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CLINICAL INVESTIGATION



Mortality and HRQoL in ICU patients with delirium: Protocol for 1-year follow-up of AID-ICU trial

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Background: Intensive care unit (ICU)-acquired delirium is frequent and associated with poor short- and long-term outcomes for patients in ICUs. It therefore constitutes a major healthcare problem. Despite limited evidence, haloperidol is the most frequently used pharmacological intervention against ICU-acquired delirium.

Agents intervening against Delirium in the ICU (AID-ICU) is an international, multi-centre, randomised, blinded, placebo-controlled trial investigates benefits and harms of treatment with haloperidol in patients with ICU-acquired delirium. The current pre-planned one-year follow-up study of the AID-ICU trial population aims to explore the effects of haloperidol on one-year mortality and health related quality of life (HRQoL).

Methods : The AID-ICU trial will include 1000 participants. One-year mortality will be obtained from the trial sites; we will validate the vital status of Danish participants using the Danish National Health Data Registers. Mortality will be analysed by

Abbreviations: AID-ICU, Agents Intervening against Delirium in the Intensive Care Unit; eCRF, Electronic case report file; HRQoL, Health-related quality of life; GLM, General linear model; ICU, Intensive care unit; IQR, Interquartile range; MAR, Data missing at random; MCAR, Missing completely at random; MI, Multiple imputation; MNAR, Not missing at random; SD, Standard deviation; SMS-ICU, Simplified mortality score in the ICU; VAS, Visual analog scale.

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Cox-regression and visualized by Kaplan-Meier curves tested for significance using the log-rank test. We will obtain HRQoL data using the EQ-5D instrument. HRQoL analysis will be performed using a general linear model adjusted for stratification variables. Deceased participants will be designated the worst possible value.

Results: We expect to publish results of this study in 2022.

Conclusion: We expect that this one-year follow-up study of participants with ICU-acquired delirium allocated to haloperidol vs. placebo will provide important information on the long-term consequences of delirium including the effects of haloperidol. We expect that our results will improve the care of this vulnerable patient group.

1 | BACKGROUND

Delirium is an acute brain dysfunction accompanying underlying somatic illness and characterized by marked and fluctuating disturbances in consciousness and in cognition. Clinical hallmarks include memory deficits, disorientation, perceptual disturbances and inattention.¹⁻³

Delirium is a common clinical condition occurring during both acute illness and hospitalization in general.⁴ The condition is particularly prevalent in patients with critical illness treated at the intensive care unit (ICU), where prevalence of ICU-acquired delirium ranges from 20% to 80%.^{1,5}

Intensive care unit-acquired delirium is associated with significant adverse short- and long-term outcomes. In the short term, predominant associations of delirium include increased risk of prolonged mechanical ventilation and longer hospital stay, while frequent long-term associated outcomes include functional disability in activities of daily living, as well as cognitive impairments such as memory deficits and poor concentration.^{6,7} Notably, cognitive impairments may be persistent and reported years after the critical illness with delirium.^{8,9}

Compared to the general population, ICU-survivors have reported a lower health-related quality of life (HRQoL) at 1 year after critical illness.¹⁰ Moreover, ICU-survivors with delirium during the ICU admission have reported a higher prevalence of cognitive problems as compared to all ICU survivors.^{9,11} Recent studies have indicated an association between ICU-acquired delirium and increased mortality, whereas previous studies did not confirm this finding.^{6,7,11,12}

Despite limited evidence, treatment of ICU-acquired delirium with haloperidol is currently the most frequently used pharmacological intervention.¹³ The "Agents Intervening against Delirium in the Intensive Care Unit" (AID-ICU) trial, is a multicentre randomized blinded and placebo-controlled trial (RCT) that aims to assess benefits and harms of haloperidol for treatment of delirium in adult critically ill patients admitted to the ICU.¹⁴ The trial is ongoing and is expected to complete inclusions in 2021.

As concluded in a recent systematic review, long-term consequences of delirium are evident.¹⁵ Therefore it is imperative to investigate the impact of haloperidol, the most widely used treatment of this potentially disabling condition, on both short- and long-term

outcomes.¹⁵ This protocol article describes the long-term follow-up of such patients treated with haloperidol.

