Commissie Mensgebonden Onderzoek (METC)

PROTOCOL ADDENDUM FORM

Study Title: *Effects of prophylactic use of haloperidol in critically ill patients with a high risk for delirium; A randomized placebo-controlled double-blind multicentre trial*

Principal Investigator: Dr. M. van den Boogaard

Addendum Summary: The data safety management board (DSMB) advised the investigators of the present study to drop one of three treatment arms. This advise was based on the fourth interim analyses, after 1000 included patients. Importantly, no safety issues were found in this interim analyses.
The investigators will immediately comply to this advise and subsequently study arm C will be dropped from further inclusions.
Since the investigators are blinded for which treatment group study arm C is, the study protocol cannot be adjusted in detail. Therefore this adjustment serves as an addendum of study protocol version 8.
After dropping study arm C, July 24th 2015, the present study will be further performed with two study arms. One placebo arm and one intervention arm with a low dosage of haloperidol. The latter cannot be further described in more detail since the investigators are blinded.

Based on this adjustment, the information brochure for both patient, and the legal representative are adjusted.

PI Signature and Date

Dr. M. van den Boogaard, July 24th 2015

Attachments: adjusted brochure for the patient and for the legal representative, both version 5.

RESEARCH PROTOCOL
Version 8

Effects of prophylactic use of haloperidol in critically ill patients with a high risk for delirium

A randomized placebo-controlled double-blind multicentre trial

(July 2014)

PROTOCOL TITLE

Effects of prophylactic use of haloperidol in critically ill patients with a high risk for delirium

Protocol ID:	Delirium_Haldol-prophy
Short title:	Effects of prophylactic use of haloperidol in critically ill patients with a high risk for delirium
EudraCT number	2012-004012-66
Version :	Version 1
Date :	January 2013
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PROTOCOL SIGNATURE SHEET

Name	**Signature**	**Date**
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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ABR	ABR form, General Assessment and Registration form, is the application form that is required for submission to the accredited Ethics Committee (In Dutch, ABR = Algemene Beoordeling en Registratie)
AE	Adverse Event
AR	Adverse Reaction
CA	Competent Authority
CAM-ICU	Confusion Assessment Method-Intensive Care Unit
CCMO	Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek
CV	Curriculum Vitae
DOS	Delirium Observation Scale
DSMB	Data Safety Monitoring Board
E-CRF	Electronic Clinical Report Form
EU	European Union
EudraCT	European drug regulatory affairs Clinical Trials
GCP	Good Clinical Practice
IB	Investigator's Brochure
IC	Informed Consent
ICU	Intensive Care Unit
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
METC	Medical research ethics committee (MREC); in Dutch: medisch ethische toetsing commissie (METC)
PI	Principal Investigator
RASS	Richmond Agitation Sedation Scale
(S)AE	(Serious) Adverse Event
SF-12	Short Form questionnaire consisting of 12 questions
SPC	Summary of Product Characteristics (in Dutch: officiële productinfomatie IB1-tekst)
Sponsor	The sponsor is the party that reimburses commissions to the organisation for performance of the research, for example a pharmaceuticalcompany, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.
SUSAR	Suspected Unexpected Serious Adverse Reaction
Wbp	Personal Data Protection Act (in Dutch: Wet Bescherming Persoonsgevens)
WMO	Medical Research Involving Human Subjects Act (in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen

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1. SUMMARY

Rationale	Delirium is a frequent disorder in intensive care unit (ICU) patients with serious consequences. Therefore, preventive treatment for delirium may be beneficial.
Objectives	*Primary* objective of this study is to determine the effect of prophylactic haloperidol treatment on number of days of survival in 28-days. *Secondary* objectives are: 1. To determine the effect of prophylactic haloperidol treatment on number of days of survival in 90-days 2. To determine the effect of prophylactic haloperidol on delirium incidence 3. To determine the effect of prophylactic haloperidol on number of delirium-free and coma-free days in a period of 28 days 4. To determine the effect of prophylactic haloperidol on delirium-related outcome: duration of mechanical ventilation, incidence of re-intubation, incidence of ICU readmission, and incidence of unplanned removal of tubes and catheters 5. To determine the preventive efficacy of haloperidol in different patient groups based on the a priori risk to develop delirium: In patients with a predicted risk up to 50%, 50-70%, 70-90%, above 90% the effect of haloperidol will be determined 6. To evaluate side-effects of haloperidol treatment 7. To determine the efficacy of preventive haloperidol treatment on quality of life 1 and 6 months following ICU admission compared with baseline measurement.
Study design	Multicentre three-armed randomized double-blind placebo-controlled prophylactic intervention study in critically ill patients.
Study population	All consecutive non-neurological ICU patients, aged ≥ 18 years with an expected stay >1 day on the ICU, and therefore considered as high risk for delirium.
Sample size	In total 2145 patients will be randomized; 715 in each group.
Intervention	ICU patients with a high risk for delirium, determined as an expected ICU stay of more than 1 day, will receive prophylactic treatment with intravenously haloperidol (3x1mg or 3x2mg), or placebo (sodium chloride 0.9%) in a randomized, double-blind manner. In patients who, despite prophylactic treatment, develop delirium the study medication will be stopped and patients will receive open label treatment with a higher (therapeutic) dose of haloperidol.
Main study parameters/endpoints	Number of days of survival in 28-days and 90-days, onset of delirium, number of delirium- and coma free days in 28 days, side-effects of prophylactic haloperidol treatment
Statistical analysis	Descriptive summary statistics using Cox proportional hazard regression analyses to test the primary endpoint.
Nature and extent burden and risks associated with study participation	Haloperidol is worldwide the first choice of drug to treat delirious patients, but with a higher dosage than in this prophylactic study. Evidence of effectiveness of prophylactic treatment in ICU patients is scarce, however, some studies showed beneficial effects of prophylactic haloperidol. In these studies no relevant side-effects were reported.

2. INTRODUCTION AND RATIONALE

Delirium is a neuropsychiatric disorder characterized by an acute onset of confusion and consciousness alterations that fluctuate during the day (1, 2). The incidence of delirium in intensive care (ICU) patients is high (3-6), on average 30-50%, and its occurrence is associated with prolonged duration of mechanical ventilation, increased ICU- and hospital length of stay (4-6) unplanned removal of tubes and catheters (6) and an increased mortality (6-8). Therefore, preventive treatment for delirium may be beneficial.

Apart from treatment of the underlying disease, haloperidol is the most common and recommended anti-psychotic drug for the treatment of delirium. Recently, this drug was also used to prevent delirium. In non-ICU patients beneficial effects of prophylactic haloperidol treatment in older and surgical patients have been reported (9, 10). For critically ill patients, data concerning preventive treatment with anti-psychotic drugs is scarce, and inconsistent (11, 12).

In one retrospective cohort study with ICU patients treated with haloperidol a lower mortality rate was found compared to non-treated ICU patients (13). Another recent study showed that haloperidol prophylaxis in non-cardiac surgical ICU patients had beneficial effects on delirium incidence and delirium free days (14). Note worthily, in this latter study no delirium risk stratification was performed, suggesting that the beneficial effects might be diluted in the whole group of ICU patients (as also patients with a low risk to develop delirium (implying they have a smaller potential beneficial effect) were included) and that more pronounced preventive effects may be present in patients with a high risk to develop delirium. Recently, a delirium prediction model for ICU patients was developed and validated (15). With this model the extent of the preventive efficacy in different groups of the a-priori delirium-risk can be determined. In view of the high incidence of delirium, the impact of delirium on outcome, and the availability of a delirium prediction model to identify high risk ICU patients, a delirium prevention protocol was implemented in clinical practice using a low dosage of haloperidol. Subsequently, the effect of this prophylactic treatment in patients with a high risk was evaluated on several relevant delirium outcome parameters (16) and compared to the period prior to the implementation of this policy. In this study it was found that in patients with a predicted risk to develop delirium of >50%, delirium incidence was 65 versus 75% (haloperidol vs historical control, respectively) and delirium-free and coma free days within 28 days 20 versus 13, respectively. Besides this, complications related to delirium (e.g. unintended removal of catheters and tubes) were significantly lower in patients receiving prophylactic haloperidol. Naturally, the pre-/post implementation design of this trial does not result in the highest level of evidence regarding the potential beneficial effects of haloperidol. Based on these results, effects of prophylactic treatment with haloperidol need to be confirmed in a randomized controlled double-blind trial. Since no

relevant side-effects were reported in the prophylactic studies (9, 10, 14, 16) with a low dosage of haloperidol and the described moderate positive results (e.g. incidence from 75 to 65%) it is conceivable that a somewhat higher dose of haloperidol may exert more pronounced beneficial effects and therefore, this will also be determined in the present study proposal.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness:

Based on historical data we know that the median predicted delirium risk is 35% in patients with an expected stay on the ICU of over one day. This is considered a high risk to develop delirium. Also patients with a history of dementia or alcohol abuse are defined as high risk patients.

To assess patients for delirium using the Confusion Assessment Method (CAM)-ICU is part of daily clinical practice in all participating centres. In this study, high risk patients will receive three times a day a study drug of which two groups receive a low dose of haloperidol (1mg or 2mg) and a third arm will receive placebo.

Concerning haloperidol: This drug is worldwide the first choice of drug to treat delirious patients. When delirium is diagnosed, patients are treated according to delirium protocol, using a higher dosage than in the prophylactic treatment period as described in this study protocol. It is recognized that early treatment of delirium has beneficial effects compared with delayed treatment (17), and (as described earlier) there is also some evidence that delirium prevention in ICU patients has beneficial effects (14, 16), but the design of these previous studies was not optimal.

Potential side-effects of haloperidol include, extrapyramidal symptoms, drowsiness, agitation, and ventricular arrhythmias. The latter are extremely rare (only case-reports are published (18-21) and related to a higher dosage of haloperidol. With the dosage that will be used in the present study (3x1 or 3x2mg daily) no relevant side-effects are anticipated. Nevertheless, and given the preventive nature of this study, extra attention is being paid on recognition of possible side-effects of haloperidol in the protocol. Importantly, in three recent prophylactic haloperidol studies (9, 14, 16) no relevant side-effects, and in particular no ventricular arrhythmias, were reported using a similar low dosage of haloperidol as described in the present protocol.

