will be as follows: N. Andersen-Ranberg will be first and corresponding author, L. Musaeus Poulsen the second, A. Perner the third, J. Wetterslev the fourth, S. Estrup the fifth and the next authors will be the national investigators according to the number of included patients per country, then the trial statistician and trial site investigators dependent on the number of included patients per site. O. Mathiesen will be the last author.

The steering committee will grant authorship depending on personal input according to the Vancouver definitions. If a trial site investigator is to gain authorship, the site has to include 25 patients or more.

The DMSC and investigators not qualifying for authorship will be acknowledged with their names under the "AID-ICU Trial investigators' in an *appendix* to the final manuscript.

Funding sources will have no influence on data handling or analyses or writing of the manuscript.

13.4 Spin-off projects

A statistical analysis on health costs associated with delirium treatment will be performed by the Danish Institute for Local and Regional Government Research (VIVE former KORA). Other spin-off projects will be encouraged and conducted when approved by the steering committee. Presently no spin-off projects have been developed.

13.5 Intellectual property rights

Sponsor is L.M. Poulsen. Therefore, no contract on intellectual property rights is indicated. The initiative for the AID-ICU trial has been taken by L.M. Poulsen, O. Mathiesen and A. Perner and by doctors at multiple ICUs, none of whom have affiliations to institutions that may have economic interests in the trial results. Contracts between national investigators and Sponsor and between site investigators and sponsor will be signed before conduct of the trial.

13.6 Organisational framework

The trial is part of the AID-ICU research programme and Centre for Research in Intensive Care (CRIC).

13.7 Trial timeline

September 2017: Approval of protocol by co-authors

September – December 2017: Governance approval applications, education of trial sites, other preparations.

February-march of 2018: First Danish patient enrolled

September 2018: Commencement of inclusion in other countries

March 2020: Last patient enrolled

July 2020: 90 day follow-up completed

August 2020: Data analysis and submission for publication.

March 2021: One year follow-up completed

14 Appendix

Appendix 1: Research Programme Organisation
Appendix 2: Definitions
Appendix 3: Summary of Product Characteristics
Appendix 4: Charter for the independent Data Monitoring and Safety Committee
Appendix 5: Informed consent in Denmark
Appendix 6: SMS Score
Appendix 7: Power estimations
Appendix 8: CAM-ICU screening tool
Appendix 9: ICDSC screening tool
Appendix 10: International Committee of Medical Journal Editors (ICMJE) form for potential conflict of interest
Appendix 11: Preliminary results – Pharmacological interventions for delirium in intensive care patients: an overview of reviews.

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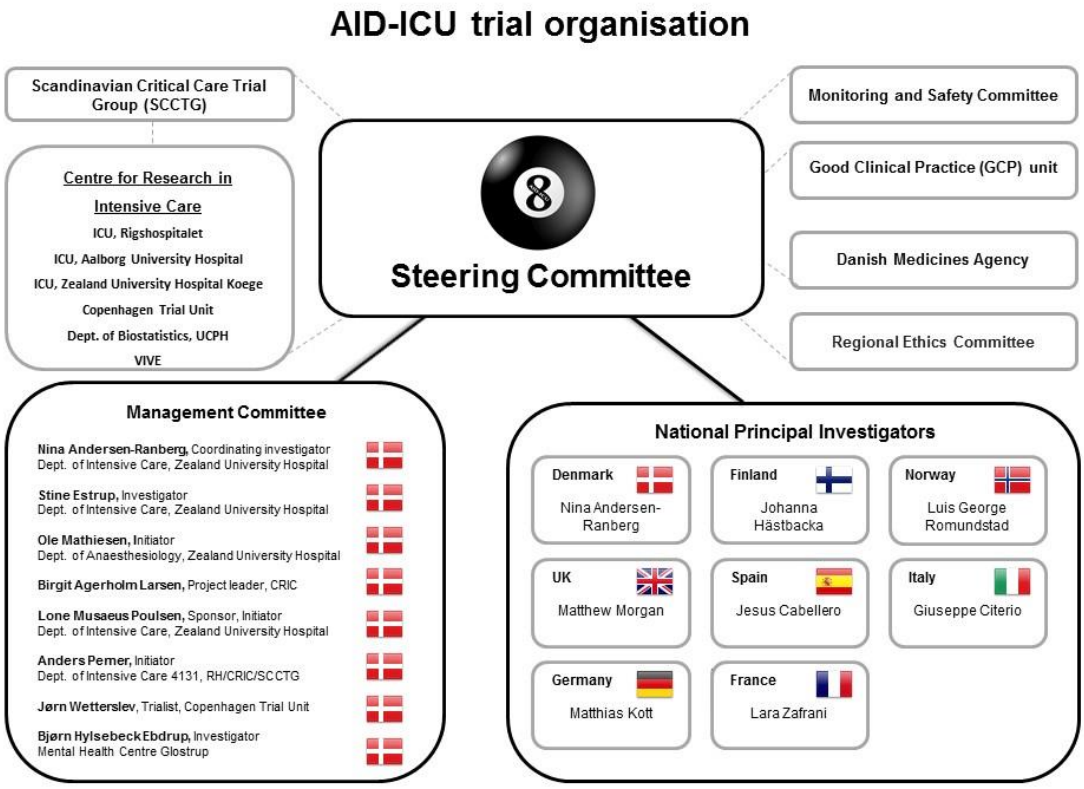
Appendix 1. Trial Organisation



Appendix 2. Definitions

Definition of stratification variables

Site: all participating intensive care units (ICUs) will be assigned a number identifying the department.

Type of delirium at randomisation: Choose between hypo- or hyperactive delirium subtype. This should reflect how the patient is clinically described at the time of randomisation.

- Hypoactive: if the patient is described as hypoactive, and is positive for delirium. Lying still with open eyes and no clear contact (GCS > 7 or RLS < 4)
- Hyperactive: If the patient is described hyperactive and is positive for delirium. Agitated and non-cooperative, pulling tubes and catheters.

Definition of inclusion criteria

Acute admission to the ICU: a non-planned admission. This does not include planned recovery after surgery or similar planned admissions. ICU admission does not include admissions to semi intensive care, intermediate intensive care or similar beds.

Age: the age of the patient in whole years at the time of randomisation. The age will be calculated from date of birth.

Delirium assessment: Delirium diagnosed by a validated screening tool as either CAM-ICU or ICDSC. Delirium assessment will be performed twice daily, morning and evening. To diagnose a patient with delirium the patient needs to be non-comatose. Coma is defined by RASS -4 to -5, Ramsey sedation score 4-6, MAAS score 1-0, GCS < 8 or RLS > 3. Further, RASS -3 may be considered as coma if this is the judgement of the treating physician. If a patient's coma is considered to be related to administration of sedative agents, an effort should be made to reduce or terminate the sedative treatment, according to the clinician's discretion. See also 6.7.1 'Special Circumstances: Comatose patients' in the protocol. Common to all delirium assessment tools are the assessment of a change in mental status (acute or fluctuating), inattention and alteration in level of consciousness. The following assessment tools are allowed; CAM-ICU and ICDSC see appendix 8 and 9.

Definition of exclusion criteria

Contraindications to haloperidol:

- Any history of intolerance to haloperidol or additives
- Known Parkinson disease or other extrapyramidal symptoms
- Known QTc prolongation
- History of tardive dyskinesia
- Comatose patients (non pharmacological). Coma is defined by the following scales of level of consciousness: RASS -4 to -5, Ramsey sedation score 4-6, MAAS 1-0, GCS < 8, RLS > 3, SAS 1-2. Further, RASS -3 may be considered as coma if this is the judgement of the treating physician.
- Previous ventricular arrhythmia or torsades de pointes
- Uncorrected hypokalaemia: A Potassium level needing action judged by clinician. Only if not corrected.

Habitual antipsychotic medication: Daily intake or prolonged release medication (any form) of any antipsychotic with the ATC code N05A, which includes the following drug

Typical antipsychotics	Atypical antipsychotics
Chlorprothixen	Amisulprid
Flupentixol	Aripiprazol
Haloperidol	Asenapin
Levomepromazin	Clozapin
Loxapin	Lurasidon
Melperon	Olanzapin
Perfenazin	Paliperidon
Periciazin	Quetiapin
Pimozid	Risperidon
Prochlorperazin	Sertindol
Zuclopenthixol	Ziprasidon
Pipamperon	
Sulpirid	

Treatment with antipsychotics in the ICU prior to inclusion: If the patient has been treated with antipsychotics (above mentioned) in the ICU before inclusion, the patient cannot be included in the trial. Antipsychotic treatment (not habitual) in the general ward (e.g. due to

delirium) prior to ICU admittance is accepted. However, the antipsychotic treatment should be discontinued when the patient is admitted to the ICU.

Permanently incompetent patient is a patient who permanently is unable to make decisions about his/her affairs (e.g. dementia, mental retardation). Patients may or may not have a legal guardian. The attending physician makes this assessment.

Delirium assessment non applicable:
Comatose patients are not applicable for delirium assessment. Coma is defined by the following scales of level of consciousness: RASS -4 to -5, Ramsey sedation score 4-6, MAAS 1-0, GCS < 8, RLS > 3, SAS 1-2. Further, RASS -3 may be considered as coma if this is the judgement of the treating physician. If a patient's coma is considered to be related to administration of sedative agents, an effort should be made to reduce or terminate the sedative treatment, according to the clinician's discretion. See also 6.7.1 'Special Circumstances: Comatose patients' in the protocol. Language barriers include foreign language where delirium assessment cannot be confidently performed by the site staff. Patients who are deaf, blind or aphasic are also excluded.

Withdrawal from active therapy or brain death: patients where withdrawal or brain death is documented in the patient charts.

Known pregnancy: fertile women with positive urine human chorionic gonadotropin (hCG) or plasma-hCG

Consent not obtainable according to national regulations: patients where the clinician or investigator is unable to obtain necessary consent before inclusion of the patient according to the national regulations

Patients under involuntary hospitalization (coercive measures) by regulatory authorities.

Alcohol induced delirium/delirium tremens (ICD10: F10.4x): Delirium caused by withdrawal of alcohol after persistent use of the substance. The withdrawal may be complicated by convulsions.

Definition of baseline variables

- Sex: the genotypic sex of the patient
- Age: defined in inclusion criteria
- Date of admission to hospital: the date of admission to the first hospital the patient was admitted to during the current hospital admission
- Date and time of admission to the ICU: the date of admission to the first ICU the patient was admitted to during the current hospital admission
- Elective surgery: surgery during current hospital admission scheduled 24 hours or latter in advance
- Emergency surgery: surgery during current hospital admission that was added to the operating room scheduled 24 hours or less prior to surgery
- Recent traumatic brain injury: when an external mechanical force causes permanent or temporary brain dysfunction within the last 6 months.
- Recent stroke: Ischemic or haemorrhagic stroke on CTC or MRI scan within the last 6 months.
- History of mental illness: Mental illness is defined as schizophrenia (or other psychotic disorder) or major affective disorders (ICD10: F2x or F3x). The diagnosis will be verified by an established (previous or current) diagnosis, and/or previous or current treatment with psychotropic medication (antipsychotics; antidepressants or mood stabilizers)
- History of neurodegenerative disease: Neurodegenerative disease is defined by an established diagnosis of dementia or Parkinson's disease (ICD10: F02-F04; DG20), and/or previous or current treatment with psychotropic medication (acetylcholinesterase inhibitors, dopaminagonists, or levodopa)
- Previous haloperidol treatment: Yes, if the patient during the current hospitalization has received one or more doses of oral or IV haloperidol, before admittance to the ICU
- Smoking: Yes, if the patient smokes every day.
- Alcohol abuse: Yes, if the patient drinks more than 3 units of alcohol per day. (1 unit is defined as 12g of alcohol)
- Substance abuse: Yes, if the patient has a daily use of morphine, benzodiazepines or barbiturates not prescribed by a physician. Or any other use of illegal substances.

- Benzodiazepine use: Yes, if the patient is being treated with benzodiazepines (N05BA) (N05CD08) at admission or before admission to ICU, such as Diazepam, Oxazepam, Lorazepam, Bromazepam, Cloxazolam and Midazolam.