1.1 | Aim

To assess the effect of haloperidol treatment on mortality and health-related quality of life in ICU patients with delirium 1 year after randomization into the AID-ICU trial.

1.2 | Hypothesis

We expect that the allocation to haloperidol vs placebo has an impact on mortality and the duration of delirium in patients suffering ICU-acquired delirium and hypothesize that haloperidol will reduce mortality and increase quality of life 1 year after discharge.

2 | MATERIALS AND METHODS

2.1 | Ethical considerations

Ethical approval for the AID-ICU trial including the 1-year follow-up study, has been obtained from the Danish Medicines Agency (EudraCT no. 2017-003829-15), the National Committee on Health Research Ethics (SJ-646) and the Danish Data Protection Agency (REG-169-2017). After achievement of approvals from national authorities and according to national law, inclusion at international sites has been initiated. Informed consent given to the AID-ICU trial also include approval for this 1-year follow-up study. Further details can be obtained in the protocol of the AID-ICU trial which also includes a description of protection of data.¹⁴ The trial is registered at Clinicaltrials.gov: NCT03392376.

2.2 | AID-ICU trial

Adult ICU patients with delirium confirmed by either the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) or the

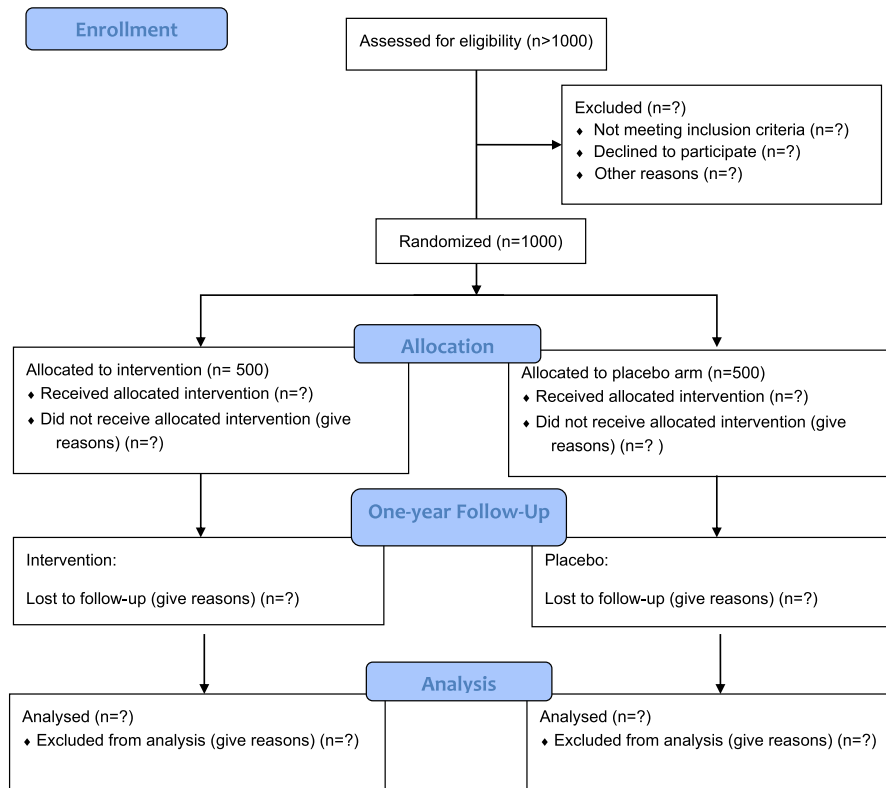


FIGURE 1 CONSORT flow diagram for the AID-ICU trial 1-yr follow-up [Colour figure can be viewed at wileyonlinelibrary.com]

Intensive Care Delirium Screening Checklist (ICDSC), are screened by trained nurses or doctors for enrolment into the AID-ICU trial. Enrolled participants are randomized 1:1 to intravenous haloperidol 2.5 mg or placebo (isotonic saline), three times daily and additional as-needed doses of 2.5 mg haloperidol or placebo up to a total daily dose of 20 mg haloperidol or placebo. An escape protocol is available in case of uncontrollable delirium or patient discomfort. Open label antipsychotic treatment is not allowed. The primary outcome of the AID-ICU trial is days alive out of the hospital within 90 days post-randomization. More details about the AID-ICU trial protocol have been published elsewhere (www.cric.nu/aid-icu-trial-documents/).^{14,16}