Study proposal:

In this study we aim to examine the effects of a low dosage of prophylactic haloperidol in patients with a high risk to develop delirium, defined by an expected ICU length of stay of >1 day. We use two different dosages of haloperidol in this study to compare with placebo. A dosage of 1mg, or 2mg three times a day in a double-blinded fashion resulting in a three-armed multicentre randomized double-blinded placebo-controlled trial. To relate the potential beneficial effects of haloperidol to

the a priori risk to develop delirium, the PREDELIRIC-model (15) will be used. This will enable us to determine the preventive efficacy of haloperidol in patient groups based on their risk to develop delirium. Patients that are included in the study, but leave the ICU within 24 hours will be discarded for further analysis.

Since it is recognized that the onset of delirium is on day 2 (median), early treatment is likely to be more effective, and the fact that low dosage and a short treatment duration with haloperidol has no relevant side-effects, randomization will be started immediately following identification of a high risk patient, prior to the informed consent procedure. The informed consent procedure will be started as soon as possible, and if no informed consent is be obtained patients will be excluded for this study (and study drug administration will be stopped) and the patient will be replaced until group size is achieved.

3. OBJECTIVES

Primary objective: To determine the effect of prophylactic haloperidol on number of days of survival in 28-days

Secondary Objective(s): There are five secondary objectives:

1. To determine the effect of prophylactic haloperidol on number of days of survival in 90-days
2. To determine the effect of prophylactic haloperidol on delirium incidence
3. To determine the effect of prophylactic haloperidol on number of delirium-free and coma-free days in a period of 28 days
4. To determine the effect of prophylactic haloperidol on delirium related outcome: duration of mechanical ventilation, incidence of re-intubation, incidence of ICU readmission, and incidence of unplanned removal of tubes and catheters
5. To determine the preventive efficacy of haloperidol in different patient groups based on the a priori risk to develop delirium: patients with a predicted risk up to 50%, 50-70%, 70-90%, above 90% will be evaluated
6. To evaluate side-effects of haloperidol treatment
7. To determine the efficacy of preventive haloperidol treatment on quality of life 1 and 6 months following ICU admission compared with baseline measurement

4. STUDY DESIGN

A prospective multicentre three armed block-randomized double-blind placebo-controlled prophylactic intervention study in critically ill patients with a high risk to develop delirium.

Number of centres: In total 8 centres in the Netherlands with a level 2 or 3 Intensive Care Unit will participate in this study.

Estimated study duration: Follow-up of included patients is until discharge from the ICU or in case delirium occurred until the delirium has resolved (defined by three consecutive days of negative delirium screenings) to a maximum of 28 days.
Total duration for the conduct of the study: 1 year.

5. STUDY POPULATION

5.1 Population (base)

The study population consists of consecutive critically ill patients with an expected length of ICU stay of over one day admitted to the Intensive Care Unit (ICU) of one of the participating centres:

1. Radboud University Nijmegen Medical Centre
2. University Medical Centre Utrecht
3. Gelre Hospital, Apeldoorn
   ~~Medical Centre Leeuwarden~~
4. Onze Lieve Vrouwen Gasthuis, Amsterdam
   ~~Isala Klinieken, Zwolle~~
5. Canisius Wilhelmina Ziekenhuis, Nijmegen
6. Medisch Spectrum Twente, Enschede
7. Atrium Medical Centre, Heerlen
8. Jeroen Bosch Hospital, Den-Bosch
9. Maxima Medical Centre, Veldhoven
10. Medical Centre Haaglanden, Westeind hospital, Den-Haag
11. Medical Centre Haaglanden, Antoniushove hospital, Den-Haag
12. Bronovo hospital, Den-Haag
13. St. Jansdal hospital, Harderwijk
14. University Medical Centre Groningen
15. Amphia hospital, Breda
16. Viecuri hospital, Venlo
17. Elkerliek hospital, Helmond
18. Scheperziekenhuis, Emmen
19. Diakonessenhuis, Utrecht
20. Haga hospital, Den-Haag

5.2 Inclusion criteria

All consecutive critically ill patients admitted to the Intensive Care Unit:

- age ≥ 18
- expected length of ICU stay of over one day

5.3 Exclusion criteria

- history of epilepsy, Parkinson's disease, hypokinetic rigid syndrome dementia or alcohol withdrawal
- patients admitted to the ICU for neurological reasons (including post-resuscitation patients)
- patients treated with other anti-psychotics
- prolonged QTc-time (>500msec) or history of serious ventricular arrhythmia (in last 12 months)
- pregnancy/breast feeding
- delirious before ICU admission
- serious auditory or visual disorders
- ICU-stay ≤1 day
- unable to understand Dutch

- severely mentally disabled
- serious receptive aphasia
- moribund and not expected to survive 2 days
- known allergy to haloperidol

5.4 Sample size calculation

Sample size calculation is based on the effect on number of days of survival in 28-days derived from the evaluation study using low dosage of prophylactic haloperidol (16). In our previous evaluation study the median survival time in the control group was 18 days. If the true hazard ratio of control patients relative to intervention patients is 0.85, taken into account an accrual time of 90 days with 28 days of follow-up, we will need to study 647 patients per intervention group and 647 control patients to be able to reject the null hypothesis that the experimental and control survival curves are equal with probability (power) 0.80. The Type I error probability associated with this test of this null hypothesis is 0.05. Taken into account a drop out of 10% we will include 715 patients per group. A fixed sequence procedure will be followed. First the highest dosage of prophylactic haloperidol will be compared with placebo using alpha 0.05 (two-sided). Only if H_0 is rejected, subsequently the lower dosage of prophylactic haloperidol will be compared with placebo. Cox-regression analysis will be used to test differences on 28-day survival in the intervention group compared with the placebo group.

6. TREATMENT OF SUBJECTS

6.1 Investigational product /treatment

This study involves a comparison of prophylactic haloperidol in a dosage of 1mg or 2mg administered intravenously three times a day compared with placebo of 0.9% sodium chloride.

Prophylactic treatment with haloperidol will be continued until discharge from the ICU or when delirium occurs. In the latter case, patients are subsequently treated according to the delirium protocol (with higher dosage of haloperidol).

To avoid unnecessary risks for side-effects, the dosage of the study drug will be halved in patients:

- aged ≥ 80 years
- weight ≤ 50 kg
- liver failure (serum bilirubin level > 50 µmol/L) present at time of inclusion or during the study

Patients with an adjusted dose remain allocated to their original group (intention to treat). Patients randomized to the placebo group receive sodium chloride solution 0.9% three times a day 1 ml intravenously.

<u>Haloperidol:</u>

Structure

The general structure of haloperidol

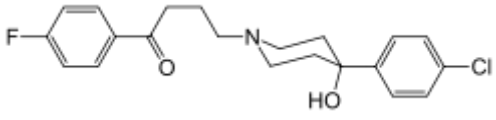

Figure 1. *General structure of haloperidol* 4-[4-(4-chlorophenyl)-4-hydroxy-1-piperidyl]-1-(4-fluorophenyl)-butan-1-one.

Properties of Haloperidol (22)

Haloperidol is a butyrophenone derivative with antipsychotic and mild sedation properties. It is a dopamine (D_2) antagonist as well as alpha-1 adrenergic antagonistic with strong central anti-dopaminergic and mild central anti-cholinergic properties.

The study drug will be prepared from the commercially available product (Haldol®) labeled by the department of Clinical Pharmacy of the Radboud University Nijmegen Medical Centre.

6.2 Use of co-intervention

Not applicable.

6.3 Escape medication

In patients that develop delirium, prophylactic treatment with the study drug (haloperidol 3x1mg, 3x2mg or placebo) will be replaced by open label treatment with haloperidol according to the delirium protocol (with higher doses of haloperidol).

6.4 Duration of treatment with study medication

Included patients are treated with the study medication for a maximum period of 28 days. Study medication will be stopped when patients are discharged from the ICU or on day 28, whatever comes first.
In case delirium occurs patients will be treated with open label haloperidol according to the delirium treatment protocol and will be followed on intention to treat analyses.

6.5 Delirium treatment

Patients with delirium (positive CAM-ICU screening) will be treated with 2mg haloperidol three times daily. In case of hypoactive delirium (only RASS scores between 0 and -3) patients are treated with a lower dosage of 3x1mg. Dosage can be increased till maximum 3x5mg in case of serious agitation or anxiety due to delirium. Patients ≥80 year or ≤50kg or with liver insufficiency should be treated with a half dosage.
Patients treated for more than three days the dosage should be reduced half when delirium disappears. When delirium does not reoccur the following day, the dosage should be halved again and can then be stopped the next day when the patient remains non-delirious. In case delirium occurs again during the reducing phase, the dosage should be doubled.

6.6 Eudract number

The EudraCT number 2012-004012-66 has been issued for our Sponsor's Protocol Code Number Delirium_Haldol-prophy.

7. INVESTIGATIONAL MEDICINAL PRODUCT

More information regarding properties, side-effects and patient information of Haloperidol is added as Appendix A (in Dutch) to this study protocol.

7.1 Name and description of investigational medicinal product

Haloperidol (trade name Haldol) is available in ampoules for parenteral use. This drug is the primary treatment of delirium for over decades, clinical experience is extensive. Prescribed dose in case of delirium is 2.5 to 5mg until a maximum dose of 20mg per day. In case of serious distress or anxiety 5mg every 30 minutes until a maximum dose of 20mg/day is recommended.
The used prophylactic dose in this study is a total of 3 (3x1 mg) or 6 (3x2mg) mg a day.

7.2 Summary of findings from non-clinical studies

Not applicable.

7.3 Summary of findings from clinical studies

Findings are comprehensively described in a Cochrane review (23) and are further listed in the Summary of Product Characteristics (Appendix-A). The Cochrane review concluded that: “There is no evidence that haloperidol in low dosage has different efficacy in comparison with the atypical antipsychotics olanzapine and risperidone in the management of delirium or has a greater frequency of adverse drug effects than these drugs. High dose haloperidol was associated with a greater incidence of side effects, mainly parkinsonism, than the atypical antipsychotics. Low dose haloperidol may be effective in decreasing the degree and duration of delirium in post-operative patients, compared with placebo. These conclusions must be tempered by the observation that they are based on small studies of limited scope, and therefore will require further corroborating evidence before they can be translated into specific recommendation for the treatment of delirium.“ Use of haloperidol was associated with lower mortality in a retrospective observational trial (13) and preventive treatment of high-risk ICU-patients resulted in lower mortality and more delirium-free days compared to a historical control group in another study (16). Effects of preventive treatment in non-ICU patients have demonstrated beneficial effects, but no adequately powered randomized controlled trial in high risk ICU patients has been conducted up to now.