Coexisting illness must have been present in the past medical history prior to ICU admission and are defined as follows:

- Metastatic cancer: proven metastasis by surgery, CT scan or any other method
- Haematological malignancy includes any of the following:
    - Leukemia: Acute lymphoblastic leukemia (ALL), acute myelogenous leukemia (AML), chronic myelogenous leukemia (CML), chronic lymphocytic leukemia (CLL).
    - Lymphoma: Hodgkin's disease, Non-Hodgkin lymphoma (e.g. small lymphocytic lymphoma (SLL), diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), mantle cell lymphoma (MCL),
    - hairy cell leukemia (HCL), marginal zone lymphoma (MZL), Burkitt's lymphoma (BL), post-transplant lymphoproliferative disorder (PTLD), T-cell prolymphocytic leukemia (T-PLL), B-cell prolymphocytic leukemia (B-PLL), Waldenström's macroglobulinemia, other NK- or T-cell lymphomas
    - Multiple myeloma/plasma cell myeloma
- Malignancy includes metastatic cancer and hematologic malignancy (defined above)

The simplified mortality score (appendix 6) is based on 7 variables obtained at randomisation of a patient in the trial. The variables include:

- Age: defined in inclusion criteria
- Lowest systolic blood pressure: Lowest systolic blood pressure at randomisation or 24h prior to randomisation
- Acute surgical admission: surgery during current hospital admission that was added to the operating room schedule 24 hours or less prior to randomisation.
- Hematologic malignancy or metastatic cancer: Defined in baseline variables. At the time of randomisation.
- Vasopressors/inotropes: continuous infusion of vasopressor or inotrope (norepinephrine, epinephrine, phenylephrine, vasopressin analogues, dopamine, dobutamin, milirinone or levosemindan) within the last 24h prior to randomisation.

- Respiratory support: invasive or non-invasive mechanical ventilation including continuous mask CPAP or CPAP via tracheostomy within the last 24h prior to randomisation. Intermittent CPAP is NOT considered as respiratory support.
- Renal replacement therapy: acute or chronic intermittent or continuous renal replacement therapy within the last 24h prior to randomisation.

Definition of daily collected variables:

Mechanical ventilation: invasive and non-invasive mechanical ventilation including continuous mask CPAP or CPAP via tracheostomy. Intermittent CPAP is NOT mechanical ventilation.

Coma: Coma is defined by a RASS -4 to -5 or Ramsey sedation score 4-6, MAAS score 1-0, GCS < 8, RLS > 3. Further, RASS -3 may be considered as coma if this is the judgement of the treating physician.

Delirium assessment: result from delirium assessment by either CAM-ICU or ICDSC (Appendix 8 and 9) morning and evening. Yes, if positive in CAM-ICU or a score ≥ 4 in ICDSC.

Motor subtype: Hypo- or hyperactive are defined below:
Hypoactive: if the patient is described as hypoactive, and is positive for delirium. Lying still with open eyes and no clear contact (GCS > 7 or RLS < 4)
Hyperactive: If the patient is described hyperactive and is positive for delirium. Agitated and non-cooperative, pulling tubes and catheters.
At delirium assessment the clinician/nurse should decide if the patients delirium is hypo- or hyperactive. Mixed subtype is diagnosed over time when a patient exhibit changing delirium subtypes.

Delivery of trial medication: confirmation of administration of the trial drug morning, midday and evening.

Additional trial medication: If the patient has received additional as needed doses of haloperidol/placebo. If yes, the total daily dose of trial medication should be registered.

Use of escape protocol: Only defined as escape if the medication has been used to treat uncontrollable delirium (e.g. agitation, insomnia). Administration of these agents for other

purposes should not be registered as escape medication. Escape medication should be acknowledged as administration of these agents (propofol, α2 agonist, benzodiazepines) in a 'as needed' formula, bolus or increased infusion rate of ongoing infusions of these agents.

If the patient has received escape medication. If yes, the agent used for escape should be registered.

- Propofol sedation: If the patient has received propofol sedation at any time during the day to manage their delirium/agitation.
- Benzodiazepines: If the patient has received any kind of benzodiazepines during the day to manage their delirium/agitation.
- α2 agonist infusion: If the patient has received dexmedetomidine infusion during the day to manage their delirium/agitation.

Definition of outcome measures

Primary outcome:

Days alive out of the hospital within 90 days post-randomisation, includes two measurements:

- 90 day mortality: death from any cause within 90 days post-randomisation.
- Days out of hospital: total number of days out of the hospital within 90 days post-randomisation

Secondary outcomes:

Days alive without delirium or coma: Total number of days without delirium (negative CAM-ICU and ICDSC < 4) and coma (defined above) in the ICU.

Serious adverse reactions: total number of serious adverse reactions and number of serious adverse reactions per patient in the ICU. Serious adverse reactions are defined below.

Usage of escape medicine: Total number of days receiving 1 or more escape medications per patient.

Number of days alive without mechanical ventilation: Mechanical ventilation is defined in baseline variables. Total number of days alive without mechanical ventilation within 90 days post-randomisation.

1-year mortality: landmark mortality 1 year post-randomisation.

Definition of Serious Adverse Reactions

A serious adverse reaction (SAR) is defined as any adverse reaction that results in death, is life threatening, requires hospitalization or prolongation of existing hospitalization, or results in persistent or significant disability or incapacity.

Patients will be monitored for onset of SARs occurring between the first dose of trial medication and until discharge from the ICU. If a patient is withdrawn from the trial intervention, SARs will be recorded for 24 hours after the last dose of trial medication or discharge from ICU. If the patient is readmitted to the ICU and trial intervention is reintroduced, data collection for SARs will be resumed. If a patient experiences SAR the patient will be withdrawn from the trial intervention but data collection and follow-up will be continued (see section 4.3.2)

SARs will be defined as follows:

Anaphylactic reactions defined as urticaria and at least one of the following

- Worsened circulation (>20% decrease in blood pressure or >20% increase in vasopressor dose)
- Increased airway resistance (>20% increase in the peak pressure on the ventilation)
- Clinical stridor or bronchospasm
- Subsequent treatment with bronchodilators

Agranulocytosis is defined as any new drop in granulocytes to $< 0.5 \times 10^9$/l.

Pancytopenia is defined as any new drop in red blood cells (as severe anaemia, b-Hgb < 4.3mM (70g/dL), white blood cells ($< 0.5 \times 10^9$/l) and platelets ($<20 \times 10^9$/l)

Ventricular arrhythmia is defined as any first onset of ventricular arrhythmia (except PVCs) seen on ECG or continuous cardiac monitoring.

Extrapyramidal symptoms (EPS) include dystonia (continuous spasm and muscle contractions), akathisia (motor restlessness), parkinsonism (characteristic symptoms such as rigidity, bradykinesia and tremor). Mild forms of tremor or akathisia are NOT considered a SAR.

Tardive dyskinesia is defined as rhythmical involuntary movements of tongue, face, mouth or jaw.

Malignant neuroleptic syndrome (NMS): Syndrome characterized by hyperpyrexia, muscle rigidity, catatonia, autonomic instability (irregular pulse or blood pressure, tachycardia, sweating, cardiac dysrhythmias).

Acute hepatic failure is defined as severe hepatic failure as judged by the treating doctor or the investigator.

Adverse reactions not registered

QT-prolongation is not considered dangerous as an isolated event only if it leads to ventricular arrhythmia e.g. torsades de pointes, which will be registered as a SAR. Since all patients in the ICU are under continuous cardiac monitoring any case of ventricular arrhythmia predisposed by QT prolongation will be treated immediately.

Thrombocytopenia will not be registered as a serious adverse reaction (SAR) since it is a frequent condition among critically ill patients.

Leukopenia will not be registered. Reduced white blood cell counts are frequent among ICU patients and can be associated with many different systemic or haematological disorders in critically ill patients.

Urinary retention will not be registered since this is common in critically patients and are routinely monitored and treated for this condition. Furthermore, the majority of the ICU patients have a urinary catheter minimizing the risk of urinary retention.

Increased plasma levels of bilirubin, (jaundice) and liver enzymes (hepatocellular injury) is not registered as they in themselves are not considered serious conditions. The potential serious consequence hepatic failure will be registered daily as a SAR.

Hyponatremia will not be registered as electrolyte disturbances as they are frequent among ICU patients. These conditions are monitored and treated daily in all ICU patients.

The following possible adverse reactions will not be registered as SARs as they are not considered serious conditions:

- Weight changes
- Supraventricular tachycardia
- Sleep disorders, depression, dizziness, headaches, blurred vision, confusion, restlessness
- Constipation, dry mouth, nausea, vomiting, increased salivation, anorexia, dyspepsia, diarrhoea
- Rash, exanthema, photosensitivity, pruritus, diaphoresis, vasculitis, dermatitis, loss of hair
- Hyperprolactinaemia, SIADH
- Hypoglycaemia, hyperglycaemia,
- Orthostatic hypotension
- Gait disturbances
- Increased or lowered body temperature
- Oedema
- Erectile dysfunction, breast disorders, gynecomastia, menstrual irregularities.
- Cataracts, retinopathy

Appendix 3. The Danish summary of product characteristics

6. July 2015

SUMMARY OF PRODUCT CHARACTERISICS
for
Haloperidol/Serenase, injection

0. D.SP.NR.
01907

1. NAME OF THE MEDICINAL PRODUCT
Haloperidol/Serenase

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
1 ml contains 5 mg haloperidol.
All excipients are listed in section 6.1.

3. PHARMACEUTICAL FORM
Solution for injection.
Clear, colorless solution, free of visual particles.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications
Psychotic conditions except depressions.

4.2 Posology and method of administration
Haloperidol injection solution should preferably be administrated intramuscularly, but when this is not appropriate intravenous injection may be used.

The below mentioned doses are only average doses; Dosage should be adjusted to the individual patient's response. This usually involves dose escalation in the acute phase and gradual reduction in the maintenance phase to estimate the minimum dose that is clinically effective. Higher doses should only be administered to patients who are non-responders to lower doses.

Adults:
The maximum daily dose is 20 mg. Doses of 5 mg should be administered intramuscularly and may be repeated every hour, until satisfactory clinical response, or to a maximum of 20 mg daily.

Paediatric population:
The safety and efficacy of haloperidol in the paediatric population is not clear.

4.3 Contraindications

- Hypersensitivity to haloperidol, or to any of the excipients in section 6.1.
- Comatose states
- CNS depression caused by alcohol, or other drugs with CNS depression potential.
- Parkinsonism

- Extrapyramidal diseases
- Clinically significant cardiac disorders
- Prolongation of
- Previous ventricular arrhythmia
- Torsade de pointes
- Uncorrected hypokalaemia
- Concomitant administration with other QT-prolonging drugs.

4.4 Special warnings and precautions for use

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of seventeen placebo- controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10 week controlled trial, the rate of death in drug- treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death varied, most of the deaths appeared to be either cardiovascular (e.g. heart failure, sudden death) or infectious (e.g. pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear.

Patients with the following disorders/conditions should be closely monitored during treatment:

- Cardiovascular conditions, bradycardia, hypokalaemia or a family history of QT-prolongation, due to the risk of further prolongation of the QT-syndrome, which may increase risk of developing torsade de pointes, tachycardia and sudden death. Very rare reports of QT-prolongation and/or ventricular arrhythmias, in addition to rare reports of sudden death, have been reported with haloperidol. They may occur more frequently with high doses and in predisposed patients.
- The risk of QT-prolongation and/or ventricular arrhythmias may be increased with parenteral administration, particularly intravenous administration.
- Continuous ECG monitoring should be performed for QT-prolongation and for serious cardiac dysrhythmias if haloperidol is administered intravenously.
- Baseline ECG is recommended prior to treatment in all patients, (see section 4.3).
- During therapy, the need for ECG monitoring should be assessed on an individual basis. During therapy, the dose should be reduced if QT is prolonged, and haloperidol should be discontinued if the QT-interval exceeds 500ms.
- Periodic electrolyte monitoring is recommended.
- Renal failure
- Pheochromocytoma

- Epilepsy and in conditions predisposing to convulsions (e.g. alcohol withdrawal and brain damage). Due to the risk of reducing seizure threshold and triggering convulsions.
- In schizophrenia, the response to antipsychotic drug treatment may be delayed. Also, if drugs are withdrawn, recurrence of symptoms may not become apparent for several weeks or months.

Tachycardia and hypotension have been observed in some patients.

When depression and psychosis occur at the same time, treatment should be combined with antidepressants (see section 4.5. for TCA).

Gradual withdrawal is advisable to avoid acute withdrawal symptoms including nausea, vomiting and insomnia.

Concomitant treatment with other antipsychotics should be avoided.

Neuroleptic malignant syndrome

In common with other antipsychotic drugs, haloperidol has been associated with neuroleptic malignant syndrome: a rare idiosyncratic response characterised by hyperthermia, generalised muscle rigidity, autonomic instability, altered consciousness and increased levels of creatine phosphokinase. Hyperthermia is often an early sign of this syndrome. If the described symptoms occur haloperidol should be withdrawn immediately and appropriate supportive therapy and careful monitoring instituted.

Tardive dyskinesia

As with all antipsychotic agents, tardive dyskinesia may appear in some patients on long-term therapy or after drug discontinuation. The syndrome is mainly characterised by rhythmic involuntary movements of the tongue, face, mouth or jaw. The manifestations may be permanent in some patients. The syndrome may be masked when treatment is reinstituted, when the dosage is increased or when a switch is made to a different antipsychotic drug. Treatment should be discontinued as soon as possible.