2.3 | Study population

The study population for this 1-year follow-up consists of participants randomized in the AID-ICU trial. See Figure 1

2.4 | Outcomes measures

2.4.1 | Primary outcomes

- Difference in mortality 1 year after randomization between participants in the haloperidol group and the placebo group
- Difference in EQ-5D 1 year after randomization between participants in the haloperidol group and the placebo group.

2.4.2 | Secondary outcomes

- Difference in EQ-5D 1 year after randomization between the survivors only in the haloperidol group and the placebo group
- Differences in the single sub-domains of the EQ-5D 1 year after randomization between survivors in the haloperidol group and the placebo group: mobility, self-care, usual activities, pain/discomfort, anxiety/depression and overall health rated by EQ-VAS (visual analog scale).

2.5 | Data collection

2.5.1 | One-year mortality

Survival status of the participants will be obtained by patient records and entered into the database by the individual site or national investigators 1 year after randomization. For the Danish sites vital status will be validated by information from the Danish National Patient Registry and the Danish Civil Registration System.

2.5.2 | EQ-5D

The five-level EQ-5D tool includes EQ-VAS and EQ-5D-5L and is a validated self-reported questionnaire recommended for use in ICU settings.^{16,17} The EQ-VAS is a scale ranging from 0 to 100

where participants indicate their overall health status on that day and where 100 is rated as the best possible health.¹⁷ The questionnaire EQ-5D measures five health problems according to a five-dimensional classification: mobility, self-care, usual activities, pain/discomfort and anxiety/depression, where the participants are asked to grade their level of function or disability. Each of the five dimensions are ranked on five levels of perceived problems ranging from 1 to 5; where 1 = no problems, 2 = slight problems, 3 = moderate problems, 4 = severe problems and 5 = extreme problems. The participant will be asked to rate their problems for each of the five dimensions.

The response of each dimension provides a simple descriptive profile (a digit-code (1-5)), which is used to generate a unique health state. The health state cannot be summarized since each number represent the five severity levels of each dimension and has no arithmetic properties.¹⁸

In countries where there is no current calculation norm for translation of health state in EQ-5D-5L, but only EQ-5D-3L, we will use EQ-5D-5L crosswalk index to 'convert' the EQ-5D-3L to EQ-5D-5L.¹⁹

2.5.3 | Collection of EQ-5D data

Surviving participants in the AID-ICU trial will be contacted 1 year after randomization by the national investigators or their delegates. In case of no response to phone calls, a mail survey will be dispatched. Collection of EQ-5D data outside of Denmark will be obtained by the national or site investigators and handled according to local practice. All data will be registered in the electronic case report file (eCRF) by investigators blinded to the trial intervention.

3 | STATISTICAL ANALYSES

All primary analyses will be performed in the intention-to-treat population of the AID-ICU trial population. There is no specific sample size calculation for this follow-up study.

Demographic data and patient characteristics including baseline data obtained at randomization will be analysed by descriptive statistics and will be presented as mean and standard deviation (SD), median and interquartile range (IQR), or proportions with percentages where relevant. For further information, see the AID-ICU trial protocol.^{14,20}

3.1 | Choice of statistical method

3.1.1 | One-year mortality

On assessing the landmark mortality at 1 year (every patient in the AID-ICU trial will be followed up 1 year from randomization), data will

be analysed using logistic regression adjusted for stratification variables (site and delirium motor subtypes (hypoactive or hyperactive) at randomization) for differences in the binary outcome (alive/dead) and presented as odds ratios. Furthermore, survival data will be analysed by Cox-regression and visualized by a Kaplan-Meier curve. Also, for 1-year mortality including, overall mortality and mortality between the two groups additional analyses of the stratification variables site and delirium motor subtypes (hypoactive or hyperactive) and the baseline characteristics, site, sex, age (<69 year and \geq 69 year) and Simplified Mortality Score in the ICU (SMS-ICU) (<25- \geq 25) will be applied.¹⁴