7.4 Summary of known and potential risks and benefits

Summary of potential risks are listed in the Summary of Product Characteristics (Appendix-A).

7.5 Description and justification of route of administration and dosage

All prophylactic haloperidol will be administered intravenously on the Intensive Care Unit which is the regular used route of administration for this drug on the ICU. As described earlier, a dosage of 3x1 mg was associated with some beneficial effects in this population in a previous study. To determine if a higher dosage (that is still lower than the therapeutic dosage) is more effective, a additional treatment arm is added to the study, in which patients will receive 3x2 mg haloperidol.

7.6 Dosages, dosage modifications and method of administration

In this study we have two prophylactic haloperidol groups and one placebo group. Patients allocated to the treatment group will receive either 3x1mg or 3x2mg prophylactic haloperidol until discharge from the ICU or when delirium occurs. In the latter case study drug will be stopped and patients will be subsequently treated according to the delirium protocol with open-label haloperidol. To avoid unnecessary risk for side-effects the dose will be halved in patients:

- aged ≥ 80 years
- weight ≤ 50 kg
- liver failure (serum bilirubin level > 50 µmol/L)

Patients with an adjusted dosage of study drug remain allocated to their original group.
In case of occurrence of QTc-time prolongation of over 500msec combined with an increase of >10% compared to baseline QTc-time, the study drug will be stopped. After normalisation of QTc-time (<500msec.) the study drug will be restarted. If QTc-time becomes prolonged again, the study drug will be stopped definitively. The patient will remain allocated to the original study group.

7.7 Preparation and labelling of Investigational Medicinal Product

Haloperidol will be provided and labeled by the Department of Clinical Pharmacy of the Radboud University Nijmegen Medical Centre according to GMP standards. The safety Product characteristics sheet of haloperidol can be retrieved from http://www.cbg-meb.nl

7.8 Drug accountability

The department of Clinical Pharmacy of the Radboud University Nijmegen Medical Centre will fabricate the prophylactic dose of haloperidol and placebo and is responsible for the packaging and labelling. The products are transported to the intensive care units of the participating hospitals and stored there under GMP conditions.
Patients who develop delirium during the study period are treated with open label haloperidol with a dosage according to the hospital delirium protocol.

Each participating centre will keep a list of drug accountability of the included patients. On the list should be noted:

- CRF number of the patient
- Randomization group
- Inclusion date and date of last gift of study medication
- Total amount of administered ampoules

The apart list must be kept and send as soon as possible to the *PI* after all patients on the list have finished the study.

8. METHODS

8.1 Study parameters/endpoints

8.1.1 Main study parameter/endpoint

All analyses will be performed on an intention to treat basis. Main study endpoint is number of days of survival in 28-days.

8.1.2 Secondary study parameters/endpoints

Secondary Objective(s): There are six secondary outcome measures**:**

1. Survival in 90-days
2. delirium incidence
3. number of delirium-free and coma-free days in a period of 28 days
4. delirium related outcome: duration of mechanical ventilation, incidence of re-intubation, incidence of ICU readmission, and incidence of unplanned removal of tubes and catheters
5. the preventive efficacy of haloperidol in different patient groups based on the a priori risk to develop delirium: patients with a predicted risk up to 50%, 50-70%, 70-90%, above 90% will be evaluated
6. side-effects of haloperidol treatment
7. effect on quality of life

8.2 Methods of determination

Survival days in 28-days and 90-days:

This is defined as the number of days that patients survive in 28-days and 90-days, respectively. All patients will be classified as either 'alive at study day 28' or, if dead, 'dead at study day 28' on an intention to treat basis.

Delirium diagnosis:

Patients are diagnosed as delirious when they have at least one positive CAM-ICU screening during their complete ICU stay. Patients who were not delirious during their ICU-stay are considered as non-delirious patients. The duration of delirium is defined as time from first positive CAM-ICU until the beginning of three consecutive days of negative delirium screenings (ICU patients: negative CAM-ICU, ward patients: delirium observation scale score <3). Patients which are discharged from the hospital while delirious are discarded for the delirium duration calculations. When delirium occurs patients remains in the study and in their original study group for follow-up.

Delirium-and-coma-free days in 28 days:

This is defined as the amount of days that the patient is not delirious and is not in coma in 28 days starting from the day of inclusion. A delirium-and-coma-free day is defined as a negative CAM-ICU screening without Richmond Agitation Sedation Score (RASS) -4/-5 during a complete day. Or, in case a delirious patient is discharged to the ward a delirium observation scale (DOS) score (24) of less than 3 during a complete day is defined as a delirium-free day.

Duration of mechanical ventilation:

Registered time in hours that the patient is on the mechanical ventilator. If the patient is ventilated mechanically several times during one ICU admission, then the ventilator times are added. Both invasive and non-invasive ventilation will be registered.

Incidence of re-intubation:
Patients who need to be intubated within 28 days, following a previous extubation, irrespectively the reason for re-intubation, are counted as incident case for re-intubation.

Incidence of ICU readmission:
Patients who need to be readmitted to the ICU during within 28 days, irrespectively the reason for readmission, are counted as incident cases for ICU readmission.

Incidence of unplanned removal of tubes and catheters:
Incidents in which patients remove their tube or catheter themselves are counted as incident cases for unplanned removal. The period in which this is measured is during patients' ICU stay or during the period when the patients is delirious with a maximum of 28 days.

8.3 Other study and safety parameters

Since it is recognized that early-mobilization of intensive care patients may influence delirium outcome we register if this intervention was used during patients admission on the ICU and this intervention will serve as a covariate.

Reported side-effects of haloperidol treatment
During patient's treatment with the study medication, known side-effects of haloperidol (22) are pro-actively collected with a special focus on prolonged QTc-time, drowsiness, extrapyramidal symptoms, and agitation and sedation effects. All side-effects will be collected during patients' treatment with the study medication till maximum of 24 hours after stopping the study medication.
In case of the occurrence of side-effects physicians can reduce the dosage or stop the study medication, depending on the severity of the occurred side-effect and at the discretion of the attending physician. Only for prolonged QTc-time, strict stopping rules are applied, as described below.
To detect side-effects of haloperidol patients are physically examined every day for known signs of extrapyramidal symptoms (signs of parkinsonism and/or akathisia and/or dystonia). Furthermore, daily QTc-time is calculated using a 12-lead ECG or a monitor lead ECG. A QTc-time of over 500msec combined with an increase of over 10% of baseline QTc-time is defined as prolonged QTc-time. In case of QTc-time prolongation the study drug is temporary stopped until QTc-time is normalized. After normalisation of QTc-time (<500msec.) the study drug will be restarted. If QTc-time becomes prolonged again, the study drug will be stopped definitively. The patient will remain allocated to the original study group.
To determine long-term side effects, such as rigidity, and quality of life a recommended and validated quality of life questionnaire, Short Form-12 , (25), is taken at time of admission and is sent one month after ICU admission to the patients (Appendix-B)

This study is monitored by an independent data and safety monitoring board (DSMB), see 9.5.

8.4 Randomisation, blinding and treatment allocation

In this three-armed double-blinded study, patients will be allocated to either the prophylactic haloperidol 3x1mg group, or the 3x2mg group, or the placebo group. Randomisation will take place electronically using the electronic clinical report form (E-CRF). The numbered study medication will be delivered to the participating ICUs in identical packs. Code of the randomization is kept by the pharmacist and will be broken only if necessary for safety reasons. The physicians, nurses, investigators and participating patients will be blinded for treatment allocation. Patients who develop delirium are subsequently treated with open-label haloperidol according to the hospital delirium protocol and remains included in the study and allocated to their original study group.

8.5 Study procedures (Flowchart)

Delirium screening:

All consecutive ICU patients are screened for delirium and the risk for delirium which is part of daily ICU care. Delirium is assessed using the CAM-ICU at least two times a day. All patients receive high quality care which does not differ between the three study groups. So, except for delirium prophylaxis there are no other differences in intensive care treatment.

Inclusion and informed consent:

Based on historical data we know that the median predicted delirium risk is 35% in patients with an ICU stay >1 day.

Based on i) pathophysiological mechanisms, ii) studies that demonstrate that early treatment of delirium is associated with a better outcome compared to delayed treatment (17) and iii) the fact that the highest incidence of delirium occurs on day 2, we wish to randomise patients as soon as possible following their ICU admission.

Therefore randomization will be started immediately after the identification of an ICU-patient with an expected ICU length of stay of >1 day by the attending physician. Informed consent will be obtained as soon as possible, and always within 24 hours. This method of informed consent strategy is previously used in ICU patients (26). When informed consent is not obtained, study drug will be stopped immediately. In this case a maximum of one day dosage of study medication is administered to the patient resulting in a negligible risk of undesired side-effects of haloperidol.

After inclusion:

According to the randomization, study medication (haloperidol 1mg or 2 mg or placebo) is started three times a day.

Daily QTc-time (by 12-lead ECG or ECG-monitor strip) is determined and patient is examined for drowsiness and extrapyramidal symptoms. Findings are recorded in an E-CRF. The E-CRF is a secure website where the participating hospitals must login with a unique password. We already have good experience with this secure procedure in a previous international study (publication in progress). Participating hospitals only have access to their own data.

When the CAM-ICU assessments remains negative, so no delirium emerged, prophylactic haloperidol is stopped at the time the patient is discharged from the ICU or on day 28, whatever comes first.

In case delirium occurs the patient is treated for delirium according to the protocol in a dosage of haloperidol 2-5mg/8hours. These patients remain included for this study and included for analysis, on an intention to treat basis.

Delirious patients are followed until three consecutive days of negative delirium screenings occur.

End of study
The study ends when the non-delirious patient is discharged from the ICU or when the delirium follow-up is ended according to the definition of ended delirium episode until a maximum period of 28 days.