Extrapyramidal symptom

In common with all neuroleptics, extrapyramidal symptoms may occur, e.g. tremor, rigidity, hypersalivation, bradykinesia, akathisia and acute dystonia.
Antiparkinson drugs of the anticholinergic type may be prescribed as required, but should not be prescribed routinely as a preventive measure. If concomitant antiparkinson medication is required, it may have to be continued after stopping haloperidol if its excretion is faster than that of haloperidol in order to avoid the development or aggravation of extrapyramidal symptoms. The physician should keep in mind the possible increase in intraocular pressure when anticholinergic drugs, including antiparkinson agents, are administered concomitantly with haloperidol.

Hepatobiliary concerns

As haloperidol is metabolised by the liver, caution is advised in patients with liver disease. Isolated cases of liver function abnormalities or hepatitis, most often cholestatic, have been reported.

Endocrine system concerns

Thyroxin may facilitate haloperidol toxicity. Antipsychotic therapy in patients with hyperthyroidism should be used only with great caution and must always be accompanied by therapy to achieve a euthyroid state.

Venous thromboembolism
Cases of venous thromboembolism (VTE) have been reported with antipsychotic drugs. Since patients treated with antipsychotics often present with acquired risk factors for VTE, all possible risk factors for VTE should be identified before and during treatment with haloperidol and preventive measures undertaken.

Increased mortality in elderly with dementia
Data from two large observational studies have shown an increased risk of death among elderly patients with dementia treated with antipsychotics, compared with elderly with dementia not treated with antipsychotics. There is not sufficient data to give an estimate of the magnitude of the increased risk and the causality of the increased mortality is not known.

Haloperidol is not licensed for the treatment of dementia-related behavioural disturbances.

Pediatric population
Data regarding safety in the pediatric population show a risk of extrapyramidal symptoms, including tardive dyskinesia and sedation. There is no long-term safety data available.

Hormonal effects of antipsychotic neuroleptic drugs include hyperprolactinaemia, which may cause galactorrhea, gynecomastia and oligo- or amenorrhea. Very rare cases of hypoglycaemia and of Syndrome of Inappropriate ADH Secretion have been reported.

4.5 Interactions with other medicinal products and other forms of interaction.

There is a potential risk of interaction with concomitant use of metabolic inhibitors, drugs known to prolong QT-interval or cause electrolyte disturbances.

Haloperidol is metabolised by several routes, including glucuronidation and the cytochrome P450 enzyme system (particularly CYP 3A4 or CYP 2D6). Inhibition of these routes of metabolism by another drug or a decrease in CYP 2D6 enzyme activity may result in increased haloperidol concentrations and an increased risk of adverse reactions, including QT-prolongation.

In pharmacokinetic studies, mild to moderately increased haloperidol concentrations have been reported when haloperidol was given concomitantly with drugs characterised as substrates or inhibitors of CYP 3A4 or CYP 2D6 isozymes, such as, venlafaxine, alprazolam, fluvoxamine, fluoxetine, sertraline, chlorpromazine, quinidine, itraconazol and promethazine. A decrease in CYP 2D6 enzyme activity may result in increased haloperidol concentrations.
Increased haloperidol concentrations may increase the risk of QT-interval prolongation and it may be necessary to reduce the haloperidol dosage.
Increases in QTc have been observed when haloperidol was given with a combination of the metabolic inhibitors ketoconazole (400mg/day) and paroxetine (20mg/day).

Caution should be applied if haloperidol is used in combination with drugs known to cause electrolyte imbalances.

Effect of other drugs on haloperidol
When prolonged treatment with enzyme-inducing drugs such as carbamazepine, phenobarbital, rifampicin is added to haloperidol therapy, this results in a significant reduction of haloperidol plasma levels. Therefore, during combination treatment, the haloperidol dose should be adjusted, when necessary. After stopping such drugs, it may be necessary to reduce the dosage of haloperidol.

Sodium valproate, a drug known to inhibit glucorinidation, does not affect haloperidol plasma concentrations.

Effects of haloperidol on other drugs
In common with all neuroleptics, haloperidol can increase the central nervous system depression produced by other CNS-depressing drugs, including alcohol, hypnotics, sedatives or potent analgesics (see section 4.4).

Haloperidol may antagonise the action of adrenaline and other sympathomimetic agents and reverse the blood-pressure-lowering effects of adrenergic-blocking agents such as e.g. guanethidine.

Haloperidol may impair the antiparkinsonistic effects of levodopa.

Haloperidol is an inhibitor of CYP 2D6. Haloperidol inhibits the metabolism of tricyclic antidepressants, thereby increasing plasma levels of these drugs.

Other types of interaction
Caution should be applied when concomitant use of haloperidol and drugs known to induce hypokalaemia, e.g. diuretics and laxatives.

Fluvoxamine (repeated dosage) increases plasma concentration of haloperidol, hereby increasing haloperidol's antipsychotic effect on patients with schizophrenia. Increase in plasma concentration is dose-dependent.

Concomitant treatment with orphenadrine increases plasma concentration of haloperidol, and thereby increases the risk of extrapyramidal symptoms. It may be necessary to reduce dosage of haloperidol.

Concomitant treatment with methyldopa has shown an increased CNS effect.

Concomitant use of haloperidol and lithium may increase the risk of neurotoxic adverse reaction, if such symptoms occur haloperidol should be stopped immediately.

4.6 Pregnancy and lactation

Pregnancy
Animal studies have shown harmful effects on reproduction (see section 5.3.)

Neonates exposed to antipsychotics (including haloperidol) during third trimester of pregnancy, are at risk of adverse reactions including extrapyramidal and/or withdrawal symptoms that may vary in severity and duration following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence,

respiratory distress or feeding disorder. Consequently, newborns should be monitored carefully
Haloperidol may be used during pregnancy only if the anticipated benefit for the mother outweighs the possible risks to the fetus.

In population studies, no significant increase in birth defects was found.
In isolated cases, there have been reports on birth defects following fetal exposure to haloperidol.

Lactation
Haloperidol should only be used during lactation on compelling indication.
Haloperidol is excreted in breast milk.
Extrapyramidal symptoms have been observed in breast-fed children by women treated with haloperidol.

4.7 Effects on ability to drive and use machines

No mark.
Haloperidol may, particularly with higher doses and at start of treatment, affect the ability to drive or use machines to a lesser or moderate extent.

4.8 Undesirable reactions

The safety of haloperidol was evaluated in 284 haloperidol-treated subjects who participated in 3 placebo-controlled, and in 1295 haloperidol-treated subjects who participated in sixteen double-blind active comparator-controlled clinical trials. The safety of haloperidol decanoate was evaluated in 410 subjects who participated in 3 comparator trials (one comparing haloperidol vs. fluphenazine and two comparing the decanoate formulation to the oral formulation), 9 open label trials and 1 dose response trial. Based on pooled safety data from these clinical trials, the most commonly reported (% incidence) Adverse Drug Reactions (ADRs) were: extrapyramidal disorder (34), insomnia (19), agitation (15), hyperkinesia (13), headache (12), psychotic disorder (9), depression (8), weight increases (8), orthostatic hypotension (7) and somnolence (5).
Including the above mentioned adverse reactions, the following adverse reactions have been observed from clinical trials and post-marketing experiences reported with the use of haloperidol and haloperidol Decanoate.

Frequencies displayed use the following convention:
Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).

Investigations Common Rare	 Weight gain, weight loss. Prolonged QT-interval on ECG.
Heart Uncommon Not known	 Tachycardia. Ventricular fibrillation, torsade de pointes, ventricular tachycardia. Extrasystoles

Blood and lymphatic system Very rare Not known	 Leukopenia. Agranulocytosis, neutropenia, pancytopenia, trombocytopenia.
Nervous system Very common Common Uncommon (≥1/1.000 to ‹1/100) Rare	 Ekstrapyramidal symptoms, hyperkinesia, Headache Tardiv dyskinesia, oculogyric crisis, dystonia, dyskinesia, akathisia, bradykinesia, hypokinesia, hypertonia, somnolence, masked facies, tremor, dizziness. Convulsion, parkinsonism, akinesia, cogwheel rigidity, sedation, involuntary muscle contractions. Motoric dysfunction, neuroleptic malignant syndrome, nystagmus.
Eyes Common Uncommon (≥1/1.000 to ‹1/100)	 Visual disturbance Blurred vision
Gastrointestinal Common	 Constipation, dry mouth, salivary hypersecretion, nausea, vomiting.
Kidneys and urinary tract Common	 Urinary retention.
Skin and subcutaneous tissue Common Uncommon Not known	 Rash. Photosensitivity reaction, urticaria, pruritus, hyperhidrosis. Leukocytoclastic vasculitis, exfoliative dermatitis.
Musculoskeletal and connective tissue Uncommon Rare	 Torticollis, muscle rigidity, muscle spasms, Musculoskeletal stiffness. Trismus, muscle twitching.
The endocrine system Rare Not known	 Hyperprolactinaemia. Inappropiate antidiuretic hormone secretion
Metabolism and nutrition Not known	 hypoglycaemia

Vascular disorders Common	 Orthostatic hypotension, hypotension.
Respiratory, thoracic and mediastinal disorders Uncommon Rare Not known	 Dyspnoea Bronchospasm Laryngeal oedema, laryngospasm.
General disorders and administration site condition Uncommon Not known	 Gait disturbances, hyperthermia, oedema. Sudden Death, facial oedema, hypothermia.
Immune system Uncommon Not Known	 Hypersensitivity. Anaphylactic reaction.
Hepatobilliary disorders Common Uncommon Not known	 Abnormal liver function Hepatitis, jaundice. Acute hepatic failure, cholestasis.
Pregnancy, puerperium and perinatal disorders Not known	 Neonatal drug withdrawal syndrome (see 4.6)
Reproductive system and breast disorders Common Uncommon Rare Not known	 Erectile dysfunction. Amenorrhea, dysmenorrhea, galactorrhoea, breast discomfort, breast pain. Menorrhagia, menstrual disorders, sexual dysfunction. Gynecomastia, priapism.
Psychiatric disorders Very common Common Uncommon	 Agitation, insomnia. Depression, Psychotic disorders Confusional state, decreased libido, loss of libido, restlessness

Cases of venous thromboembolism, including cases of pulmonary embolism and cases of deep vein thrombosis have been reported during treatment with antipsychotic drugs (frequency unknown).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions to:

Sundhedsstyrelsen
Axel Heides Gade 1,
DK-2300 København S.
Web: www.meldenbivirkning.dk.
E-mail: sst@sst.dk.

4.9 Overdose

Symptoms:
Increased amount of known pharmacological effects and adverse reaction. The most prominent symptoms are: severe extrapyramidal symptoms, hypotension and sedation. Hypertension may occur.

In extreme cases, the patient may appear comatose with respiratory depression and hypotension, which could be severe enough to produce a shock-like state. The risk of ventricular arrhythmias possible associated with QT-prolongation should be considered.

Treatment
There is no specific antidote to haloperidol. Treatment is mainly supportive measures. Activated charcoal may be administered.

In comatose patients a patent airway should be established. Mechanically assisted ventilation may be needed due to respiratory depression.

ECG and vital signs should be monitored until ECG is normalized. Severe arrhythmia should be treated anti-arrhythmic agents.

Hypotension and circulatory collapse should be treated by intravenous administration of fluids, plasma or concentrated albumin and vasopressors like dopamine or noradrenaline. Adrenaline should not be used, since it may cause severe hypotension with concomitant use of haloperidol.

In cases of severe extrapyramidal symptoms, appropriate parenteral antiparkinson medication should be administered.

4.10 Extradition

B

5. PHARMACOLOGICAL PROPERTIES

5.0 Therapeutic classification

ATC-code: N 05 AD 01. Psycholeptics, antipsychotics, butyrophenon.

5.1 Pharmacodynamic properties

Haloperidol is a neuroleptic belonging to the group of butyrophenones. Haloperidol is a potent central dopamine antagonist and thereby classified among the very incisive neuroleptics. Haloperidol has no antihistamine- or anticholinergic properties. Because of the central dopamine antagonism, haloperidol has a compendious effect on delusions and imaginations (possibly caused by an interaction of the mesocortic and limbic system) and activity in the basal ganglia. Haloperidol causes an effective psychomotoric sedation, which explains the effect on mania and other behavioral-motoric syndromes. The influence on the basal ganglia possibly explains the extrapyramidal symptoms (dystonia, akathisia and parkinsonism). The effect on peripheral dopamine receptors explains the effect on nausea and vomiting (through the chemoreceptor trigger zone), the gastro-intestinal relaxation and increased secretion of prolactin (through inhibition of PIF, prolactin inhibiting factor, at the anterior pituitary gland level).

5.2 Pharmacokinetic properties

Absorption

The bioavailability of the drug is 60-70% when administered orally. Haloperidol's Cmax appear within 2-6 hours after oral administration and within 20 minutes after intramuscular administration.