3.1.2 | EQ-5D

For the primary analysis of EQ-5D will EQ-VAS which is the respondent's self-rated health be used for all participants. Differences in means of EQ-VAS are compared between the two groups and assuming that the distribution of EQ-VAS or log-transformed data comes close to a normal distribution, the analysis of choice will be multiple linear regression adjusted for stratification variables site and delirium motor subtype. However, if the distribution of EQ-VAS is clearly non-normal, we will use the Van Elteren test to explore differences of medians between the two groups, after adjusting for stratification variables site and delirium motor subtype. Secondary analyses of the single sub-domains of EQ-5D (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) will also be performed with a generalized linear model (GLM) or Van Elteren adjusted for the stratification variables site and delirium motor subtype. As a supplement to the primary analysis, an analysis adjusting for both the stratification variables site and delirium motor subtypes (hypoactive or hyperactive) and the pre-defined covariates of sex, age (<69 year and \geq 69 year) and SMS-ICU (<25- \geq 25) will be applied.

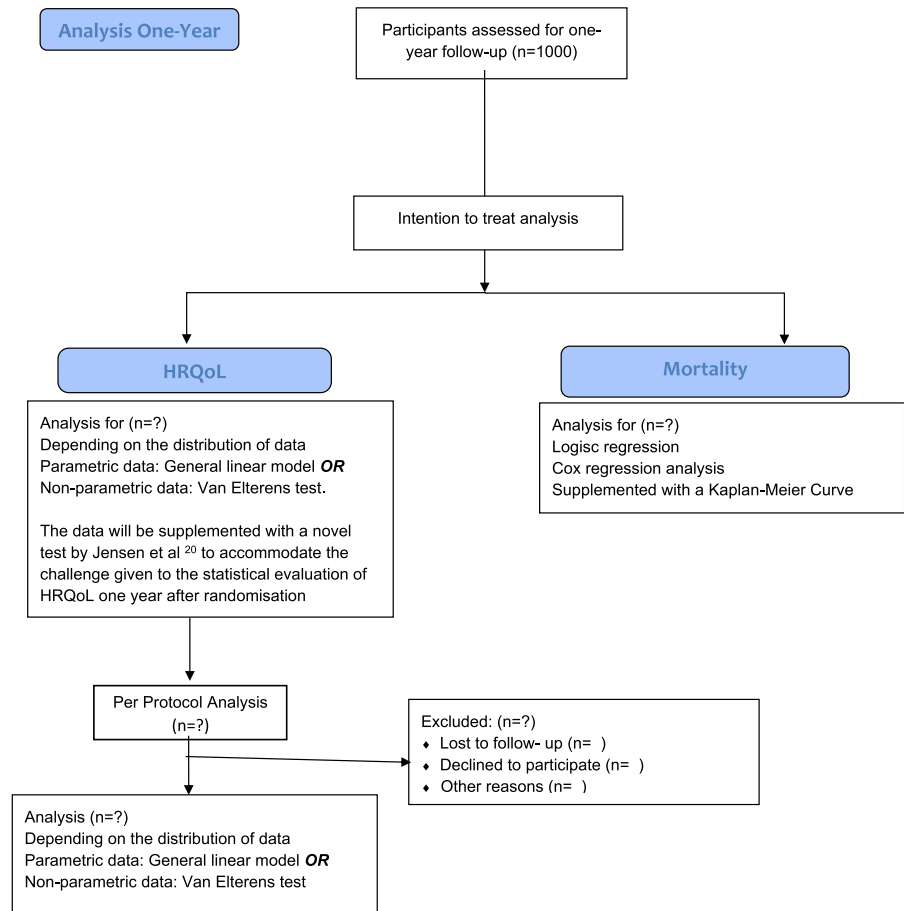
3.1.3 | Evaluation of treatment despite 1-year mortality

High 1-year mortality rate challenges the statistical evaluation of the treatment effects in this population if not taken into consideration.²¹ To account for the expected high mortality, participants dying within 12 months after randomization are 'truncated due to death', meaning assignment of the worst possible value; the value of zero.²¹ With respect to the intention-to-treat principle, we will compare this highly non-normal distributed outcome between treatment groups using a novel method described by Jensen et al²² In addition, the analysis will be supplemented with a per-protocol analysis within the population of the 1-year survivors. See Figure 2 for an overview of statistical analysis.