8.6 Withdrawal of individual subjects

If known, the reason for a patient to discontinue the study will be recorded in the E-CRF. A discontinuation occurs when an enrolled patient dies or ceases participation, regardless of the circumstances, prior to completion of the protocol. The investigator will determine the primary reason for discontinuation. Withdrawal due to an adverse event should be distinguished from withdrawal due to insufficient response. A discontinuation must be reported within 24 hours to the investigator if it is due to a serious adverse event. The final evaluation required by the protocol will be performed at the time of study discontinuation. The investigator will record the reason for study discontinuation, provide or arrange for appropriate follow-up (if required) for such patients, and document the cause of the patient's discontinuation.
Importantly, patients or next of kin can withdraw from the study at any time without any consequences and without the need to give an explanation if they wish to do so.

8.7 Specific criteria for withdrawal

When informed consent is received, the patient is irrevocably admitted to the study. Even if the patient is withdrawn from receiving further prophylactic haloperidol, documentation according to the study protocol must be as complete as possible.

A patient can or will be withdrawn from the study:

- upon request of the patient
- at the discretion of the investigator after serious protocol violation

Study medication MUST be discontinued if any of the following occur:

- A serious adverse event possibly related to study medication
- Other treatment-related adverse event: when it is considered by the investigator to be in the best interest of the patient to withdraw study medication
- Subject withdrawal: if the patient or the next of kin decides to withdraw from study participation
- Any other reason which may significantly affect the quality of data obtained from the study

8.8 Replacement of individual subjects after withdrawal

After withdrawal of a patient, the patient will remain allocated to the original study group for the intention to treat analysis. Withdrawn patients will not be replaced. Patients that received the first doses of study drug, in whom no informed consent is obtained will be replaced to maintain power.

8.9 Follow-up of subjects withdrawn from treatment

After withdrawal patients are monitored if medically necessary for the time of the study protocol for primary endpoint, number of days of survival in 28-day. For all patients who are prematurely withdrawn from treatment, the reason will be documented carefully. The patients who had a dose of

study medication will at least be included in the safety evaluation. For all subjects who were withdrawn after randomization, but before treatment with study medication, the reason why will be documented.

8.10 Premature termination of the study

The coordinating investigators have the right to discontinue the clinical study at any time for medical or procedural reasons.

9. SAFETY REPORTING

9.1 Section 10 WMO event

In accordance to section 10, subsection 1, of the WMO, the investigator will inform the subjects and the reviewing accredited METC if anything occurs, on the basis of which it appears that the disadvantages of participation may be significantly greater than was foreseen in the research proposal. The study will be suspended pending further review by the accredited METC, except insofar as suspension would jeopardise the patients' health. The investigator will take care that all patients are kept informed.

9.2 Adverse and serious adverse events

Adverse events are defined as any undesirable experience occurring to a patient during a clinical trial, whether or not considered related to the investigational drug. All adverse events that are considered by the investigator to be related to the study drug are classified as either serious or non-serious, and will be recorded on the adverse event page(s) of the E-CRF.

Events that are related to the underlying illness are exempt from all adverse events reporting unless investigator deems the event to be possibly related to the administration of study drug. For instance, a patient admitted because of septic shock that develops anuria due to a low blood pressure than the anuria will not be reported as adverse event. Events that are not clearly related to the underlying disease will be reported as adverse event and also the presentation of all known side-effects of haloperidol will be reported as adverse events.

For all adverse events, the investigator will pursue and obtain information both to determine the outcome of the adverse event and to assess whether it meets the criteria for classification as a serious adverse event requiring immediate notification. For all adverse events, sufficient information should be obtained by the investigator to determine the causality of the adverse event (i.e. study drug or other illness). The investigator is required to assess causality and indicate that assessment on the E-CRF. Information on other possible causes of the event, including concomitant medications and illnesses must be provided. The investigator's assessment of causality must also be provided. If causality is unknown, it should be attributed to the study drug. In the case of a subject death, a summary of available autopsy finding must be submitted. The investigator should ensure that information reported immediately by telephone or other means and information entered in the E-CRF are accurate and consistent.

The following adverse events will be collected:

- Serious adverse events (SAEs)
- Non-serious adverse events that are considered by the investigator to be possibly related to study drug. Non-serious adverse events that are known side-effects of haloperidol are: prolonged QTc-time (>500msec combined with >10% increase compared to baseline) drowsiness, extrapyramidal symptoms, agitation and sedation effects
- Adverse events that lead to permanent discontinuation of the study drug administration

A Serious adverse event is any untoward medical occurrence or effect at any dose that results in one of the following outcomes and is <u>not classified as a clinical outcome of delirium or the underlying disease</u> using the description above:

- death that is not related to the underlying disease or sequel of the underlying disease, or death that is considered by the investigator to be related to study drug
- prolonged inpatient hospitalization or rehospitalization
- a life-threatening experience (that is, immediate risk of dying)
- persistent or significant disability/incapacity
- congenital anomaly/birth defect
- considered significant by the investigator for any other reason

Serious adverse event (SAE) collection begins after the informed consent has been signed and the patient has received study drug. If a patient experiences a serious adverse event after signing informed consent, but prior to receiving study drug, the event will NOT be collected unless the investigator feels the event may have been caused by a protocol procedure.

All SAEs will be reported, through the webportal *ToetsingOnline,* to the accredited METC that approved the protocol, according to the requirements of that METC. Reporting of SAEs will be done within 15 days after the first knowledge of the principle investigator of the serious adverse reaction. Furthermore, the DSMB will be notified upon all deaths (whether or not related to study drug administration) and any other of previous mentioned SAEs , and will be provided with all relevant clinical details of the event. The DSMB can decide to unblind the subject and terminate the trial. SAEs that result in death or are life threatening should be reported expedited. The expedited reporting will occur not later than 7 calendar days after the responsible investigator has first knowledge of the adverse reaction. This is for a preliminary report with another 8 days for completion of the report.

9.3 Suspected unexpected serious adverse reactions (SUSAR)

Adverse reactions are all untoward and unintended responses to an investigational product related to any dose administered.

Unexpected adverse reactions are adverse reactions, of which the nature, or severity, is not consistent with the applicable product information (e.g. Investigator's Brochure for an unapproved IMP or Summary of Product Characteristics (SPC) for an authorised medicinal product).

The principle investigator will report expedited the following SUSARs to the METC:

- SUSARs that have arisen in the clinical trial that was assessed by the METC;
- SUSARs that have arisen in other clinical trials and with the same medicinal product, and that could have consequences for the safety of the subjects involved in the clinical trial that was assessed by the METC.

All SUSARs will be reported, through the webportal *ToetsingOnline,* to the accredited METC that approved the protocol, according to the requirements of that METC.

All SUSARs are recorded in an overview list (line-listing) that will be submitted to the METC. This line-listing provides an overview of all SUSARs from the study medicine, accompanied by a brief report highlighting the main points of concern.

The principal investigator (PI) will report expedited all SUSARs to the competent authority, the Medicine Evaluation Board and the competent authorities in The Netherlands.

The expedited reporting will occur not later than 15 days after the PI has first knowledge of the adverse reactions. For fatal or life threatening cases the term will be maximal 7 days for a preliminary report with another 8 days for completion of the report.

9.4 Follow-up of adverse events

All adverse events will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.

9.5 Data Safety Monitoring Board (DSMB)

A DSMB is established for this study to perform ongoing safety surveillance and to perform interim analyses on the safety data. This committee is an independent committee and is composed of the following persons:

Prof. dr. G. Scheffer, anaesthesiologist
Radboud University Nijmegen Medical Centre
Department of Anesthesiology, PO box 9101, 6500 HB Nijmegen, The Netherlands

Dr. M. Pop-Purseleanu, psychiatrist
Radboud University Nijmegen Medical Centre
Department of Psychiatry, PO box 9101, 6500 HB Nijmegen, The Netherlands

Drs. T. de Haan, statistician
Radboud University Nijmegen Medical Centre
Department of Epidemiology, Biostatistics and HTA, PO box 9101, 6500 HB Nijmegen, The Netherlands

Meetings of DSMB

The initial DSMB meeting will be scheduled before the start of the trial.
An interim analysis will be performed after inclusion of 175 and 350, 500 and 1000 patients in the study. For reasons of safety and futility interim analyses will be performed after 175, 350 and 500 patients. Interim analyses after 1000 patients will be performed for safety and determining superiority. To make it possible to review the side-effects of haloperidol and to determine superiority of the intervention or placebo the DSMB will be deblinded for this study, all researchers remains blinded. Determining superiority of the intervention will take place only once during the study, after 1000 patients using an alpha level of 0.00304 (two sided). When no significant differences are found during this interim analysis, the study continues, and an alpha of 0.049 for the final analysis can be used. For the distribution of both alpha levels we used the Lan-DeMets cumulative alpha spending function of the O-Brien-Fleming alpha spending method. In case a significant difference between groups is found, deblinding will take place and the study will be terminated. Note, this deblinding is for DSMB members only. Therefore, the DSMB will be partially deblinded during the interim analysis to assess the safety. Only following data-base lock, deblinding will be open to all investigators.
The interim analysis will focus on the following issues:

- Serious Adverse Events (according to the definition of the study protocol): type, severity, duration, action taken and attributability to the drug
- Superiority of haloperidol or superiority of placebo (only after 1000 patients)
- Vital signs and other safety parameters
- Procedures and methodology.

A DSMB meeting may be requested by DSMB members, the Project Leader or Principal Investigator at any time to discuss safety concerns. Decisions to hold ad hoc meetings will be made by the PI and DSMB Chair. Meetings may be held by conference calls or videoconferences or as face-to-face meetings. In the event a DSMB member cannot attend a meeting, he/she may receive a copy of the closed session DSMB report.

The following criteria are defined on which basis the DSMB may decide to terminate the trial prematurely:

- Any serious adverse event
- A proven superiority (*p=0.00304, two-sided)* of any dose of haloperidol over placebo or a proven superiority (*p=0.00304, two-sided)* of placebo over haloperidol determined during the interim analysis

10. STATISTICAL ANALYSIS

10.1 Descriptive statistics

For the descriptive statistics, values will be given as mean ± SD or median and interquartile ranges, depending on their distribution. For comparisons, unpaired Students t –tests, Mann–Whitney U-tests or Chi-square tests for parametric and nonparametric data as appropriate will be used. Survival (Cox regression) analyses with Kaplan-Meier curves will be used as graphical presentation. Cox proportional hazard regression analyses will be used to estimate the hazard ratio for survival with the use of haloperidol versus placebo. Furthermore adjusting for relevant covariates (APACHE-II score, age, sex and sepsis) will be performed

All statistical tests are two-sided and statistical significance is defined as a *P*-value <0.05. All data are analyzed using SPSS version 20.01 (SPSS, Chicago, IL).