Distribution

92% of the drug is bound to plasma proteins. The distribution volume at steady state (Vdss) is large (7,9 l/kg). Haloperidol passes the blood-brain barrier.

Metabolization

Haloperidol is metabolized through various systems including cytochrome P450 (especially CYP3A4 and CYP 2D6) and glucoronidation.

Elimination

The average half-life in plasma (terminal elimination) is 24 hours (range 12-38 hours) after oral administration and 21 hours (range 13-36 hours) after intramuscular administration. Excretion is through feces (60%) and urine (40%). Approximately 1% of haloperidol is excreted unaffected in the urine.

Therapeutic concentrations

The proposed plasma concentration needed to reach a therapeutic response lies between 4 µg/L and a maximum of 20-25 µg/L.

5.3 Preclinical safety data

Preclinical data show no increased risk in humans based on conventional research on toxicology after repeated doses, genotoxicity and carcinogenicity. In rodents, exposure to haloperidol showed a decreased fertility and limited reproductive toxicity and embryo-toxic effects.

Haloperidol has been shown to block the cardiac hERG channel in several published in vitro studies. In a number of in vivo studies intravenous administration of haloperidol in some animal models has caused significant QTc-prolongation, at doses around 0.3 mg/kg i.v., giving Cmax pplasma levels 3 to 7 times higher than the effective human plasma concentrations of 4 to 20 ng/ml. These intravenous doses which prolonged QTc did not cause arrhythmias. In some studies, higher intravenous

doses of 1 to 5 mg/kg haloperidol i.v. caused QTc prolongation and/or ventricular arrhythmias at Cmax plasma levels 19 to 68 times higher than the effective human plasma concentrations.

6. FARMACEUTICAL PARTICULARS

6.1 List of excipients
Lactic acid
Water for Injections

6.2 Incompatibilities
Not relevant.

6.3 Shelf life
5 years.

6.4 Special precautions for storage
No specific requirements for storage.

6.5 Nature and contents of container
Ampules

6.6 Special precautions for disposal and handling
Ampules should be disposed in appropriate packaging e.g. needle container.

7. MARKETING AUTHORISATION HOLDER
Janssen-Cilag A/S
Bregnerødvej 133
3460 Birkerød

8. MARKETING AUTHORISATION NUMBER(S)
09661

9. DATE OF FIRST AUTHORISATION APPROVAL
21. July 1959

10. DATE OF REVISION OF THE TEXT
6. July 2015

Appendix 4. Charter for the independent Data Monitoring and Safety Committee (DMSC) of the AID-ICU trial.

ClinicalTrials.gov no. NCT03392376

Research ethical committee no. **SJ-646**

Zeeland University Hospital, Koege 2017

Introduction

The DMSC will constitute its own plan of monitoring and meetings. However, this charter will define the minimum of obligations and primary responsibilities of the DMSC as perceived of the steering committee (SC), its relationship with other trial components, its membership, and the purpose and timing of its meetings. The charter will also outline the procedures for ensuring confidentiality and proper communication, the statistical monitoring guidelines to be implemented by the DMSC, and an outline of the content of the open and closed reports which will be provided to the DMSC.

Primary responsibilities of the DMSC

The DMSC will be responsible for safeguarding the interests of trial participants, assessing the safety and efficacy of the interventions during the trial, and for monitoring the overall conduct of the clinical trial. The DMSC will provide recommendations about stopping or continuing the trial to the SC of the AID-ICU trial. To contribute to enhancing the integrity of the trial, the DMSC may also formulate recommendations relating to the selection/recruitment/retention of participants, their management, improving adherence to protocol-specified regimens and retention of participants, and the procedures for data management and quality control.

The DMSC will be advisory to the SC. The SC will be responsible for promptly reviewing the DMSC recommendations, to decide whether to continue or terminate the trial, and to determine whether amendments to the protocol or changes in trial conduct are required.

The DMSC may meet physically or by phone at their own discretion in order to evaluate the planned interim analyses of the AID-ICU trial. The interim analyses will be performed by an independent statistician selected by the members of the DMSC, Andreas Kryger Jensen from Biostatistical Department at Copenhagen University. The DMSC may additionally meet whenever they decide or contact each other by telephone or e-mail in order to discuss the safety for trial participants. The

sponsor has the responsibility to report the overall number of Serious Adverse Reactions (SARs) yearly to the DMSC. The DMSC can, at any time during the trial, request the distribution of events, including outcome measures and SARs according to intervention groups. Further, the DMSC can request unblinding of the interventions if suggested by the data, see section on 'closed sessions'. The recommendations of the DMSC regarding stopping, continuing or changing the design of the trial should be communicated without delay to the SC of the AID-ICU trial. As fast as possible, and no later than 48 hours, the SC has the responsibility to inform all investigators of the trial and all the sites including patients in the trial, about the recommendation of the DMSC and the SC decision hereof.

Members of the DMSC

The DMSC is an independent multidisciplinary group consisting of clinicians and a biostatistician that, collectively, has experience in the management of ICU patients and in the conduct, monitoring and analysis of randomized clinical trials.

DMSC Clinician

Hallie Prescott
Assistant Professor in Internal Medicine
Division of Pulmonary & Critical Care Medicine
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NCRC Bldg. 16, room 341E / 2800 Plymouth Rd.
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DMSC Trialist

Danny McAuley
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University Road
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United Kingdom

DMSC Biostatistician

Andreas Kryger Jensen
Assistant professor, PhD
University of Copenhagen
Section of Biostatistics
Institute of Public Health, Faculty of Health Sciences
Øster Farimagsgade 5, Building 10
1014 Copenhagen K
Denmark

Conflicts of interest

DSMC members will fill in and sign a declaration of conflicts of interests see appendix 10. DMSC membership has been restricted to individuals free of conflicts of interest. The source of these conflicts may be financial, scientific, or regulatory in nature. Thus, neither trial investigators nor individuals employed by the sponsor, nor individuals who might have regulatory responsibilities for the trial products, are members of the DMSC. The DMSC members do not own stock in the companies having products being evaluated by the AID-ICU trial.

The DMSC members will disclose to fellow members any consulting agreements or financial interests they have with the sponsor of the trial, with the contract research organisation (CRO) for the trial (if any), or with other sponsors having products that are being evaluated or having products that are competitive with those being evaluated in the trial.

The DMSC will be responsible for deciding whether these consulting agreements or financial interests materially impact their objectivity.

The DMSC members will be responsible for advising fellow members of any changes in these consulting agreements and financial interests that occur during the course of the trial. Any DMSC members who develop significant conflicts of interest during the course of the trial should resign from the DMSC.

DMSC membership is to be for the duration of the clinical trial. If any members leave the DMSC during the course of the trial, the SC will appoint the replacement(s).

Formal interim analyses meeting

One formal interim analysis meeting will be held to review data relating to treatment efficacy, patient safety, and quality of trial conduct. The three members of the DMSC will meet when 90-day follow-up data of 500 (approximately 50% of sample size estimation) patients have been obtained.

Proper communication

To enhance the integrity and credibility of the trial, procedures will be implemented to ensure the DMSC has sole access to evolving information from the clinical trial regarding comparative results of efficacy and safety data, aggregated by treatment group. An exception will be made to permit access to an independent statistician who will be responsible for serving as a liaison between the database and the DMSC.

At the same time, procedures will be implemented to ensure that proper communication is achieved between the DMSC and the trial investigators. To provide a forum for exchange of information among various parties who share responsibility for the successful conduct of the trial, a format for open sessions and closed sessions will be implemented. The intent of this format is to enable the DMSC to preserve confidentiality of the comparative efficacy results while at the same time providing opportunities for interaction between the DMSC and others who have valuable insights into trial-related issues.

Closed sessions

Sessions involving only DMSC membership who generates the closed reports (called closed sessions) will be held to allow discussion of confidential data from the clinical trial, including information about the relative efficacy and safety of interventions. In order to ensure that the DMSC will be fully informed in its primary mission of safeguarding the interest of participating patients, the DMSC will be blinded in its assessment of safety and efficacy data. However, the DMSC can request unblinding from the SC.

Closed reports will include analysis of the primary outcome measure. In addition, analyses of the secondary outcome measures and SARs will also be reported. These closed reports will be prepared by independent biostatistician being a member of the DSMC, with assistance from the trial data manager, in a manner that allow them to remain blinded.

The closed reports should provide information that is accurate, with follow-up on mortality that is complete to within two months of the date of the DMSC meeting.

Open reports

For each DMSC meeting, open reports will be provided available to all who attend the DMSC meeting. The reports will include data on recruitment and baseline characteristics, and pooled data on eligibility

violations, completeness of follow-up, and compliance. The independent statistician being a member of the DMSC will prepare these open reports in co-operation with the trial data manager.

The reports should be provided to DMSC members approximately three days prior to the date of the meeting.

Minutes of the DMSC Meetings

The DMSC will prepare minutes of their meetings. The closed minutes will describe the proceedings from all sessions of the DMSC meeting, including the listing of recommendations by the committee. Because it is possible that these minutes may contain unblinded information, it is important that they are not made available to anyone outside the DMSC.

Recommendations to the Steering Committee

After the interim analysis meetings, the DMSC will make a recommendation to the SC to continue, hold or terminate the trial.

Interim analyses will be conducted after patient no. 500 have been followed for 90 days.

The independent DMSC will recommend pausing or stopping the trial if group-difference in the primary outcome measure, SARs or SUSARs is found at the interim analyses with statistical significance levels adjusted according to the LanDeMets group sequential monitoring boundaries based on O'Brien Fleming alfa-spending function. If the recommendation is to stop the trial the DSMC will discuss and recommend on whether the final decision to stop the trial will be made after the analysis of all patients included at the time (including patients randomized after patient number 500) and whether a moratorium shall take place (setting the trial at hold) in the further inclusion of patients during these extra analyses. If further analyses of the patients included after 500 patients is recommended the rules for finally recommending stopping of the trial should obey the Lan DeMets stopping boundary.

Furthermore, the DMSC can recommend pausing or stopping the trial if continued conduct of the trial clearly compromises patient safety. However, stopping for futility to show an intervention effect of 31% RRR (or RRI) for mortality or 8% for 'days alive outside hospital' will not be an option as intervention effects less than these may be clinically relevant as well.

This recommendation will be based primarily on safety and efficacy considerations and will be guided by statistical monitoring guidelines defined in this charter and the trial protocol.

The SC is jointly responsible with the DMSC for safeguarding the interests of participating patients and for the conduct of the trial. Recommendations to amend the protocol or conduct of the trial made by the DMSC will be considered and accepted or rejected by the SC. The SC will be responsible for deciding whether to continue, hold or stop the trial based on the DMSC recommendations.

The DMSC will be notified of all changes to the trial protocol or conduct. The DMSC concurrence will be sought on all substantive recommendations or changes to the protocol or trial conduct prior to their implementation.

Statistical monitoring guidelines

The outcome parameters are defined in the statistical analyses plan in the AID-ICU trial protocol. For the two intervention groups, the DMSC will evaluate data on:

<u>The primary outcome measure</u>

Days alive out of the hospital in the 90 days after randomisation. They will also assess the two components of this: mortality and days out of the hospital within the 90 day period.

<u>The secondary outcome measures</u>

- The occurrence of SARs in the ICU
- Usage of escape medicine per patient

The DMSC will be provided with these data from the coordinating centre as:
Number of patients randomized
Number of patients randomized per intervention group
Number of patients stratified pr. stratification variable per intervention group
Number of events, according to the outcomes, in the two groups

Based on evaluations of these outcomes, the DMSC will decide if they want further data from the coordinating centre and when to perform the next analysis of the data.

For analyses, the data will be provided in one file as described below.

DMSC should yearly be informed about SARs occurring in the two groups of the trial.

The DMSC may also be asked to ensure that procedures are properly implemented to adjust trial sample size or duration of follow-up to restore power, if protocol specified event rates are inaccurate. If so, the algorithm for doing this should be clearly specified.

Conditions for transfer of data from the Coordinating Centre to the DMSC

The DMSC will be provided with a SAS file containing the data defined as follows:
Row 1 contains the names of the variables (to be defined below).
Row 2 to N (where N-1 is the number of patients having entered the trial) each contains the data of one patient.
Column 1 to p (where p is the number of variables to be defined below) each contains in row 1 the name of a variable and in the next N rows the values of this variable.

The values of the following variables should be included in the database:

1. screening_id: a number that uniquely identifies the patient

2. rand_code: The randomisation code (group 0 or 1). The DMSC is not to be informed on what intervention the groups received

3. day_90_indic: 90 day-mortality indicator (2 = censored, 1=dead, 0=alive at day 90)

4. days alive outside hospital during the 90 days observation period for each patient.