3.1.4 | Significance

A two-sided $P < .05$ will be considered statistically significant and if data are normally distributed (or nearly), we will provide 95% confidence

FIGURE 2 Analysis diagram for the AID-ICU 1-yr follow-up [Colour figure can be viewed at wileyonlinelibrary.com]



intervals between means. For non-normally distributed data, 95% confidence intervals between medians will be estimated by bootstrapping.

3.2 | Handling missing values

EQ-5D data may be missing in participants who are alive 1 year after randomization (non-responders or migrated participants). If data of the EQ-5D questionnaires are missing for less than 5% of the participants or data are missing completely at random (MCAR), that is, negative Little's test ($P > .05$), we will not impute missing data. If data are missing for outcomes and adjusted covariates in more than 5% of the participants, assuming data missing at random (MAR), we will impute data using multiple imputation (MI) generating 50 imputed data sets. If MI is considered necessary, aggregated analysis of the imputed datasets is calculated. However, assuming data are not missing at random (MNAR), we will conduct analyses in best-worse and worse-best scenarios imputing data from missing response from survivors, using the mean plus/minus 1 SD of the EQ-5D in participants with complete data.

4 | DISCUSSION

This protocol article describes the 1 year follow-up study on mortality and health-related quality of life for participants in the AID-ICU trial.

4.1 | One-year mortality

While delirium has been linked to long-term mortality, limited evidence exists for the impact of delirium treatment with haloperidol on long-term mortality.¹² Three placebo controlled RCTs have explored the effect of haloperidol on short-term mortality (from 28 to 90 days) and found no differences in mortality between the treatment groups.²³⁻²⁵ None of the three RCTs have reported on 1-year mortality.

4.2 | Long-term HRQoL

Two recently published systematic reviews found no studies exploring explicitly if haloperidol treatment has an impact on long-term HRQoL. Few studies have explored the impact of ICU-acquired delirium on HRQoL in ICU survivors after discharge.^{9,11} In these studies, no difference in HRQoL was found between the delirious and the non-delirious participants when adjusting for confounders.^{9,11} Both studies were prospective, but one of the studies⁹ did not report on non-responders nor their characteristics, rendering the results subject to attrition bias therefore compromising the internal and external validity.^{9,11} In order to ensure high validity, the AID-ICU trial will provide detailed description of all the participants' baseline information and include deceased participants into the analyses.

Hereby, we believe, that it is the best possible way to explore a true difference in outcomes caused by the intervention.

We will perform a secondary analysis of EQ-5D data, including only the survivors for further exploration of the treatment effect between the intervention and control group. Measuring HRQoL of ICU survivors is complex and difficult because of the heterogeneity of the patient population and the different trajectories of illness before and after critical illness. However EQ-5D is characterized by being brief, easy-to-use and flexible in different settings and has been recommended for use in ICU settings.^{26,27} Furthermore, applying a simple short generic instrument like EQ-5D is suitable for participants that might be challenged with cognitive impairment. In spite of its brevity, EQ-5D still encompasses a global description of HRQoL which includes a medical interpretation and an interpretation of the social, emotional and physical function.²⁸

4.3 | Strengths

The AID-ICU trial is a large multicentre RCT designed to provide high-quality data with low risk of bias and high external validity. The AID-ICU trial is the largest treatment study on haloperidol and will add evidence concerning the benefits and harms of haloperidol for treatment of delirium among critically ill patients. This protocol article includes a statistical analysis plan for 1-year follow-up and has been drafted to measure the effect of the intervention on HRQoL and death. Secondly, it also helps to explore difference in HRQoL between the survivors in the two interventional groups.