Intention to treat analysis will be performed.

10.2 Interim analysis

As described previously, a safety, futility and superiority interim analysis will be performed by DSMB after 175, 350, 500 (safety and futility) and 1000 (safety and superiority) included patients to determine side-effects on all measure points and for determining futility or superiority of intervention or placebo on the primary endpoint number of days of survival in 28-days.

11. ETHICAL CONSIDERATIONS

11.1 Regulation statement

The study will be conducted according to the principles of the Declaration of Helsinki (version 2008) and in accordance with the Medical Research Involving Human Subjects Act (WMO).

11.2 Recruitment and consent

Patients recognized as high risk for delirium are recruited as soon as possible following ICU admission. In view of the relative early onset of delirium after ICU admission it is important to start randomization as soon as possible. Patients with delirium have a two times higher risk to die (after adjusting for severity of illness) and delirium is recognized as an independent predictor of mortality. Furthermore, early delirium treatment results in a lower mortality compared with delayed treatment. Therefore we believe this is an emergency situation, hence randomization is started immediately after the recognition of the high risk patient. Informed consent is followed as soon as possible. If the patient or the next of kin refuses study participation than the delirium prophylaxes is stopped immediately.

11.3 Benefits and risks assessment, group relatedness

Based on previous studies we expect that patients prophylactic treated with haloperidol would benefit from the treatment on several health aspects as previously described. Regarding the reported side-effects of a low dosage of haloperidol we expect less side-effects. Included patients will be closely monitored for possible side-effects.

11.4 Compensation for injury

The sponsor/investigator has a liability insurance which is in accordance with article 7, subsection 6 of the WMO.

The sponsor has an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO and the Measure regarding Compulsory Insurance for Clinical Research in Humans of 23th June 2003). This insurance provides cover for damage to research subjects through injury or death caused by the study.

1. € 450.000,-- (i.e. four hundred and fifty thousand Euro) for death or injury for each subject who participates in the Research;
2. € 3.500.000,-- (i.e. three million five hundred thousand Euro) for death or injury for all subjects who participate in the Research;
3. € 5.000.000,-- (i.e. five million Euro) for the total damage incurred by the organisation for all damage disclosed by scientific research for the Sponsor as 'verrichter' in the meaning of said Act in each year of insurance coverage.

The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

11.5 Compensation for injury

Patients or next of kin will receive no compensation for study participation.

12. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

12.1 Handling and storage of data and documents

All data will be collected electronically in an E-CRF. The E-CRF is a secure website where the participating hospitals must login with a unique password. We already have good experience with this secure procedure in a previous international study (publication in progress).
The handling of patients data complies with the Dutch Personal Data Protection Act (in Dutch: De Wet Bescherming Persoonsgegevens, Wbp). Participating hospitals only have access to their own data. The key to the login code will be safeguarded by the PI.

12.2 Monitoring and Quality Assurance

The study will be monitored by an internal monitor of the Radboud University Nijmegen Medical Centre. The stored data in the E-CRF will be monitored as well as labels of the study medication per included patient. Furthermore all informed consents, SAE reports and the trial master file will be monitored. The study will be monitored after 175, 350, 500 patients, 1000 patients, and after finishing the inclusion according to the Monitoring plan (Appendix C)

12.3 Annual progress report

The *PI* of the study will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

12.4 End of study report

The *PI* of the study will notify the accredited METC of the end of the study within a period of 90 days. The end of the study defined as the last patient's last visit.
In case the study is ended prematurely, the investigator will notify the accredited METC within 15 days, including the reasons for the premature termination.
Within one year after the end of the study, the *PI* will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC.

12.5 Public disclosure and publication policy

The PI and PL are first and last author of the manuscript. Furthermore, each participating centre delivers one co-author for the publication. This trial is not sponsored by a pharmaceutical company of in any other way. Authors have no conflict of interest to declare. The study will be published regardless the results of the trial.

13. STRUCTURED RISK ANALYSIS

13.1 Potential issues of concern

In this study we examine the effectiveness of prophylactic treatment with haloperidol in ICU patients. Haloperidol is worldwide the first choice of drug in delirious patients. When delirium is diagnosed, patients are treated according to delirium protocol, using a higher dosage (up to 20 mg/day) than in the prophylactic treatment period (maximally 6 mg/day) as described in this study protocol.

Potential side-effects of haloperidol include, extrapyramidal symptoms, drowsiness, agitation, and ventricular arrhythmias. The latter are extremely rare (only case-reports are published (18-21) and related to a higher dosage of haloperidol. With the dosage that will be used in the present study (3x1 or 3x2mg daily) no relevant side-effects are anticipated. Importantly, in three recent prophylactic haloperidol studies (9, 14, 16) no relevant side-effects and in particular no ventricular arrhythmias were reported using a similar low dosage of haloperidol as described in the present protocol.

All potential side-effects can only be detected by physical examination of the patient and by measurement of the QTc-time, not by measurement of special biomarkers. Therefore in this study we will pay extra attention on the physical examination of the patient to detect these potential side-effects. The most important side-effect, which is rarely been seen, is ventricular arrhythmia due to a prolonged QTc-time. For this reason daily measurement of the QTc-time is obligated and in case of prolongation the study drug has to be stopped.

Furthermore a DSMB is appointed for timely recognition of a possible imbalance between harm and benefit result of the study.

It has been shown that delirium occurs frequently (3-6) in ICU patients and is associated with serious health consequences (4-6) and increased mortality (6-8). Early treatment of delirium has beneficial effects compared with delayed treatment (17), and also there is some evidence that delirium prevention in ICU patients has beneficial effects (14, 16). In prophylactic studies using a low dosage of haloperidol no relevant side-effects were reported while indeed positive effects were demonstrated (14, 16).

13.2 Synthesis

In ICU patients with a high risk for delirium the adverse effects of delirium may not outweigh the potential beneficial effects of a low dosage prophylactic haloperidol. Also it is important to know that the standard treatment of delirium is haloperidol, but using a higher dosage as we use in this prophylactic study.

In our study we have made every effort for early recognition of potential side-effects and to minimize any adverse effects of our study. In no other study using a low dosage of haloperidol important adverse effects were demonstrated. Therefore we feel that the remaining risk for the patient of possible side-effects of prophylactic treatment with a low dosage of haloperidol is acceptable in this study.

14. REFERENCES

1. American Psychiatric A. Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR). Washington D.C.2000.
2. Dubois MJ, Bergeron N, Dumont M, Dial S, Skrobik Y. Delirium in an intensive care unit: a study of risk factors. Intensive Care Med. 2001;27(8):1297-304.
3. American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference: definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. Crit Care Med. 1992;20(6):864-74.
4. Ely EW, Gautam S, Margolin R, Francis J, May L, Speroff T, et al. The impact of delirium in the intensive care unit on hospital length of stay. Intensive Care Med. 2001;27(12):1892-900.
5. Ouimet S, Kavanagh BP, Gottfried SB, Skrobik Y. Incidence, risk factors and consequences of ICU delirium. Intensive Care Med. 2007;33(1):66-73.
6. van den Boogaard M, Schoonhoven L, van der Hoeven JG, van Achterberg T, Pickkers P. Incidence and short-term consequences of delirium in critically ill patients: A prospective observational cohort study. Int J Nurs Stud. 2012;49(7):775-83.
7. van den Boogaard M, Peters SA, van der Hoeven JG, Dagnelie PC, Leffers P, Pickkers P, et al. The impact of delirium on the prediction of in-hospital mortality in intensive care patients. Crit Care. 2010;14(4):R146.
8. Ely EW, Shintani A, Truman B, Speroff T, Gordon SM, Harrell FE, Jr., et al. Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit. JAMA: Journal of the American Medical Association. 2004;292(2):168-9.
9. Kalisvaart KJ, de Jonghe JF, Bogaards MJ, Vreeswijk R, Egberts TC, Burger BJ, et al. Haloperidol prophylaxis for elderly hip-surgery patients at risk for delirium: a randomized placebo-controlled study. J Am Geriatr Soc. 2005;53(10):1658-66.
10. Kaneko T, Cai J, Ishikura T, Kobayashi M, Naka T, Kaibara N. Prophylactic consecutive administration of haloperidol can reduce the occurrence of postoperative delirium in gastrointestinal surgery. Yonago Acta Medica. 1999;42(3):179-84.
11. Prakanrattana U, Prapaitrakool S. Efficacy of risperidone for prevention of postoperative delirium in cardiac surgery. Anaesth Intensive Care. 2007;35(5):714-9.
12. Gamberini M, Bolliger D, Lurati Buse GA, Burkhart CS, Grapow M, Gagneux A, et al. Rivastigmine for the prevention of postoperative delirium in elderly patients undergoing elective cardiac surgery--a randomized controlled trial. Crit Care Med. 2009;37(5):1762-8.
13. Milbrandt EB, Kersten A, Kong L, Weissfeld LA, Clermont G, Fink MP, et al. Haloperidol use is associated with lower hospital mortality in mechanically ventilated patients. Crit Care Med. 2005;33(1):226-9.
14. Wang W, Li HL, Wang DX, Zhu X, Li SL, Yao GQ, et al. Haloperidol prophylaxis decreases delirium incidence in elderly patients after noncardiac surgery: A randomized controlled trial. Crit Care Med. 2012;40(3):1-9.
15. van den Boogaard M, Pickkers P, Slooter AJ, Kuiper MA, Spronk PE, van dV, et al. Development and validation of PRE-DELIRIC (PREdiction of DELIRium in ICu patients) delirium prediction model for intensive care patients: observational multicentre study. BMJ. 2012;344:e420.
16. van den Boogaard M, Schoonhoven L, Van Achterberg T, Van der Hoeven JG, Pickkers P. Haloperidol prophylaxis in critically ill patients with a high risk for delirium. Critical Care. 2013;17:R9.
17. Heymann A, Radtke F, Schiemann A, Lutz A, MacGuill M, Wernecke KD, et al. Delayed treatment of delirium increases mortality rate in intensive care unit patients. J Int Med Res. 2010;38(5):1584-95.
18. Ginwalla M, Biblo LA, Paydak H. Torsade de pointes following intravenous haloperidol administration in a patient with complete heart block. WMJ. 2009;108(1):48-50.
19. O'Brien JM, Rockwood RP, Suh KI. Haloperidol-induced torsade de pointes. Ann Pharmacother. 1999;33(10):1046-50.
20. Perrault LP, Denault AY, Carrier M, Cartier R, Belisle S. Torsades de pointes secondary to intravenous haloperidol after coronary bypass grafting surgery. Can J Anaesth. 2000;47(3):251-4.
21. Sharma ND, Rosman HS, Padhi ID, Tisdale JE. Torsades de Pointes associated with intravenous haloperidol in critically ill patients. Am J Cardiol. 1998;81(2):238-40.
22. Kompas F. Farmacotherapeutisch Kompas 2012. J.R.B.J.Brouwers, editor. Amstelveen: Prelum Uitgevers; 2012.