5. SAR_indic: SAR indicator (1 = one or more SARs, 0 = no SARs)

6. Number of days alive without delirium and coma in the ICU

Appendix 5. Informed consent, Denmark

In Denmark temporarily incompetent patients will be enrolled after informed consent from one physician, who is independent of the trial (first trial guardian). As soon as possible after enrolment, consent will be obtained from the patient's next of kin and a second physician (second trial guardian). The second trial guardian must be different from the first trial guardian, but also independent of the trial. Patients, who regain consciousness, will be asked for informed consent as soon as possible. The process leading to the achievement of informed consent will be in compliance with all applicable regulations. The consenting party will be provided with written and oral information about the trial so he/she is able to make an informed decision about participation in the trial. The information will be given in a separate room, and the consenting party has the right to bring a companion.
Written information and the consent form will be subjected to review and approval by the relevant ethic committees.

Lack of informed consent from the patient's next of kin

If information about the patient's next of kin is not available after inclusion the investigator will seek information from e.g. the patient's general practitioner, the police, nursing homes etc. In these situations it may take 1-2 weeks to conclude that no next of kin can be identified. If no one is identified and the patient remains incompetent the trial intervention will be discontinued. All initiatives to identify the patient's next of kin will be documented in patient files, logs or similar.

Lack of informed consent from the patient's next of kin and the patient deceases

If the patient deceases before informed consent has been obtained (due to rapid progression of critical illness or because the patient's next of kin is not yet identified) and the patient has been correctly included in the trial, collected data will be kept for analysis.

Deviation from the standard informed consent

According to the standard informed consent form from the National Ethics Committee regarding competent patients, the patient can choose not to receive information about the data collected during the trial. However, the purpose of this trial is not to generate new knowledge about the specific

patient, so we find that this question is redundant, and have omitted the question from the consent form to spare the patient from making unnecessary decisions.

Appendix 6. Simplified Mortality Score for the Intensive Care Unit (SMS-ICU)

In trial settings the variables are measured from randomisation, not admittance to the ICU. See definitions for further details appendix 2.

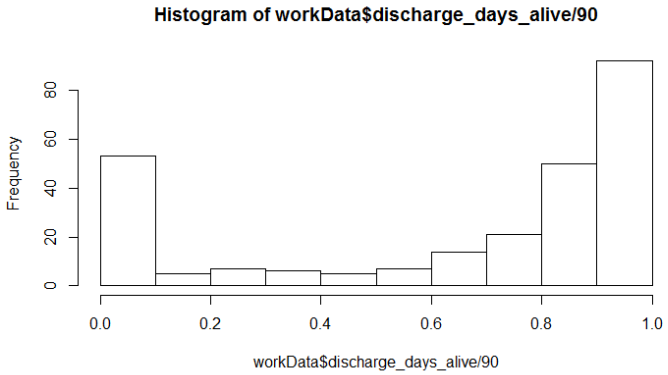
SMS-ICU	
Age	
≤ 39 years → **0**	
40-59 years → **5**	
60-79 years → **10**	
≥ 80 years → **13**	
Lowest systolic blood pressure	
≤ 49 mmHg → **6**	
50-69 mmHg → **5**	
70-89 mmHg → **3**	
≥ 90 mmHg → **0**	
Acute surgical admission	
No → **3**	Yes → **0**
Hematologic malignancy or metastatic cancer	
No → **0**	Yes → **7**
Vasopressors/inotropes	
No → **0**	Yes → **4**
Respiratory support	
No → **0**	Yes → **5**
Renal replacement therapy	
No → **0**	Yes → **4**
Total score: 0-42 points	

Total score and predicted 90-day mortality risk			
0	3.3 %	22	40.1 %
3	4.8 %	23	43.4 %
4	5.5 %	24	46.7 %
5	6.2 %	25	50.1 %
6	7.1 %	26	53.5 %
7	8.0 %	27	56.9 %
8	9.1 %	28	60.2 %
9	10.3 %	29	63.4 %
10	11.6 %	30	66.4 %
11	13.1 %	31	69.4 %
12	14.7 %	32	72.2 %
13	16.5 %	33	74.8 %
14	18.4 %	34	77.3 %
15	20.5 %	35	79.6 %
16	22.8 %	36	81.7 %
17	25.3 %	37	83.7 %
18	28.0 %	38	85.4 %
19	30.8 %	39	87.0 %
20	33.8 %	41	89.8 %
21	36.9 %	42	91.0 %
Use the worst values recorded during the first 24 hours in the ICU.			

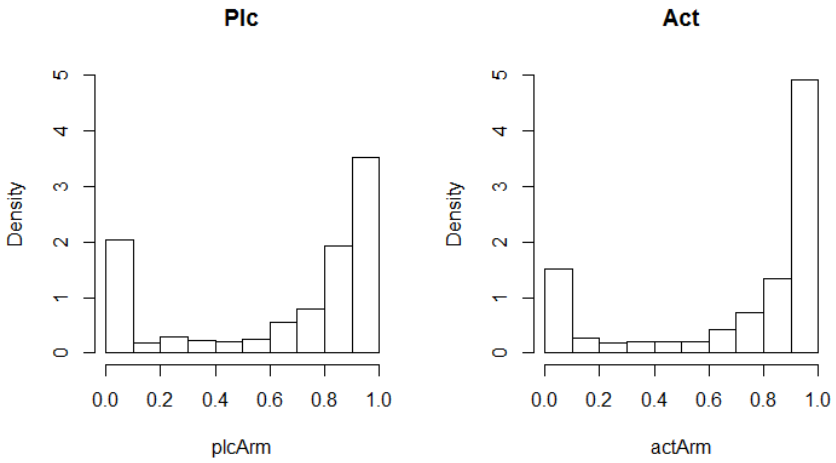
Appendix 7. Power considerations for the AID-ICU trial

By T. Lange, May 2017

Following the protocol draft the primary outcome should be "Antal dage i live udenfor hospital på dag 90". For technical reasons we will divide this number by 90 to produce an outcome in the range 0 to 1 where high is good. Based on observational data the distribution of this outcome is expected to look like the histogram below.



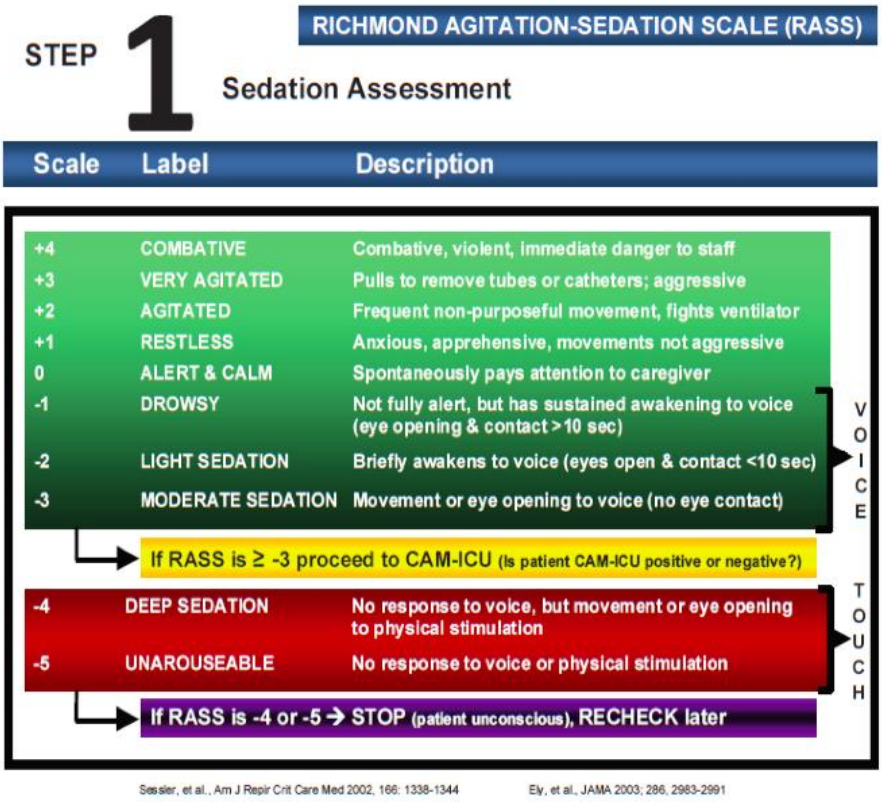
The peak at zero corresponds to in-hospital mortality. It is evident that the distribution is highly non-normal and regular power calculations based on t-test will not be applicable. Accordingly the following calculations are based on employing a Wilcox rank sum test. Assuming that the treatment will a) lower in-hospital mortality by 15% and b) shift the distribution of for the rest to the right by an amount such that the combined effect on the mean is an improvement of 8% and that 500 patients are randomized to each arm we will have 90% power at the 5% significance level. Note that this power calculation does not take stratification into account. To illustrate the hypothesized intervention effect the two histograms below present the placebo and active arm distributions of the outcome.

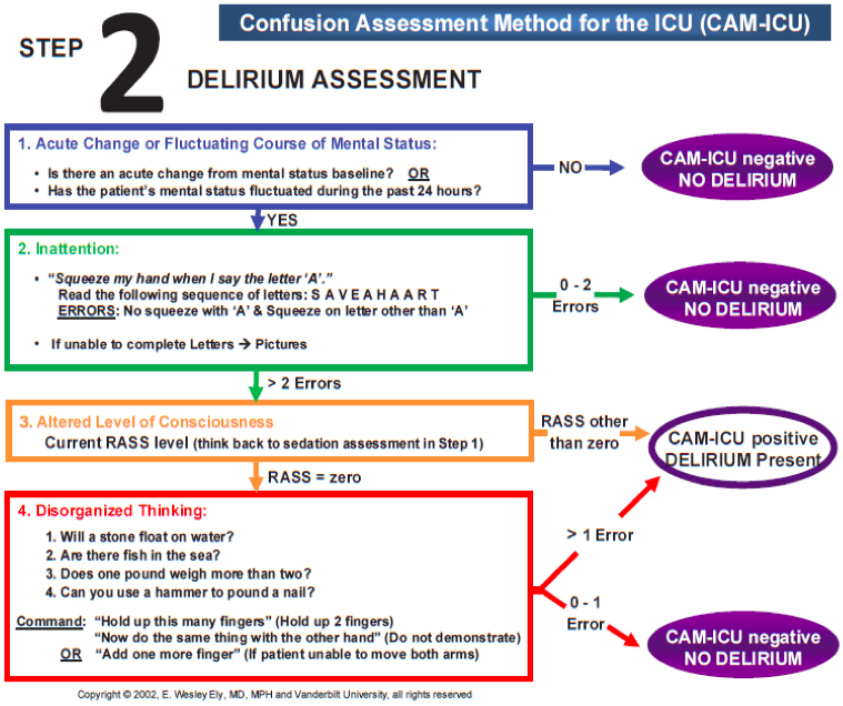


As the hypothesized effect size in unconventional we also compute a standard t-distribution based power assessment. Here we maintain an improvement in mean of 8% and get an estimated power of 60%. While this seems low it is to be expected as the standard derivation computed from the observed data is vastly overstating the true variation in the data because of the non-normality.

We also compute the power from a 500 patient-in-each-arm design on 90 day mortality. Here the observational data yields a current mortality of 27%. Using standard formulas we conclude that we will have 90% power to detect a drop of 8.5%-point corresponding to a risk ratio of 0.68 on 90 day mortality.

Appendix 8. CAM-ICU screening tool





Appendix 9. Intensive Care Delirium Screening Checklist (ICDSC)

Intensive Care Delirium Screening Checklist (ICDSC)

Give a score of "1" to each of the 8 items below if the patient clearly meets the criteria defined in the scoring instructions. Give a score of "0" if there is no manifestation or unable to score. If the patient scores ≥4, notify the physician. The diagnosis of delirium is made following clinical assessment; document in the Assessment and Intervention record (RN) and progress note (MD).

Assessment	Scoring Instructions	Score
1. Altered Level of Consciousness*	• If MASS portion of VAMASS is 0 (no response) or 1 (response to noxious stimulus only), record "U/A" (unable to score) and do not complete remainder of screening tool • Score "0" if MASS score is 3 (calm, cooperative, interacts with environment without prompting) • Score "1" if MASS score is 2, 4, 5 or 6 (MASS score of 2 is a patient who only interacts or responds when stimulated by light touch or voice – no spontaneous interaction or movement; 4, 5 and 6 are exaggerated responses)	
If MASS ≠ 0 or 1, screen items 2-8 and complete a total score of all 8 items.		
2. Inattention	"1" for any of the following: • Difficulty following conversation or instructions • Easily distracted by external stimuli • Difficulty in shifting focuses	
3. Disorientation	"1" for any obvious mistake in person, place or time	
4. Hallucination/ delusions/ psychosis	"1" for any one of the following: • Unequivocal manifestation of hallucinations or of behaviour probably due to hallucinations (e.g.catching non-existent object) • Delusions • Gross impairment in reality testing	
5. Psychomotor agitation or retardation	"1" for any of the following: • Hyperactivity requiring additional sedatives or restraints in order to control potential dangerousness (e.g. pulling out IV lines, hitting staff) • Hypoactivity or clinically noticeable psychomotor slowing (differs from depression by fluctuation in consciousness and inattention)	
6. Inappropriate speech or mood	"1" for any of the following (score 0 if unable to assess): • Inappropriate, disorganized or incoherent speech • Inappropriate display of emotion related to events or situation	
7. Sleep wake/cycle disturbance	"1" for any of the following: • Sleeping less than 4 hours or waking frequently at night (do not consider wakefulness initiated by medical staff or loud environment) • Sleeping during most of day	
8. Symptom fluctuation	"1" for fluctuation of the manifestation of any item or symptom over 24 hours (e.g., from one shift to another)	
TOTAL SCORE 0-8 / 8	A score ≥ 4 suggests delirium. A score > 4 is not indicative of the severity of the delirium	

Appendix 10. International Committee of Medical Journal Editors (ICMJE) form for potential conflicts of interest.