4.4 | Limitations

To explore a complex association between haloperidol treatment of ICU-acquired delirium and mortality 1 year later might be challenged by attrition bias due to loss to follow-up. ICU survivors are a vulnerable patient cohort that struggles with both physical and psychological disabilities and follow-up in such population has previously shown to be challenging.^{29,30} A major concern in longitudinal studies is, that with a long follow-up period, the risk of attrition and loss to follow-up will increase. If too many participants are lost to follow-up there is a risk of selection bias if missing data are not taken into consideration.³¹ This might compromise the study's ability to fully describe the diversity of the study population. If data are missing, that is, lost to follow-up by more than 5%, we will handle missing data as previously described.

4.5 | Perspective

Critically ill patients admitted to the ICU are at high risk of developing delirium, and currently, there is limited evidence of the effect of haloperidol treatment on both short- and long-term outcomes. This follow-up study of the AID-ICU trial will provide important information about the benefits and harms of haloperidol treatment on long-term

mortality and HRQoL. The cohort consists of a representative sample of ICU patients with onset of delirium at different times during the ICU admission, and thereby has a high degree of generalizability.

4.6 | Trial status

The AID-ICU trial began recruitment in June 2018. Currently 553 of 1000 planned participants have been enrolled (July 6th, 2020). We expect the enrolment target to be met by 2021. The data collection of the present follow-up study was initiated in June 2019.

CONFLICT OF INTEREST

BHE has received lecture fees and/or is part of Advisory Boards of Bristol-Myers Squibb, Eli Lilly and Company, Janssen-Cilag, Otsuka Pharma Scandinavia AB, Takeda Pharmaceutical Company and Lundbeck Pharma A/S. The Department of Intensive Care, Rigshospitalet receives research funds from the Novo Nordisk Foundation.

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REFERENCES

1. Pandharipande P, Cotton BA, Shintani A, et al. Prevalence and risk factors for development of delirium in surgical and trauma intensive care unit patients. *J Trauma*. 2008;65:34-41.
2. Ely EW, Inouye SK, Bernard GR, et al. Delirium in mechanically ventilated patients: validity and reliability of the confusion assessment method for the intensive care unit (CAM-ICU). *JAMA*. 2001;286:2703-2710.
3. Association AP. *Diagnostic and Statistical Manual of Mental Disorders (DSM-5®)*. Philadelphia: American Psychiatric Pub; 2013.
4. Inouye SK. Delirium in older persons. *N Engl J Med*. 2006;354:1157-1165.
5. Morandi A, Jackson JC, Ely EW. Delirium in the intensive care unit. *Int Rev Psych*. 2009;21:43-58.
6. Devlin JW, Skrobik Y, Gélinas C, et al. Clinical practice guidelines for the prevention and management of pain, agitation/sedation, delirium, immobility, and sleep disruption in adult patients in the ICU. *Crit Care Med*. 2018;46:e825-e873.
7. Ely EW, Shintani A, Truman B, et al. Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit. *JAMA*. 2004;291:1753-1762.
8. Girard TD, Jackson JC, Pandharipande PP, et al. Delirium as a predictor of long-term cognitive impairment in survivors of critical illness. *Crit Care Med*. 2010;38:1513-1520.
9. van den Boogaard M, Schoonhoven L, Evers AWM, van der Hoeven JG, van Achterberg T, Pickkers P. Delirium in critically ill patients: impact on long-term health-related quality of life and cognitive functioning. *Crit Care Med*. 2012;40:112-118.
10. Flaatten H, Kvåle R. Survival and quality of life 12 years after ICU. A comparison with the general Norwegian population. *Intensive Care Med*. 2001;27:1005-1011.