23. Lonergan E, Britton AM, Luxenberg J, Wyller T. Antipsychotics for delirium. Cochrane Database Syst Rev. 2007(2):CD005594.
24. Schuurmans MJ, Shortridge-Baggett LM, Duursma SA. The Delirium Observation Screening Scale: a screening instrument for delirium. Res Theory Nurs Pract. 2003;17(1):31-50.
25. Gandek B, Ware JE, Aaronson NK, Apolone G, Bjorner JB, Brazier JE, et al. Cross-validation of item selection and scoring for the SF-12 Health Survey in nine countries: results from the IQOLA Project. International Quality of Life Assessment. J Clin Epidemiol. 1998;51(11):1171-8. Epub 1998/11/17.
26. Annane D, Outin H, Fisch C, Bellissant E. The effect of waiving consent on enrollment in a sepsis trial. Intensive Care Med. 2004;30(2):321-4. Epub 2004/01/10.

15. APPENDIX-A

Added to this protocol as supplemental file.

16. APPENDIX-B

VRAGENLIJST

Short Form (SF)-12

1. Hoe zou u over het algemeen uw gezondheid noemen?

Uitstekend	Zeer goed	Goed	Matig	Slecht
☐	☐	☐	☐	☐

2. De volgende vragen gaan over uw bezigheden die u mogelijk doet op een doorsnee dag. Wordt u door uw gezondheid beperkt bij deze bezigheden? Zo ja, in welke mate?

	Ja, ernstig beperkt	Ja, een beetje beperkt	Nee, helemaal niet beperkt
a. **Matige inspanning,** zoals het verplaatsen van een tafel, stofzuigen, zwemmen of fietsen	☐	☐	☐
b. **Een paar** trappen oplopen	☐	☐	☐

3. **Heeft u in de <u>afgelopen 4 weken</u> één van de volgende problemen bij uw werk of andere dagelijkse bezigheden gehad, <u>ten gevolge van uw lichamelijke gezondheid</u>?**

	Ja	Nee
a. U heeft **minder bereikt** dan u zou willen	☐	☐
b. U was beperkt in het **soor*t*** werk of andere bezigheden	☐	☐

4. Heeft u in de <u>afgelopen 4 weken</u>, een van de volgende problemen ondervonden bij uw werk of andere dagelijkse bezigheden <u>ten gevolge van emotionele problemen</u> (zoals depressieve of angstige gevoelens)?

	Ja	Nee
a. U heeft **minder** *bereikt* dan u zou willen	☐	☐
b. U deed uw werk of andere bezigheden niet zo **zorgvuldig** als gewoonlijk	☐	☐

5. In welke mate bent u <u>afgelopen 4 weken</u> door <u>pijn</u> gehinderd in uw normale werk (zowel werk buitenshuis als huishoudelijk werk)?

Helemaal niet	Een klein beetje	Nogal	Veel	Heel erg veel
☐	☐	☐	☐	☐

6. Deze vragen gaan over hoe u zich voelt en hoe het met u ging in de <u>afgelopen 4 weken</u>. Wilt u a.u.b. bij elke vraag het antwoord geven dat het best benadert hoe u zich voelde. Hoe vaak gedurende de <u>afgelopen 4 weken</u>*:*

	Altijd	Meestal	Vaak	Soms	Zelden	Nooit
a. Voelde u zich rustig en tevreden?	☐	☐	☐	☐	☐	☐
b. Had u veel energie ?	☐	☐	☐	☐	☐	☐
c. Voelde u zich somber en neerslachtig?	☐	☐	☐	☐	☐	☐

7. Hoe vaak hebben uw <u>lichamelijke gezondheid of emotionele problemen</u> gedurende de <u>afgelopen 4 weken gehinderd</u> bij uw sociale activiteiten (zoals vrienden of familie bezoeken, etc)?

Altijd	Meestal	Soms	Zelden	Nooit
☐	☐	☐	☐	☐

8. Ik heb de laatste 4 weken last van stijfheid bij bewegen?

Altijd	Meestal	Soms	Zelden	Nooit
☐	☐	☐	☐	☐

17. APPENDIX-C

Monitoring Plan

Studie	:	Effects of prophylactic use of haloperidol in critically ill patients with a high risk for delirium
Onderzoeker	:	Dr. M. van den Boogaard (Principal Investigator)
Hoofdonderzoeker	:	Prof. Dr. P. Pickkers (Project Leader)
Afdeling	:	Intensive Care
Monitor	:	Dr. D. Thijssen
Datum	:	17-09-2012

Voor bovengenoemde studie zijn de volgende afspraken gemaakt over het monitoren:

Data verificatie

Op site monitoren wordt toegepast om de kwaliteit en validiteit van onderzoeksdata te waarborgen. Getrainde en onafhankelijke monitors voeren brondata verificatie uit op de onderzoeksdata door de data in de Case Report Forms (CRF's) te vergelijken met de beschikbare brondocumentatie.

Een volledige controle zal plaatsvinden op:

- Trial Master File
- Informed Consent formulieren (aanwezigheid en correctheid)
- In- en exclusiecriteria
- Melding en follow-up van (serious) adverse events
- Alle E-CRF data van 10% van de geïncludeerde patiënten en de labels van de toegediende studie medicatie (drug accountability).
- Kritische items voor de studie, te weten: compleetheid E-CRF data met name uitkomstmaten delirium, mortaliteit, delirium vrije dagen en bijwerkingen studie medicatie

Naast de volledige controle van bovengenoemde items, wordt 10% van de patiënten gecontroleerd. Deze patiënten worden door de monitor steeksproefsgewijs geselecteerd voor aanvang van het monitorbezoek.

De kwaliteit van de data wordt beoordeeld op basis van het aantal queries. Indien de data minder dan 90% correct zijn, wordt overlegd met de hoofdonderzoeker of extra monitoring nodig is.

Naast brondata verificatie, worden openstaande actiepunten van voorgaande monitorbezoeken langsgelopen en controleert de monitor de Trial Master File.

Frequentie van monitoring

De monitor bezoekt de site tijdens de studie (na 175, 350, 500 en na 1000 patiënten en na beëindiging van de studie).

Rapportage

De monitor rapporteert schriftelijk aan de onderzoeker en de hoofdonderzoeker na elk monitorbezoek aan de onderzoeksafdeling. Dit rapport bevat de volgende informatie:

- Een lijst van de controles die uitgevoerd zijn
- Een algemene beschrijving van de kwaliteit en de relevante bevindingen
- Een lijst van specifieke queries en tekortkomingen
- Een overzicht van de genomen acties en aanbevelingen om de naleving van het protocol en de richtlijnen te waarborgen

Daarnaast wordt een schriftelijk rapport gemaakt van het initiatie en close-out bezoek.

Geschreven door: [naam monitor]

_____ _____

Handtekening Datum

Akkoord: [naam onderzoeker]

_____ _____

Handtekening Datum

Akkoord: [naam hoofdonderzoeker]

_____ _____

Handtekening Datum

STATISTICAL ANALYSIS PLAN

REDUCE study, pRophylactic halopEriDol Use for Delirium in iCu patiEnts with a high risk for delirium;

A randomized placebo-controlled double-blind multicentre trial

Statistical Analysis Plan (SAP)

Author: Mark van den Boogaard, senior researcher at department of Intensive Care Medicine, Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands

Date: April 04th, 2014

Version: 1

Signed agreement on Statistical Analysis Plan

This analysis plan was reviewed and approved by,

- ✓ Peter Pickkers, Professor in Intensive Care Medicine, Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands
- ✓ Hans van der Hoeven, Professor in Intensive Care Medicine, Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands
- ✓ Saskia Houterman, Epidemiologist, Catharina Hospital, Eindhoven, the Netherlands
- ✓ Ton de Haan, Statistician, Department for Health Evidence, Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands

List of abbreviations

APACHE-II:	Acute Physiology and Chronic Health Evaluation-II
CAM-ICU:	Confusion Assessment Method-Intensive Care Unit
DOS:	Delirium Observation Scale
DSMB:	Data Safety Monitoring Board
E-CRF:	Electronic Clinical Report Form
GMP:	Good Manufacturing Practice
ICU:	Intensive Care Unit
ITT:	Intention-to-treat
IV:	Intravenously
METC:	Medical research ethics committee (MREC)
MITT:	Modified Intention-to-Treat
(E-)PREDELIRIC:	(early) Prediction delirium risk in ICU patients
PP:	Per Protocol
RASS:	Richmond Agitation Sedation Scale
SAE:	Serious Adverse Event
SUSAR:	Suspected Unexpected Serious Adverse Reaction
WMO:	Medical Research Involving Human Subjects Act

Inhoud

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1. DESCRIPTION OF THE STUDY

AIM

The aim of this study is to determine the effect of a prophylactic low dosage of haloperidol on 28-day survival, and in a subgroup of patients the incidence of delirium and other delirium related outcome measures and quality of life, compared with placebo, in ICU patients with an expected ICU stay of more than one day.

Secondly, to relate the potential beneficial effects of haloperidol to the a-priori risk to develop delirium, using two ICU delirium prediction models.[1-3]

Lastly, to evaluate the safety of prophylactic haloperidol.