ICMJE INTERNATIONAL COMMITTEE of MEDICAL JOURNAL EDITORS

SAVE

ICMJE Form for Disclosure of Potential Conflicts of Interest

Instructions

The purpose of this form is to provide readers of your manuscript with information about your other interests that could influence how they receive and understand your work. The form is designed to be completed electronically and stored electronically. It contains programming that allows appropriate data display. Each author should submit a separate form and is responsible for the accuracy and completeness of the submitted information. The form is in six parts.

1. Identifying information.

2. The work under consideration for publication.

This section asks for information about the work that you have submitted for publication. The time frame for this reporting is that of the work itself, from the initial conception and planning to the present. The requested information is about resources that you received, either directly or indirectly (via your institution), to enable you to complete the work. Checking "No" means that you did the work without receiving any financial support from any third party -- that is, the work was supported by funds from the same institution that pays your salary and that institution did not receive third-party funds with which to pay you. If you or your institution received funds from a third party to support the work, such as a government granting agency, charitable foundation or commercial sponsor, check "Yes".

3. Relevant financial activities outside the submitted work.

This section asks about your financial relationships with entities in the bio-medical arena that could be perceived to influence, or that give the appearance of potentially influencing, what you wrote in the submitted work. You should disclose interactions with ANY entity that could be considered broadly relevant to the work. For example, if your article is about testing an epidermal growth factor receptor (EGFR) antagonist in lung cancer, you should report all associations with entities pursuing diagnostic or therapeutic strategies in cancer in general, not just in the area of EGFR or lung cancer.

Report all sources of revenue paid (or promised to be paid) directly to you or your institution on your behalf over the 36 months prior to submission of the work. This should include all monies from sources with relevance to the submitted work, not just monies from the entity that sponsored the research. Please note that your interactions with the work's sponsor that are outside the submitted work should also be listed here. If there is any question, it is usually better to disclose a relationship than not to do so.

For grants you have received for work outside the submitted work, you should disclose support ONLY from entities that could be perceived to be affected financially by the published work, such as drug companies, or foundations supported by entities that could be perceived to have a financial stake in the outcome. Public funding sources, such as government agencies, charitable foundations or academic institutions, need not be disclosed. For example, if a government agency sponsored a study in which you have been involved and drugs were provided by a pharmaceutical company, you need only list the pharmaceutical company.

4. Intellectual Property.

This section asks about patents and copyrights, whether pending, issued, licensed and/or receiving royalties.

5. Relationships not covered above.

Use this section to report other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work.

Definitions.

Entity: government agency, foundation, commercial sponsor, academic institution, etc.
Grant: A grant from an entity, generally [but not always] paid to your organization
Personal Fees: Monies paid to you for services rendered, generally honoraria, royalties, or fees for consulting, lectures, speakers bureaus, expert testimony, employment, or other affiliations
Non-Financial Support: Examples include drugs/equipment supplied by the entity, travel paid by the entity, writing assistance, administrative support, etc.
Other: Anything not covered under the previous three boxes
Pending: The patent has been filed but not issued
Issued: The patent has been issued by the agency
Licensed: The patent has been licensed to an entity, whether earning royalties or not
Royalties: Funds are coming in to you or your institution due to your patent

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ICMJE INTERNATIONAL COMMITTEE of MEDICAL JOURNAL EDITORS

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ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name)
2. Surname (Last Name)
3. Date

4. Are you the corresponding author? ☐ Yes ☐ No

5. Manuscript Title

6. Manuscript Identifying Number (if you know it)

Section 2. The Work Under Consideration for Publication

Did you or your institution **at any time** receive payment or services from a third party (government, commercial, private foundation, etc.) for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

Are there any relevant conflicts of interest? ☐ Yes ☐ No

ADD

Section 3. Relevant financial activities outside the submitted work.

Place a check in the appropriate boxes in the table to indicate whether you have financial relationships (regardless of amount of compensation) with entities as described in the instructions. Use one line for each entity; add as many lines as you need by clicking the "Add +" box. You should report relationships that were **present during the 36 months prior to publication.**

Are there any relevant conflicts of interest? ☐ Yes ☐ No

ADD

Section 4. Intellectual Property -- Patents & Copyrights

Do you have any patents, whether planned, pending or issued, broadly relevant to the work? ☐ Yes ☐ No

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ICMJE INTERNATIONAL COMMITTEE of MEDICAL JOURNAL EDITORS

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ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 5. Relationships not covered above

Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?

☐ Yes, the following relationships/conditions/circumstances are present (explain below):

☐ No other relationships/conditions/circumstances that present a potential conflict of interest

At the time of manuscript acceptance, journals will ask authors to confirm and, if necessary, update their disclosure statements. On occasion, journals may ask authors to disclose further information about reported relationships.

Section 6. Disclosure Statement

Based on the above disclosures, this form will automatically generate a disclosure statement, which will appear in the box below.

Generate Disclosure Statement

Evaluation and Feedback

Please visit http://www.icmje.org/cgi-bin/feedback to provide feedback on your experience with completing this form.

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Appendix 11: Overview of reviews

June 2017

Preliminary results - Pharmacological interventions for delirium in intensive care patients: an overview of reviews.
Marija Barbateskovic, Sara Russo Kraus, Janus Christian Jakobsen, Marie Oxenbøl-Collet, Laura Krone Larsen, Jørn Wetterslev.

To critically assess the evidence of reviews of randomised clinical trials on the effect of pharmacological management and prevention of delirium in ICU patients, we searched the following databases: Cochrane Library, MEDLINE, EMBASE, Science Citation Index, BIOSIS, Cumulative Index to Nursing and Allied Health Literature, Latin American and Caribbean Health Sciences Literature, and Allied and Complementary Medicine Database (search ran on 23.03.16, MB; update ongoing).
We retrieved **435 references** that have been divided in the following subgroups/folders:

1. Clinical trials (both interventional and observational studies)
2. Reviews with wrong population (ICU pts, elective cardiac surgical pts, acutely operated pts)
3. Reviews with wrong intervention (not pharm)
4. Reviews with wrong indication (not delirium)
5. Other (letters, commentaries, viewpoints, correspondences, editorials, erratum, case reports/series, conference abstracts)
6. **Reviews** on the effect of pharmacological management and prevention of delirium in ICU patients

We identified **249 reviews in group 6** eligible for inclusion.
Three reviewers (LK, MOC, SRK) further classified the reviews in **non-narrative** and **narrative** based on the presence/absence of a database search and a method section. Non-narrative reviews were further checked against the PRISMA statements. The methodological quality of the non-narrative reviews fulfilling the PRISMA statements, was assessed using the ROBIS tool. Non-narrative reviews fulfilling all the PRISMA statements checklist are hereafter called **systematic** reviews. Furthermore, we identified those non-narrative reviews fulfilling all the PRISMA statements checklist except the presence of a published protocol and the presence of a published full search strategy. These reviews are hereafter called **non-narrative non-systematic** reviews. Below is a summary of the different type of reviews identified.

- 249 reviews: → 219 narrative

  → 28 non-narrative
  - Out of the non-narrative:
    i. 1 systematic review
    ii. 6 "non-narrative non-systematic" (in agreement with PRISMA statements except presence of a published protocol and the presence of a published full search strategy).

iii. 21 "non-narrative/non-systematic in disagreement with 3 or more PRISMA statements"

In the previously published protocol for this overview of reviews, Barbateskovic et al reported 4 examples of guidelines and recommendations for delirium in the ICU patients: recommendation 1 from the Society of Critical Care Medicine; recommendation 2 from the Intensive Care Society in the UK; recommendation 3 from the German guidelines for the management of analgesia, sedation and delirium in intensive care recommendation 4 from the Danish Society of Anesthesiology and Intensive Care. We screened the abovementioned recommendations in order to identify whether they were based on published reviews, but we found that it was not the case. We also registered potential **recommendations** resulting from the 249 reviews that were eligible for inclusion in this overview. Within these reviews, we could only find one recommendation (ref "American College of Critical Care Medicine of the Society of Critical Care Medicine, American Society of Health-System Pharmacists American College of Chest Physicians. Clinical practice guidelines for the sustained use of sedatives and analgesics in the critically ill adult. 2002". Recommendation: "Haloperidol is the preferred agent for the treatment of delirium in critically ill patients (Grade of recommendation=C)").

We will present and discuss the main results of the **1 systematic review** and the **6 "non-narrative non-systematic" reviews** identified.

1. Systematic review by **Chen K**, Lu Z, Xin YC, Cai Y, Chen Y, Pan SM - Alpha-2 agonists for long-term sedation during mechanical ventilation in critically ill patients. Cochrane Database of Systematic Reviews 2015.

The **objective** of this review was to assess the safety and efficacy of alpha-2 agonists for sedation of more than 24 hours, compared with traditional sedatives, in mechanically-ventilated critically ill patients. Seven studies, covering 1624 **participants**, met the inclusion criteria. All included studies investigated adults and compared dexmedetomidine with traditional sedatives, including propofol, midazolam and lorazepam. Risk of **delirium** was one of the primary outcome of the review. There was not statistically significant evidence that dexmedetomidine decreased the risk of delirium (RR 0.85; 95% CI 0.63 to 1.14; seven studies, 1624 participants, very low-quality evidence) as results were consistent with both no effect and appreciable benefit). The authors observed high levels of heterogeneity in risk of delirium (I^2= 70%), but due to the limited number of studies they were unable to determine the source of heterogeneity through subgroup analyses or meta-regression. The authors judged six of the seven studies to be at high risk of **bias**. Based on the **ROBIS** tool, we judged the overall risk of bias of the review itself to be low.

Does the review address haloperidol?	No
Type of review (in regard to delirium)	Prophylactic
Number of trials included	7
Number of participants included	1624
ICU population (e.g. medical)	All the studies recruited adults from mixed intensive care units (ICUs) which may include medical, surgical and trauma patients. All the studies required participants to have an anticipated need for sedation of at least 24 to 36 hours.
Diagnostic criteria of delirium	CAM-ICU
Type of pharmacological agent(s) included	All the included studies compared dexmedetomidine with traditional sedatives (midazolam, lorazepam, propofol or standard care (Either propofol or midazolam))
Primary and secondary outcomes	Primary outcomes:

	1. Duration of mechanical ventilation 2. Risk of delirium 3. Risk of coma Secondary outcomes: 1. Adverse events: 2. Proportion of sedation time spent at target sedation level 3. Duration of weaning 4. Intensive care unit length of stay 5. Mortality
Results on primary and secondary outcomes	Primary outcomes: **1.** Duration of mechanical ventilation: Alpha-2 agonists reduced geometric mean duration of mechanical ventilation by 0.25 (95% CI 0.10 to 0.40), corresponding to a reduction of 22% in the geometric mean (95% CI 10% to 33%). **2.** Risk of delirium: there was not statistically significant evidence that dexmedetomidine decreased the risk of delirium (RR 0.85; 95% CI 0.63 to 1.14; seven studies, 1624 participants, very low-quality evidence) as results were consistent with both no effect and appreciable benefit. **3.** Risk of coma: only one study assessed the risk of coma, but lacked methodological reliability (RR 0.69; 95% CI 0.55 to 0.86, very low-quality evidence). Secondary outcomes: **1.** Incidence of bradycardia: not significant **2.** Duration of weaning: Only one study assessed this outcome and only reported median and range. We were not able to estimate a relative effect. **3.** ICU length of stay: Sedation using alpha-2 agonists reduced geometric mean ICU LOS by 0.15 (95% CI 0.01 to 0.28), corresponding to a reduction of 14% in the geometric mean (95% CI 0.01% to 24%). **4.** Mortality: not significant (RR 0.99; 95% CI 0.79 to 1.24; six studies, 1584 participants, very low quality evidence)
Type of meta-analytic and sequential analysis used	Meta-analysis

Authors' conclusion	In this review, we found no eligible studies for children or for clonidine. Compared with traditional sedatives, long-term sedation using dexmedetomidine in critically ill adults reduced the duration of mechanical ventilation and ICU length of stay. There was no evidence for a beneficial effect on risk of delirium and the heterogeneity was high. The evidence for risk of coma was inadequate. The most common adverse event was bradycardia. No evidence indicated that dexmedetomidine changed mortality. The general quality of evidence ranged from very low to low, due to high risks of bias, serious inconsistency and imprecision, and strongly suspected publication bias. Future studies could pay more attention to children and to using clonidine.