11. Wolters AE, van Dijk D, Pasma W, et al. Long-term outcome of delirium during intensive care unit stay in survivors of critical illness: a prospective cohort study. *Crit Care*. 2014;18:R125.
12. Pisani MA, Kong SYJ, Kasl SV, Murphy TE, Araujo KLB, Van Ness PH. Days of delirium are associated with 1-year mortality in an older intensive care unit population. *Am J Respir Crit Care Med*. 2009;180:1092-1097.
13. Collet MO, Caballero J, Sonnevile R, et al. Prevalence and risk factors related to haloperidol use for delirium in adult intensive care patients: the multinational AID-ICU inception cohort study. *Intens Care Med*. 2018;44(7):1081-1089.
14. Andersen-Ranberg NC, Poulsen LM, Perner A, et al. Agents intervening against delirium in the intensive care unit (AID-ICU) - protocol for a randomised placebo-controlled trial of haloperidol in patients with delirium in the ICU. *Acta Anaesthesiol Scand*. 2019;63:1426-1433.
15. Barbateskovic M, Krauss SR, Collet MO, et al. Haloperidol for the treatment of delirium in critically ill patients: a systematic review with meta-analysis and trial sequential analysis. *Acta Anaesthesiol Scand*. 2020;64(2):254-266.
16. Dowdy DW, Eid MP, Sedrakyan A, et al. Quality of life in adult survivors of critical illness: a systematic review of the literature. *Intens Care Med*. 2005;31:611-620.
17. Badia X, Diaz-Prieto A, Gorriz MT, et al. Using the EuroQol-5D to measure changes in quality of life 12 months after discharge from an intensive care unit. *Intens Care Med*. 2001;27:1901-1907.
18. van Reenen MJB. EQ-5D-5L User guide Basic information on how to use the EQ-5D-5L instrument [Internet]. 2019 Sep Available from https://euroqol.org/wp-content/uploads/2019/09/EQ-5D-5L-English-User-Guide_version-3.0-Sept-2019-secured.pdf
19. van Hout B, Janssen MF, Feng Y-S, et al. Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. *Value Health*. 2012;15:708-715.
20. Andersen-Ranberg N, Poulsen LM, Perner A, et al. The agents intervening against delirium in the intensive care unit trial (AID-ICU trial): a detailed statistical analysis plan. *Acta Anaesthesiol Scand*. 2020;1-8. <https://doi.org/10.1111/aas.13661>
21. Colantuoni E, Scharfstein DO, Wang C, et al. Statistical methods to compare functional outcomes in randomized controlled trials with high mortality. *BMJ*. 2018;360:j5748.
22. Jensen AK, Lange T. A novel high-power test for continuous outcomes truncated by death. arXiv:191012267 [stat] [Internet] 2019 Oct 27 [cited 2020 Jan 17]. Available from <http://arxiv.org/abs/1910.12267>
23. Page VJ, Ely EW, Gates S, et al. Effect of intravenous haloperidol on the duration of delirium and coma in critically ill patients (Hope-ICU): a randomised, double-blind, placebo-controlled trial. *Lancet Respir Med*. 2013;1:515-523.
24. Girard TD, Exline MC, Carson SS, et al. Haloperidol and ziprasidone for treatment of delirium in critical illness. *N Engl J Med*. 2018;379:2506-2516.
25. van den Boogaard M, Slooter AJC, Brüggemann RJM, et al. Effect of haloperidol on survival among critically ill adults with a high risk of delirium: the REDUCE randomized clinical trial. *JAMA*. 2018;319:680-690.
26. Kaarlola A, Tallgren M, Pettilä V. Long-term survival, quality of life, and quality-adjusted life-years among critically ill elderly patients. *Crit Care Med*. 2006;34:2120-2126.
27. Robinson KA, Davis WE, Dinglas VD, et al. A systematic review finds limited data on measurement properties of instruments measuring outcomes in adult intensive care unit survivors. *J Clin Epidemiol*. 2017;82:37-46.
28. Gusi N, Olivares PR, Rajendram R. The EQ-5D health-related quality of life questionnaire. In: Preedy VR, Watson RR, editors. *Handbook of Disease Burdens and Quality of Life Measures*. New York, NY: Springer; 2010:87-99.
29. Paratz JD, Kenardy J, Mitchell G, et al. IMPOSE (IMProving Outcomes after Sepsis)—the effect of a multidisciplinary follow-up service on health-related quality of life in patients postsepsis syndromes—a double-blinded randomised controlled trial: protocol. *BMJ Open*. 2014;4(5):e004966.
30. Klouwenberg PMCK, Zaal IJ, Spitoni C, et al. The attributable mortality of delirium in critically ill patients: prospective cohort study. *BMJ*. 2014;349:g6652.
31. Dumville JC, Torgerson DJ, Hewitt CE. Reporting attrition in randomised controlled trials. *BMJ*. 2006;332:969-971.

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