DESIGN

A prospective, multicentre, three-armed, permuted block-randomized, double blind, placebo-controlled prophylactic intervention study will be conducted in critically ill patients with a high risk to develop delirium. The study design has an adaptive character, as the results of the interim analysis will determine whether or not the study will be completed with 2 active (and 1 placebo) arms, or if 1 active arm will be dropped.

STUDY POPULATION

Inclusion criteria

All consecutive critically ill patients admitted to the ICU aged ≥ 18 years at the time of ICU admission with an expected length of ICU stay of over one day that do not fulfil one of the exclusion criteria are eligible.

Exclusion criteria

1. No informed consent obtained;
2. Documented delirium prior to ICU admission;
3. History of epilepsy, Parkinson's disease, hypokinetic rigid syndrome, dementia or alcohol withdrawal syndrome;
4. Patients admitted to the ICU for any other neurological disease (including post-cardio-pulmonary resuscitation patients, and patients admitted with coma due to overdose);
5. Patients treated with an anti-psychotic therapy last 30 days prior to ICU admission;
6. Prolonged QTc-time (>500msec) or history of clinically relevant ventricular arrhythmia in last 12 months;
7. Pregnant/breast feeding;

8. Reasons that impair delirium assessment with the CAM-ICU:
    a. serious auditory or visual disorders
    b. unable to understand Dutch or English
    c. severely mentally disabled
    d. serious receptive aphasia;
9. Moribund and not expected to survive 2 days;
10. Known allergy/intolerance to haloperidol.

RANDOMIZATION AND PREVENTIVE TREATMENT

Block randomization will be applied by the pharmacist. The randomization numbers are coupled with the Clinical Report Form (CRF) number and the number of study medication box. Boxes are numbered and consist of 12 ampoules of study drug. If necessary, when a patient is admitted to the ICU for more than 4 days and is not delirious, a new box will be assigned to this patient consisting of the same study regime as the previous box. All study medication will be manufactured by the Department of Clinical Pharmacy of the Radboud University Nijmegen Medical Centre, which holds a Good Manufacturing Practice certificate. Ampoules of study medication consist of 1 mg/mL or 2 mg/mL haloperidol or 1 mL sodium chloride 0.9% solution, all with a total volume of 1 mL. The randomization code is kept by the pharmacist and will be broken only if necessary for safety reasons. Only the pharmacist of the Radboud University Nijmegen Medical Centre and the data safety management board (DSMB) are unblinded for this study.

Intervention and control group

This study involves a comparison of prophylactic haloperidol in a dosage of 3x1mg (intervention group 1) or 3x2mg (intervention group 2) administered as a bolus intravenously compared with placebo of 0.9% sodium chloride (control group) administered intravenously in a double-blind fashion. All ampoules and drug boxes have fully identical appearance.
The first dose of study medication needs to be administered within 24 hours after ICU admission. In case it is not possible to ask the patient or the family, a deferred consent procedure will be started. In that case, within 24 hours after the first administering of the study medication the patient or the family needs to provide their consent, otherwise study medication will be stopped and considered as not included.

To decrease the likelihood of side effects in specific cohorts, the dose of the study drug will be halved in patients:

- aged ≥ 80 years
- weight ≤ 50 kg
- suffering from liver failure (indicated by serum bilirubin level >50 µmol/L) present at time of inclusion or during the study

For the primary analysis, patients with an adjusted dose remain allocated to their original group (intention-to-treat; ITT).

End of study medication

Prophylactic treatment with haloperidol will be continued until day 28, or discharge from the ICU (whatever comes first), or until delirium occurs. In the latter case, patients will be treated according to the delirium treatment protocol (possibly with a higher dosage of open label haloperidol).

In case delirium occurs, assessed with the recommended delirium assessment tools, the CAM-ICU or the ICDSC, patient's study medication (prophylaxis treatment) will be stopped and the patient will be treated with open label haloperidol according to the delirium treatment protocol described below. Primary analyses will be on intention-to-treat basis. Study medication will not be restarted once delirium subsides. Also in patients that are re-admitted to the ICU within 28-days study medication will not be restarted. In patients in whom delirium subsides, therapeutic haloperidol is stopped and study medication is not restarted.

Delirium treatment

Patients with delirium (defined as a positive CAM-ICU test) will be treated with open label 2mg haloperidol intravenously three times daily. Patients suffering from *hypoactive* delirium (only RASS scores between 0 and -3) and patients age ≥80 years, weight ≤50kg or having liver failure, will be treated with a lower dosage (3x1mg) intravenously. Dosage can be increased up to a maximum of 3x5mg in case of serious agitation or anxiety due to delirium. Additionally, midazolam, clonidine, propofol or dexmedetomidine may be used as an escape therapy in case of serious agitation with insufficient efficacy of haloperidol according to usual patient care. Furthermore, clinicians may overrule the treatment advise for individual patients if deemed necessary.

In patients treated for more than three days, the dosage will be halved when delirium has subsided. When delirium does not re-occur the following day (CAM-ICU remains negative), the dosage will be halved again and then stopped on the third day when the patient remains non-delirious. In case delirium re-occurs during the reducing phase, the original dose will be restarted.

2. DATA COLLECTION

All data will be collected electronically in an electronic clinical report form (E-CRF). The GCP certified data management system from Castor (https://data.castoredc.com/#studies) where the participating hospitals logged in using a unique password. Participating hospitals will only have access to their own data. Of all included patients relevant demographic variables will be collected, including age, gender, (E-) PREDELIRIC score, APACHE-II score and diagnosis group. Furthermore,

outcome related variables will be collected (table 1) and variables that may influence the delirium outcome, i.e. dexmedetomidine[4] and early mobilization.[5] Concerning the study medication, we will collect data on the cumulative amount of administered study drug, as well as administered open-label haloperidol and other anti-delirium drugs in case delirium occurs.

3. OBJECTIVES and DEFINITIONS

Primary objective

To determine the effect of prophylactic haloperidol use on 28-days survival.

Secondary Objectives

There are nine secondary objectives:

- To determine the effect of prophylactic haloperidol use on 90-days survival; in both survival analyses, stratification for delirium incidence will be performed
- To determine the effect of prophylactic haloperidol use on the incidence of delirium
- To determine the effect of prophylactic haloperidol use on the number of delirium- and coma-free days in a period of 28 days
- To determine the effect of prophylactic haloperidol use on delirium related outcomes: time to successful extubation, incidence of re-intubation, incidence of ICU readmission, and incidence of unplanned removal of tubes and catheters
- To evaluate the incidence and severity of side-effects of haloperidol prophylaxis
- To determine the effect of prophylactic haloperidol use on quality of life after six months
- To determine the effect of prophylactic haloperidol in different subgroups
- To determine the effect of prophylactic haloperidol on quality of life 6 months following ICU admission

Definitions

The definition of the objective variables are depicted in table 1.

Table 1. Definition of study objectives

	Definition
Primary objective	
Survival days in 28-days	Number of days that patients survive in 28-days, following inclusion. All patients will be classified as either 'alive at study day 28' or, if dead, 'dead at study day 28' on an intention to treat basis
Secondary objectives	
Survival days in 90-days	Number of days that patients survive in 90-days following inclusion. All patients will be classified as either 'alive at study day 90' or, if dead, 'dead at study day 90' on an

	intention to treat basis
Delirium diagnosis	Patients are diagnosed as delirious when they have at least one positive CAM-ICU screening during their complete ICU stay. Patients who were not delirious during their ICU-stay are considered as non-delirious patients.
Delirium-and-coma-free days in 28 days	Number of days that the patient is alive and not delirious and not in coma in 28 days starting from the day of inclusion. A delirium-and-coma-free day is defined as a negative CAM-ICU screening with a Richmond Agitation Sedation Score (RASS) greater than (more alert than) -3/-4/-5 during a day. Delirious ICU patients discharged to the ward were followed until the end of the delirium episode defined as a delirium observation scale (DOS) score[6] of less than 3 during a complete day. Days after ICU discharge are counted as 'days without delirium and coma' if the patient is discharged without delirium from the ICU. In case of delirious patients, days after the last positive delirium screening, either the CAM-ICU or DOS, are counted as 'days without delirium and coma'. Patients who do not survive the 28-days are being censored from the day of dying
Duration of mechanical ventilation	Time in days that the patient is on mechanical ventilation. If the patient is ventilated mechanically several periods of time during one ICU admission, then the days on mechanical ventilation are added. Both invasive and non-invasive ventilation will be registered. Ventilator-free days (in 28 days) will be calculated
Length of ICU stay	Number of days the patient is admitted to the ICU. If the patient is re-admitted to the ICU during hospitalization, days of ICU admission are summed
Length of hospital stay	Number of days the patient is admitted to the hospital
Incidence of re-intubation	Patients who need to be intubated within 28 days from randomisation, following a previous extubation, irrespectively the reason for re-intubation, are counted as incident case for re-intubation
Incidence of ICU readmission	Patients who need to be readmitted to the ICU within 28 days from randomisation, irrespectively the reason for readmission, are counted as incident cases for ICU readmission
Side effects	Drowsiness, agitation, QTc-time prolongation (using 12-leads ECG or monitor strip with Bazett's formula) and development of extra pyramidal symptoms: - dystonia - tremor- myoclonus – tics – rigidity – akathisia [7], determined daily by physical

	examination by the intensivist
Serious Adverse Event	Any untoward medical occurrence or effect at any dose that results in one of the following outcomes and is not classified as a clinical outcome of delirium or the underlying disease using the description above: - death that is not related to the underlying disease or sequel of the underlying disease, or death that is considered by the investigator to be possibly related to study drug - prolonged inpatient hospitalization or rehospitalisation - a life-threatening experience (that is, immediate risk of dying) - persistent or significant disability/incapacity - congenital anomaly/birth defect - considered significant by the investigator for any other reason
Suspected Unexpected Serious Adverse Reactions	Unexpected adverse reactions are adverse reactions, of which the nature, or severity, is not consistent with the applicable product information. Adverse reactions are all untoward and unintended responses to an investigational product related to any dose administered

4. POPULATIONS and SUBGROUPS

Demographics and other Baseline Characteristics

Categorical data, including binary data, will be summarised using numbers and percentages. The percentages are based on the total number of patients with a corresponding assessment. Continuous data will be presented mean and standard deviation, or median, and 25% and 75% interquartile range [IQR], depending on distribution.