2. Non-narrative non-systematic review by **Lonergan E**, Luxenberg J, Areosa Sastre A. Benzodiazepines for delirium. Cochrane Database of Systematic Reviews 2009.
The **objective** of this review was to determine the effectiveness and incidence of adverse effects of benzodiazepines in the treatment of non-alcohol withdrawal related **delirium**. One of the secondary objectives was to examine the effect of different classes of benzodiazepines on the course of delirium. Only one trial satisfying the selection criteria could be identified. When this trial compared the effect of the benzodiazepine, lorazepam, with dexmedetomidine, a selective alpha-2-adrenergic receptor agonist, on delirium among mechanically ventilated intensive care unit patients, dexmedetomidine treatment was associated with an increased number of delirium- and coma-free days compared with lorazepam treated patients (dexmedetomidine patients, average seven days; lorazepam patients, average three days; P = 0.01). **The risk of bias judged by the authors was difficult to report**. Based on the **ROBIS** tool, we judged the overall risk of bias of the review to be high.

Does the review address haloperidol?	No
Type of review (in regard to delirium)	Treatment
Number of trials included	1
Number of participants included	106
ICU population (e.g. medical)	Hospitalized adults who had delirium due to causes other than benzodiazepine toxicity or withdrawal from alcohol.
Diagnostic criteria of delirium	Delirium diagnosed using IC-CAM method or RASS scale
Type of pharmacological agent(s) included	Patients were treated for up to 120 hrs, with: control group receiving intravenous lorazepam; study group receiving intravenous dexmedetomidine). Drug infusion rate was titrated to reach a sedation level determined by the Richmond Agitation-Sedation Scale. Rescue intervention for acute agitation while on treatment included propofol infusion; for increased pain, fentanyl was given

Primary and secondary outcomes	Primary objective: -To determine the effect of benzodiazepines on hospitalised adults with delirium. Secondary objectives: -To examine the incidence and types of adverse effects of benzodiazepines -To examine the number of withdrawals among benzodiazepine treated and control patients -To examine the number of patients withdrawing from treatment because of adverse effects of benzodiazepines -To examine adverse drug effects of benzodiazepines as they confound the evaluation of the response of delirium to treatment -To examine the effect of benzodiazepines of different classes (e.g. short-acting, intermediate acting, long acting) on the course of delirium. -To determine if response to benzodiazepines is influenced by: • The cause of delirium: surgery, infection, stroke, drugs • The character of delirium: hypoactive, hyperactive • The presence of previous cognitive impairment • Dose of drug • Duration of treatment • Age of the patient.
Results on primary and secondary outcomes	Prevalence of coma was significantly higher among lorazepam patients compared with dexmedetomidine patients (92% vs 63%; P < 0.001). Delirium-free days were not significantly different comparing the two groups (L pts av 7 d, D pts av 9 d, P = 0.09); delirium-free and coma free days were significantly greater for D patients compared with L patients (Dpts av 7 d, Lpts av 3 d; P = 0.01)
Type of meta-analytic and sequential analysis used	NI
Authors' conclusion	Implications for practice: there is no evidence to support the use of benzodiazepines in the treatment of non-alcohol withdrawal related delirium among hospitalised patients. Implications for research: further controlled studies are necessary to establish the role of benzodiazepines in the control of non-alcohol related delirium in hospitalised patients.

3. Non-narrative non-systematic review by Gilles L. **Fraser**, John W. Devlin Craig P. Worby, Waleed Alhazzani, Juliana Barr, Joseph F. Dasta, John P. Kress, Judy E. Davidson, Frederick A. Spencer - Benzodiazepine Versus Nonbenzodiazepine-Based Sedation for Mechanically

Ventilated, Critically Ill Adults: A Systematic Review and Meta-Analysis of Randomized Trials. Critical Care Medicine 2013.

The **objective** of this review was to review randomized trials comparing a benzodiazepine and nonbenzodiazepine regimen in mechanically ventilated adult ICU patients to determine if differences exist between these sedation strategies with respect to ICU length of stay, time on the ventilator, delirium prevalence, and short-term mortality. They included six trials enrolling 1,235 **participants**. **Delirium** prevalence was one of the secondary outcomes of the review. Results suggested that use of a dexmedetomidine- or propofol-based sedation regimen rather than a benzodiazepine-based sedation regimen in critically ill adults may reduce ICU length of stay and duration of mechanical ventilation. The definition of delirium varied across studies. In two trials (n = 469 patients), delirium was clearly defined and evaluated on a daily basis. The prevalence of delirium varied even between these two studies (approximately 81% and 61%, respectively). Pooling the data from these two studies did not confirm or refute a difference between delirium prevalence with these two sedation strategies (RR = 0.83; 95% CI, 0.61–1.11; $I2$ = 84%; p = 0.19). The authors assessed the Cochrane risk of **bias** score for each trial. Only one of the six studies included has a high overall Cochrane risk of bias score. Based on the **ROBIS** tool, we judged the overall risk of bias of the review to be high.

Does the review address haloperidol?	No
Type of review (in regard to delirium)	Prophylactic
Number of trials included	6 (2 about delirium)
Number of participants included	1235 (469 about delirium)
ICU population (e.g. medical)	Adult (≥ 19 yr) medical or surgical ICU patients receiving invasive mechanical ventilation and administration of IV pharmacologic sedation
Diagnostic criteria of delirium	CAM-ICU
Type of pharmacological agent(s) included	Lorazepam, Propofol, Midazolam Dexmedetomidine
Primary and secondary outcomes	Primary outcomes: -duration of ICU length of stay Secondary outcomes: -duration of mechanical ventilation -delirium prevalence (where delirium was evaluated at least daily using a validated screening tool) - all-cause, short-term mortality (i.e., ≤ 45 d after randomization or during hospital stay).
Results on primary and secondary outcomes	The use of a nonbenzodiazepine IV sedative regimen was associated with a shorter ICU length of stay (mean difference = 1.65 d; 95% CI, 0.72–2.58; $I2$ = 0%; p = 0.0005) (2–6, 27). Data from four trials (n = 1,101 patients) found that use of a nonbenzodiazepine-sedative regimen was associated with a shorter duration of mechanical ventilation (mean difference, 1.9 d; 95% CI, 1.70–2.09; $I2$ = 0%; p < 0.00001) (2, 4, 5, 27). Pooling the data from these two studies did not confirm or refute a difference between delirium prevalence with these two sedation strategies. Risk for death (RR, 0.98; 95% CI, 0.76–1.27; $I2$ = 30%; p = 0.94) was similar

	between benzodiazepine and nonbenzodiazepine regimens
Type of meta-analytic and sequential analysis used	We combined data from trials to estimate the pooled risk ratio (RR) and associated 95% CIs for binary outcomes. Pooled RRs were calculated using random effects models, applying inverse variance weighting and the methods of DerSimonian and Laird. Weighted mean difference was used to summarize the effect measure for continuous outcomes. Data were pooled using inverse variance and a random effects model.
Authors' conclusion	No conclusion paragraph The results of this meta-analysis suggest that the use of nonbenzodiazepine sedation in medical and surgical adult ICU patients (excluding cardiac surgery and obstetrical patients) is associated with 1.65 day shorter length of ICU stay and 1.9 day shorter duration of mechanical ventilation compared to patients receiving benzodiazepines for sedation. No significant difference in mortality was found in our analysis, and data on delirium prevalence were insufficient to draw clear conclusions. These results both expand and support the weak recommendation made in the 2013 ICU PAD guidelines that nonbenzodiazepine sedative options may be preferred overbenzodiazepine-based sedative regimens.

4. Non-narrative non-systematic review by Jing Lan **Mu**, Anna Lee, Gavin M. Joynt - Pharmacologic Agents for the Prevention and Treatment of Delirium in Patients Undergoing Cardiac Surgery: Systematic Review and Meta-analysis. Critical Care Medicine 2015.
The **objective** of this review was to examine the effect of pharmacologic agents for the prevention and the treatment of delirium after cardiac surgery. The authors included 14 studies involving 5,848 **participants** (one multicentered randomized controlled trial on prophylactic dexamethasone made up 77% of the total sample size). The primary outcome was **delirium** reported as incidence, severity, or duration. The authors assessed the Cochrane risk of **bias** score for each trial. Moderate to high-quality evidence supports the use of pharmacologic agents for the prevention of delirium, but results are based largely on one randomized controlled trial. Two trials were identified that addressed haloperidol as intervention: Atalan et al (strategy: treatment; quality of evidence: moderate) Tagarakis et al (strategy: treatment; quality of evidence:moderate). In the study by Tagarakis et al, the proportion of patients remaining delirious despite haloperidol treatment was similar to the ondansetron control group (15% vs 17.5%; RR, 0.86; 95% CI, 0.32–2.33). In the Atalan et al trial, there was no difference in the mean (sd) duration of hyperactive delirium between haloperidol and morphine groups (34 ± 17 vs 32 ± 17 hr; $p = 0.61$), and the risk of hospital mortality was similar between the haloperidol and the morphine groups (7.7% vs 3.7%; RR, 2.08; 95% CI, 0.20–21.55).
The evidence for treating postcardiac surgery delirium with pharmacologic agents is inconclusive. Based on the **ROBIS** tool, we judged the overall risk of bias of the review to be high.

Does the review address haloperidol?	Yes
Type of review (in regard to delirium)	Treatment/prophylactic (We performed a systematic review of randomized controlled trials to examine the effect of pharmacologic agents for the **prevention and the treatment** of delirium after cardiac surgery)
Number of trials included	13
Number of participants included	5848
ICU population (e.g. medical)	adult patients undergoing emergency or elective cardiac surgery
Diagnostic criteria of delirium	CAM (2) CAM-ICU (4), DSM (4), and ICDSC (2).
Type of pharmacological agent(s) included	The pharmacologic agents examined in the 13 RCTs included clonidine (*n* = 1), dexamethasone (*n* = 2), dexmedetomidine (*n* = 3), ketamine (*n* = 1), **haloperidol** (*n* = 2), propofol (*n* = 1), risperidone (*n* = 2), and rivastigmine (*n* = 1)
Primary and secondary outcomes	Primary outcome: -delirium reported as incidence, severity, or duration. -Secondary outcomes: - risk of mortality at hospital discharge and adverse effects associated with the use of pharmacologic agents, need for rescue pharmacologic agent for treating delirium, and duration of stays in ICU and hospital
Results on primary and secondary outcomes	In the overall analysis, pharmacologic agents reduced the risk of delirium. Overall, the intervention group had similar duration of delirium to the control group. There was no reduction in the proportion of patients needing rescue haloperidol associated with prophylactic pharmacologic agents. Pharmacologic agents reduced the length of stay in ICU (MD, –0.30 d; 95% CI, –0.57 to –0.04), but there was high heterogeneity ($I2$ = 85%) between the 10 trials. Overall, there was no difference in the risk of hospital mortality between intervention and control groups.
Type of meta-analytic and sequential analysis used	Review Manager 5.2 and STATA 13.1 software were used for data analysis. Relative risk (RR) or mean difference (MD) with 95% CI was reported. Before data synthesis, we estimated sd from se, CI, interquartile range, and range using methods previously described. We used a DerSimonian and Laird random-effects model to combine the data. We assessed

	the heterogeneity as low, moderate, and high using *I*2 values of 25%, 50%, and 75%.
Authors' conclusion	Moderate to high-quality evidence supports the use of pharmacologic agents for the prevention of delirium, but the conclusion is based largely on one dexamethasone trial. Individual pharmacologic agents differ in their effect on the risk of delirium, but the observation of the apparent effectiveness of prophylactic dexmedetomidine requires caution because the results are imprecise. No robust comparison between dexamethasone and dexmedetomidine has been performed. Finally, the evidence for treating postcardiac surgery delirium with pharmacologic agents is inconclusive.

5. Non-narrative non-systematic review by Laura **Pasin**, Giovanni Landoni, Pasquale Nardelli, Alessandro Belletti, Ambra Licia Di Prima, Daiana Taddeo, Francesca Isella, and Alberto Zangrillo - Dexmedetomidine Reduces the Risk of Delirium, Agitation and Confusion in Critically Ill Patients: A Meta-analysis of Randomized Controlled Trials. Journal of Cardiothoracic and Vascular Anesthesia 2014

The **objective** of this study was to evaluate the effect of dexmedetomidine on delirium, agitation, and confusion in the ICU setting. The authors included 14 trials randomizing 3,029 **participants**. Overall analysis showed that the use of dexmedetomidine was associated with significant reductions in the incidence of **delirium**, agitation and confusion (298/1,565[19%] in the dexmedetomidine group v 337/1,464 [23%] in the control group, RR= 0.68 [0.49to0.96], p=0.03). The authors assessed the Cochrane risk of **bias** score for each trial. Study quality appraisal indicated that trials were of medium quality; in particular 6 of them had overall low risk of bias. Based on the **ROBIS** tool, we judged the overall risk of bias of the review itself to be high.

Does the review address haloperidol?	No
Type of review (in regard to delirium)	Treatment/Prophylactic
Number of trials included	14
Number of participants included	3029
ICU population (e.g. medical)	Cardiac surgery and ICU
Diagnostic criteria of delirium	CAM-ICU, DSM-IV-TR
Type of pharmacological agent(s) included	Propofol, Midazolam, Morphine, Dexmedetomidine
Primary and secondary outcomes	The primary endpoint of the present review was the rate of delirium, including the adverse events of agitation and/or confusion.
Results on primary and secondary outcomes	The overall analysis showed that the use of dexmedetomidine was associated with significant reductions in the incidence of delirium, agitation and/or confusion (298/1,565[19%]in the dexmedetomidine group v 337/1,464 [23%]in the control group, RR = 0.68 [0.49to0.96], p for effect = 0.03, p for

	heterogeneity o 0.001, I2 = 71% with 13 studies included)
Type of meta-analytic and sequential analysis used	Computations were performed with Review Manager version5.2. Hypothesis of statistical heterogeneity was tested by means of Cochran Q test with statistical significance set at the two-tailed 0.10level, whereas extent of statistical consistency was measured with I2, defined as 100%X(Q-df)/Q where Q is Cochran's heterogeneity statistic and df the degrees of freedom. Binary outcomes were analyzed to compute the individual and pooled risk ratio (RR) with pertinent 95%confidence interval (CI), by means of the same models as just described. Binary outcomes from individual studies were analyzed to compute individual and pooled risk ratio(RR) with pertinent 95% confidence interval(CI) by means of an inverse variance method and with a fixed-effect model in case of low statistical inconsistency (I2 o25%) or with a random- effect model in case of moderate or high statistical inconsistency (I2 425%).
Authors' conclusion	This meta-analysis of randomized controlled studies suggests that dexmedetomidine could help to reduce delirium in critically ill patients.

6. Non-narrative non-systematic review by Zhi-Qiu **Xia**, Shu-Qin Chen, Xi Yao, Chuan-Bo Xie, Shi-Hong Wen, and Ke-Xuan Liu - Clinical benefits of dexmedetomidine versus propofol in adult intensive care unit patients: a meta-analysis of randomized clinical trials. Journal of surgical research 2013.

The **objective** of this meta-analysis was to assess the influence of dexmedetomidine and propofol for adult intensive care unit (ICU) sedation, with respect to patient outcomes and adverse events. Ten randomized controlled trials, involving 1202 **participants**, were included Secondary outcomes included risk of **delirium**, hypotension, bradycardia and hypertension. Dexmedetomidine significantly reduced the length of ICU stay by <1 d (five studies, 655 patients; mean difference, 0.81 d; 95% confidence interval [CI], 1.48 to 0.15) and the incidence of delirium (three studies, 658 patients; relative risk [RR], 0.40; 95% CI, 0.22-0.74) in comparison with propofol, whereas there was no difference in the duration of mechanical ventilation (five studies, 895 patients; mean difference, 0.53 h; 95% CI 2.66 to 3.72) or ICU mortality (five studies, 267 patients; RR, 0.83; 95% CI, 0.32-2.12) between these two drugs. The Cochrane Collaboration's tool was applied for assessing the risk of **bias** in each identified study. Based on the **ROBIS** tool, we judged the overall risk of bias of the review itself to be high.

Does the review address haloperidol?	No
Type of review (in regard to delirium)	Treatment/prophylactic (delirium as inclusion criteria for outcome)
Number of trials included	10 (3 about delirium)
Number of participants included	1202 (665 about delirium)
ICU population (e.g. medical)	Adult ICU

Diagnostic criteria of delirium	NI
Type of pharmacological agent(s) included	Dexmedetomidine, Propofol (plus concurrent treatment)
Primary and secondary outcomes	Primary outcomes: - Length of ICU stay - Duration of mechanical ventilation - ICU mortality Secondary outcomes: - Delirium - Hypotension - Bradycardia - Hypertension
Results on primary and secondary outcomes	Primary outcomes: - Length of ICU stay (the use of dexmedetomidine for sedation in ICU did no reduce the length of ICU stay compared with that of propofol) - Duration of mechanical ventilation (the use of dexmedetomidine for sedation in ICU did not appear to reduce the duration of mechanical ventilation compared with that of propofol) - ICU mortality (no difference in ICU mortality was found between patients receiving dexmedetomidine and those receiving Propofol) Secondary outcomes: - Delirium (Delirium rates were significantly reduced with dexmedetomidine compared with those with propofol) - Hypotension (the use of dexmedetomidine for sedation in ICU was not associated with significant reduction of the risk of hypotension compared with that of propofol) - Bradycardia (the use of dexmedetomidine for sedation in ICU was not associated with significant reduction of risk of bradycardia compared with that of propofol) - Hypertension (dexmedetomidine significantly increased the risk of hypertension compared with propofol)
Type of meta-analytic and sequential analysis used	
Authors' conclusion	For ICU patient sedation, dexmedetomidine may offer advantages over propofol in terms of decrease in the length of ICU stay and the risk of delirium. However, transient hypertension may occur when dexmedetomidine is administered with a loading dose or at high infusion rates.

7. Non-narrative non-systematic review by Bo **Li**, Huixia Wang, Hui Wu, and Chengjie Gao - Neurocognitive Dysfunction Risk Alleviation with the Use of Dexmedetomidine in Perioperative Conditions or as ICU Sedation. Medicine 2015

The **objective** of this review was to examine the effects of dexmedetomidine on postoperative cognitive function in perioperative conditions or in intensive care unit. Twenty studies were selected from which data of 2612 **participants** were used. Neurocognitive assessment was carried out with CAM-ICU in 7, DSST in 4, and MMSE in 4 studies, and 1 study each utilized intensive care **delirium** screening checklist. Dexmedetomidine treatment was associated with significantly lower risk of postoperative/postanesthesia neurocognitive dysfunction both in comparison with saline treated controls (RD [95% confidence interval, CI]: 0.17 (0.30,0.04); P=0.008) and comparators (0.16 [_0.28, 0.04]; P=0.009). The Cochrane Collaboration Risk of **Bias** Assessment Tool for the assessment of RCTs was used for the quality assessment of the randomized controlled trials included in this meta-analysis. Quality of the included studies was moderate to good, in general. Based on the **ROBIS** tool, we judged the overall risk of bias of the review itself to be high.

Does the review address haloperidol?	No
Type of review (in regard to delirium)	Prophylactic
Number of trials included	20
Number of participants included	2612
ICU population (e.g. medical)	Medical and surgical ICU patients and healthy individuals
Diagnostic criteria of delirium	CAM-ICU=cognitive assessment method for intensive care unit, DSST=digital symbol substitution test, ICDSC =intensive care delirium screening checklist, MCAT=Montreal cognitive assessment test, MMSE=minimental state examination, SAS=sedation–agitation score, SCWIT=Stroop color word interference test
Type of pharmacological agent(s) included	dexmedetomidine
Primary and secondary outcomes	Outcomes not stated clearly: postoperative/postinfusion neurocognitive function
Results on primary and secondary outcomes	Dexmedetomidine treatment was associated with significantly lower risk of postoperative/postanesthesia neurocognitive dysfunction both in comparison with saline treated controls (RD [95% confidence interval, CI]: 0.17 (0.30,0.04); P=0.008) and comparators (0.16 [0.28, 0.04]; =0.009).
Type of meta-analytic and sequential analysis used	Meta-analyses were carried out with the RevMan software (Version 5.2; The Cochrane Collaboration, 2008) under fixed effects model as well as random effects model (REM).
Authors' conclusion	Dexmedetomidine treatment during perioperative conditions or as ICU sedation has been found to be associated with significantly better neurocognitive function of the patients, but factors such as neurocognitive assessment method, drug interactions, and clinical

	heterogeneity may have impacts on these results. Further studies are required to refine the evidence achieved herein.

Summary of findings

Review	Systematic reviews according to PRISMA with low risk of bias assessed with ROBIS	Systematic reviews according to PRISMA with high risk of bias assessed with ROBIS	Non- systematic reviews according to PRISMA (in agreement with PRISMA statements except presence of a published protocol and the presence of a published full search strategy).	ROBIS
Chen 2015	yes			LOW
Lonergan 2009			yes	HIGH
Fraser 2013			yes	HIGH
Mu 2015			yes	HIGH
Pasin 2014			yes	HIGH
Xia 2013			yes	HIGH
Li 2015			yes	HIGH

Conclusions

In conclusion, we identified 249 narrative and non-narrative reviews that were eligible for inclusion in this overview of review. We identified only one truly systematic review according to the PRISMA statement - Chen 2015; Alpha-2 agonists for long-term sedation during mechanical ventilation in critically ill patients.

We identified only one "non-narrative non-systematic" (in agreement with PRISMA statements except for the presence of a published protocol and the presence of a published full search strategy) that addressed haloperidol as being the most used treatment for delirium: Mu et al 2015. In this review, only two trials (Tagarakis et al and Atalan et al) addressed the haloperidol with a moderate quality of evidence assessed by GRADE. The two trials showed the following:

- the proportion of patients remaining delirious despite haloperidol treatment was similar to the ondansetron control group (15% vs 17.5%; RR, 0.86; 95% CI, 0.32–2.33) (Tagarakis et al).
- there was no difference in the mean (SD) duration of hyperactive delirium between haloperidol and morphine groups (34±17 vs 32±17 hr; p=0.61) (Atalan et al).
- the haloperidol group was more likely to require rescue lorazapam than the morphine group (30.7% vs 3.7%;RR, 8.31;95% CI,1.12–61.87) (Atalan et al).
- the risk of reintubation (for unspecified reasons) appeared higher in the haloperidol group than in the morphine group (23.1% vs 3.7%; p = 0.05) (Atalan et al).
- the risk of hospital mortality was similar between the haloperidol and the morphine groups (7.7% vs 3.7%; RR, 2.08; 95% CI, 0.20–21.55) (Atalan et al).

The overall quality and quantity of the present evidence underline the necessity of conducting a truly systematic review on haloperidol and the urgent need for a large pragmatic trial with overall low risk of

bias for treatment of delirium with haloperidol and dextedetomidine on patient important outcomes (days alive out of hospital, mortality, duration of delirium, etc.).

Reference list for the 7 reviews contained in this report

***Chen K**, Lu Z, Xin YC, Cai Y, Chen Y, Pan SM - Alpha-2 agonists for long-term sedation during mechanical ventilation in critically ill patients. Cochrane Database of Systematic Reviews 2015.*
*Gilles L. **Fraser**, John W. Devlin Craig P. Worby, Waleed Alhazzani, Juliana Barr, Joseph F. Dasta, John P. Kress, Judy E. Davidson, Frederick A. Spencer - Benzodiazepine Versus Nonbenzodiazepine-Based Sedation for Mechanically Ventilated, Critically Ill Adults: A Systematic Review and Meta-Analysis of Randomized Trials. Critical Care Medicine 2013.*
*Bo **Li**, Huixia Wang, Hui Wu, and Chengjie Gao - Neurocognitive Dysfunction Risk Alleviation with the Use of Dexmedetomidine in Perioperative Conditions or as ICU Sedation. Medicine 2015*
***Lonergan E**, Luxenberg J, Areosa Sastre A. Benzodiazepines for delirium. Cochrane Database of Systematic Reviews 2009.*
*Jing Lan **Mu**, Anna Lee, Gavin M. Joynt - Pharmacologic Agents for the Prevention and Treatment of Delirium in Patients Undergoing Cardiac Surgery: Systematic Review and Meta-analysis. Critical Care Medicine 2015.*
*Laura **Pasin**, Giovanni Landoni, Pasquale Nardelli, Alessandro Belletti, Ambra Licia Di Prima, Daiana Taddeo, Francesca Isella, and Alberto Zangrillo - Dexmedetomidine Reduces the Risk of Delirium, Agitation and Confusion in Critically Ill Patients: A Meta-analysis of Randomized Controlled Trials. Journal of Cardiothoracic and Vascular Anesthesia 2014*
*Zhi-Qiu **Xia**, Shu-Qin Chen, Xi Yao, Chuan-Bo Xie, Shi-Hong Wen, and Ke-Xuan Liu - Clinical benefits of dexmedetomidine versus propofol in adult intensive care unit patients: a meta-analysis of randomized clinical trials. Journal of surgical research 2013*