Descriptive statistics of baseline characteristics and prediction scores will be summarized per study arm.

Continuous demographic and baseline characteristics that will be reported are: age in years at time of ICU admission, APACHE-II score per point, (E-)PRE-DELRIC score per point. Categorical data that will be reported as percentages are: gender, sepsis, admission category (i.e. surgical, medical, trauma), invasive and non-invasive mechanical ventilation.

Subgroup analyses

The group of included patients will be divided in relevant subgroups. A priori defined post-hoc analyses include:

- To determine the preventive effectiveness of haloperidol in different patient groups based on the predicted a priori risk to develop delirium using the PRE-DELIRIC model. The group will be divided based on the inter quartile distribution.
- To determine the preventive effectiveness of haloperidol in different patient groups: medical/surgical/trauma patients, and different severity of illness: per APACHE-score (<20, 20-25, >25)
- Effectiveness of prophylaxis with haloperidol when delirium is diagnosed based on 1, 2, or more days with positive CAM-ICU scoring
- Effectiveness of duration of prophylaxis treatment in patients receiving haloperidol for maximum of up to 2 days, or more than 2 days.

5. ENDPOINTS

Primary endpoint	Secondary endpoints
- 28-day survival	- 90-day survival
	- Delirium incidence
	- Number of delirium and coma free-days in 28-days
	- Duration of mechanical ventilation
	- Incidence of unintended tube or catheter removal
	- Incidence of ICU re-admission
	- Quality of Life measured at time of ICU admission, after 6 months using SF-12
	- Incidence and severity of side effects of prophylactic haloperidol (all patients)

6. HANDLING OF MISSING VALUES AND OTHER DATA CONVENTIONS

Prediction scores

The delirium prediction score will be calculated for each patient using the predictors originating from the PRE-DELIRIC and the E-PRE-DELIRIC model and their formula.[1,3]
In case of missing values, missing data will be imputed, as was previously described.[1] In short; if a predictor value from a laboratory measurement is not determined, there is apparently no clinical reason to assume that the missing variable would have an abnormal value, and therefore we will impute the mean normal value of the whole group of patients. When the APACHE-II score or mean arterial blood pressure (MAP) is missing we will impute the mean value of the variable of the whole group of patients. Missing categorical predictors of illness or treatment are being imputed as 'not present', 'no', or 'not treated'; see table 2.
At least age and type of admission category are needed to always be available.

At least half, or more of the predictors of the prediction model are needed to calculate the ICU delirium prediction score.

Table 2. Predictors of both delirium prediction models and methods of handling missings

Predictors	**Type of variable**	**If variable is missing than following value will be imputed**
Age	Continuous	Needs to be available
APACHE-II score	Continuous	Mean value of all patients
Urgent admission	Dichotomous	No
Coma	Dichotomous	Not present
Admission category	Categorical	Needs to be available
Infection	Dichotomous	Not present
Metabolic acidosis	Dichotomous	Not present
Morphine use	Dichotomous	Not administered
Sedation	Dichotomous	Not administered
Blood Urea level	Continuous	Mean normal value of all patients
History of alcohol abuse	Dichotomous	Not present
History of cognitive impairment	Dichotomous	Not present
Use of corticosteroids	Dichotomous	Not administered
Respiratory failure	Dichotomous	Not present
Mean arterial blood pressure	Continuous	Mean value of all patients

7. STATISTICAL METHODOLOGY

Sample size calculation

Sample size calculation was based on the difference in survival from our previous prophylactic haloperidol study in ICU patients.[8] In this study, the median survival time in the control group was 18 days. If the true hazard ratio of control patients relative to intervention patients is 0.85, taken into account an accrual time of 90 days with 28 days of follow-up, we will need to study 647 patients per intervention group and 647 control patients to be able to reject the null hypothesis that the experimental and control survival curves are equal with probability (power) 0.80. The two-sided type I error probability associated with this test of this null hypothesis is 0.05. Taken into account a dropout percentage of 10% we will include 715 patients per group (figure 1). A fixed sequence analytic procedure will be followed. First the prophylactic haloperidol will be compared with placebo using alpha 0.05 (two-sided). Only if H_0 is rejected, subsequently the lower dosage of prophylactic haloperidol will be compared with placebo. If, due to results of a interim analysis an active group is dropped, the remaining active group of prophylactic haloperidol will be compared with placebo. Cox-regression analysis will be used to test differences on 28-day survival in the intervention group compared with the placebo group.

Interim analyses

Interim analyses for safety, futility and superiority will be performed by the unblinded DSMB following the enrolment of 175, 350, 500 (safety and futility) and 1000 (safety, futility, and superiority) patients. Differences in serious adverse events between intervention and placebo groups will be used for safety analyses. For determination of futility or superiority of the intervention (compared to placebo) the primary endpoint 28-days survival will be used.

After inclusion of 1000 patients superiority will be tested. A proven superiority (*p<0.003, two-sided)* of any dose of haloperidol over placebo or a proven superiority (*p<0.003, two-sided)* of placebo over haloperidol determined during the interim analysis will lead to alpha-spending and result in an alpha of 0.049 (two-sided) for the final analysis. This alpha distribution was calculated by an independent statistician according to the method of Lan-DeMets cumulative alpha spending function of O'Brien-Fleming alpha spending.[9]

Statistics

For the descriptive statistics, continuous variables will be given as mean with standard deviation or median and inter quartile ranges, depending on their distribution. Normally distributed variables will be tested using Student's t-test for comparison and Mann–Whitney U-tests for non-normally distributed variables. Categorical (and binary) variables will be presented as numbers and percentages and will be analyzed using Chi-square test. Survival analyses with Kaplan-Meier curves will be used as graphical presentation. Cox proportional hazard regression analyses will be used to estimate the hazard ratio for survival with the use of haloperidol versus placebo. Furthermore, adjusted analyses will be performed for relevant covariates including delirium, APACHE-II score, age, gender, and sepsis, irrespectively the possible imbalance between the groups. For this covariate analysis first univariate logistic regression analysis will be performed in order to test the strength of the relationship. Subsequently, variables significantly associated with the dependent variable will be included in the covariate analyses.

Furthermore, subgroup analysis will be performed by direct comparisons of a priori specified subgroups, i.e. predicted risk group, admission type group, and APACHE group, in order to determine effectiveness of prophylactic haloperidol treatment in these subgroups on 28-days survival.

7.1 STATISTICAL PROCEDURES

Regarding the analyses, the following analyses sets will be used, in accordance with International Conference on Harmonisation (ICH) recommendations (http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E9/Step4/E9_Guideline.pdf):

7.1.a. Intention To Treat analyses

Data will be analysed according to the 'intention to treat' (ITT) principle. Patients of which informed consent was obtained and who received at least one dose of study drug will remain in the study and patients in whom study medication had to be halved or stopped, e.g. because of prolonged QTc time or other side effects will remain allocated to their study-group and analysed on an intention to treat basis.

7.1.b. Per-Protocol analyses

Patients of which informed consent was obtained and who received at least one dose of the study drug will be excluded from the per-protocol analysis set due to:

- violation of exclusion criteria number 4 or 7 (see page 4-5), if the patient was treated with anti-psychotics last 30 days or if delirium was documented prior ICU admission
- patients allocated to placebo-arm that received open-label haloperidol while not being delirious
- patients allocated to the haloperidol group who did not receive the study drug with haloperidol for more than two consecutive times other than reasons of adverse events
- patients who died within 48 hours after ICU admission. This group is excluded because of the limited time of exposure to the study medication.

Furthermore, any other major protocol violation, such as serious unforeseen violations deemed to invalidate the data and affect the conclusions of the study, will lead to exclusion of data from the per-protocol analysis set.

7.1.c. Safety analyses

The safety analysis set will comprise all enrolled patients of which informed consent will be obtained and will be analysed according to the actual treatment they received. Incidence of serious adverse and adverse events that will occur during the prophylactic treatment period will be compared between the study arms using Chi-square test in the final analysis as well as during the interim analyses performed by the DSMB.

7.2 Statistical considerations

All statistical tests are two-sided and statistical significance is defined as a *P*-value <0.05. All data will be analyzed using SPSS version 22.01 (SPSS, Chicago, IL).

If the trial will be stopped prematurely because of futility or superiority based on the advice of the DSMB, data will be analyzed as planned in the statistical analyses plan.

The efficacy endpoints will be analyzed for the intention to treat and the per-protocol analysis set, with ITT as primary and the PP as supportive analyses.

8. REFERENCES

1.van den Boogaard M, Pickkers P, Slooter AJ, et al. Development and validation of PRE-DELIRIC (PREdiction of DELIRium in ICu patients) delirium prediction model for intensive care patients: observational multicentre study. Bmj 2012;344:e420.
2.van den Boogaard M, Schoonhoven L, Maseda E, et al. Recalibration of the delirium prediction model for ICU patients (PRE-DELIRIC): a multinational observational study. Intensive care medicine 2014;40:361-9.
3.Wassenaar A, van den Boogaard M, van Achterberg T, et al. Multinational development and validation of an early prediction model for delirium in ICU patients. Intensive care medicine 2015;41:1048-56.
4.Barr J, Fraser GL, Puntillo K, et al. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. Crit Care Med 2013;41:263-306.
5.Schweickert WD, Pohlman MC, Pohlman AS, et al. Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomised controlled trial. Lancet 2009;373:1874-82.
6.Schuurmans MJ, Shortridge-Baggett LM, Duursma SA. The Delirium Observation Screening Scale: a screening instrument for delirium. Research and theory for nursing practice 2003;17:31-50.
7.Abdo WF, van de Warrenburg BP, Burn DJ, Quinn NP, Bloem BR. The clinical approach to movement disorders. Nat Rev Neurol 2010;6:29-37.
8.van den Boogaard M, Schoonhoven L, Van Achterberg T, Van der Hoeven JG, Pickkers P. Haloperidol prophylaxis in critically ill patients with a high risk for delirium. Critical care 2013;17:R9.
9.O'Brien PC, Fleming TR. A multiple testing procedure for clinical trials. Biometrics 1979;35:549-56.
10.Bhatt DL, Mehta C. Adaptive Designs for Clinical Trials. The New England journal of medicine 2016;375:65-74.

Figure 1. Flow diagram