Health related quality of life after critical illness with delirium at the Intensive Care Unit: A 1-year follow up of the AID-ICU trial

CRIC - Centre for Research in Intensive Care

Camilla Bekker Mortensen
Department of Anaesthesiology
Zealand University Hospital Køge
Lykkebækvej 1
4600 Køge

Names and addresses

Sponsor
Lone Musaeus Poulsen, MD
Department of Anaesthesiology and Intensive Care
Zealand University Hospital, Køge
4600 Køge
Danmark

Principal investigator

Camilla Bekker, RN MSc (Health Science)
Department of Anaesthesiology and Intensive Care
Zealand University Hospital, Køge
Denmark

Sub-investigators

Ole Mathiesen, MD, PhD, Associate professor
Department of Anaesthesiology and Intensive Care
Zealand University Hospital, Køge
Denmark

Karin Samuelson, RN ANIC, MScN, PhD, Associate Professor
Department of Health Sciences
Lund University
Sweden

Coordinating investigator (for AID-ICU)
Nina Christine Andersen-Ranberg, MD
Department of Anaesthesiology and Intensive Care
Zealand University Hospital, Køge
Denmark

Investigator (for AID-ICU)
Stine Estrup
Department of Anaesthesiology and Intensive Care
Zealand University Hospital, Køge
Denmark

Initiator
Anders Perner, professor, MD, PhD
Department of Intensive Care 4131
Copenhagen University Hospital, Rigshospitalet
Denmark

Trialist
Jørn Wetterslev, chief physician, MD, PhD
Copenhagen Trial Unit (CTU)
Copenhagen University Hospital, Rigshospitalet
Denmark

Subinvestigatorer

Bjørn Hylsebeck Ebdrup, associate professor, MD, PhD
Mental Health Centre Glostrup/University of Copenhagen
Faculty of Health and Medical Sciences
Department of Clinical Medicine
Denmark

Ingrid Egerod, RN MSN PHD, Professor of clinical nursing
University of Copenhagen, Health & Medical Sciences
Rigshospitalet, Intensive Care Unit 4131

Statistical supervisor
Theis Lange, associate professor
Section of Biostatistics,
University of Copenhagen,
Copenhagen, Denmark

Table of Content

HEALTH RELATED QUALITY OF LIFE AFTER CRITICAL ILLNESS WITH DELIRIUM AT THE INTENSIVE CARE UNIT: A 1-YEAR FOLLOW UP OF THE AID-ICU TRIAL 1
NAMES AND ADDRESSES 2
Principal investigator *2*
Sub-investigators *2*
TABLE OF CONTENT 4
ABSTRACT 5
ABBREVIATIONS 6
INTRODUCTION 7
DELIRIUM IN THE INTENSIVE CARE UNIT 7
"Agents Intervening against Delirium in the Intensive Care Unit" trial (AID-ICU-trial). *7*
Long-term outcome and health related quality of life after critical illness *8*
Measuring health related quality of life in ICU-survivors with delirium. *9*
AIMS 10
OUTCOMES 10
METHOD 11
Study design *11*
One-year mortality *11*
EQ-5D *11*
Obtaining EQ-5D-5L *12*
STUDY POPULATION 12
Ethical considerations, including consent *13*
Protection of data *14*
Statistical analyses *14*
Missing values *15*
Finance *16*
Publication *17*
REFERENCES: 18

Abstract

Introduction:

Delirium is a common clinical condition, which affects critical ill patients admitted in the intensive care unit (ICU). Delirium in ICU is associated with multiple short and long-terms consequences. The most frequently used pharmacological intervention is haloperidol despite limited evidence. The randomised, blinded, placebo-controlled trial "Agents Intervening against Delirium in Intensive Care Unit" (AID-ICU) aims to assess the benefits and harms of haloperidol (vs. placebo (0.9% Saline)) in patients with delirium in the ICU. This is a one-year follow-up study on the AID-ICU trial.

Objectives: To explore one year outcomes of the AID-ICU trial. First to assess any differences between the two groups in mortality one year after randomisation to the AID-ICU trial. Secondly to describe self-reported health related quality of life (HRQoL) of intensive care patients included in the AID-ICU trial one year after inclusion, and compare HRQoL in those receiving haloperidol versus those receiving placebo.

Methods:

The one-year mortality will be obtained through National Data Registers or by national and site investigators. For analysis Cox-regression will be performed supplemented with a Kaplan-Meier analysis and log-rank test.

Survivors will be contacted by phone or mail and invited to participate in a HRQoL study one year after randomisation. Assessments will comprise EQ-5D-5L and EQ-VAS. For analyses general linear model adjusted for stratification variables will be performed. Handling missing values will dead patients be assigned the zero value. Patients with missing data (patients alive with no response or migrated patients) will be imputed.

Abbreviations

- AID-ICU Agents Intervening against Delirium in the Intensive Care Unit
- ADL Activities of daily living
- eCRF Electronic case report file
- EQ-5D-5L Euroqol group health-related quality of life questionnaire
- FDA U.S food and drug administration
- HRQoL Health related quality of life
- ICU Intensive care unit
- QoL Quality of Life
- SMS Score Simplified mortality score

Introduction

Delirium in the Intensive care unit

Delirium is a clinical condition, which occurs frequently in Intensive care unit (ICU) and have been reported with incidences ranging from 20% to 84% (1–7). Delirium is an acute brain dysfunction and is defined and characterised by acute and fluctuating changes in consciousness and with inattention as a clinical hallmark (2,8,9). Furthermore delirium is accompanied by cognitive disturbances (e.g. memory deficits, disorientation, perceptual disturbance)(2,8–10).

The pathophysiology of delirium seems to be multi-factorial. Numerous risk factors have been identified such as predisposing factors as age, baseline cognitive impairment and co-morbidity and furthermore precipitating factors as use of sedatives or analgesics, severity of illness, hypoxaemia and hypotension (2,5,6,11).

Delirium is associated with multiple negative consequences, including unintentional removal of devices/catheters, complications of mechanical ventilation (MV) such as self-extubation, nosocomial pneumonia, and is an independent predictor for increased duration of mechanical ventilation, prolonged length of stay in ICU and prolonged hospital stay, higher mortality, increased healthcare cost and a strong predictor for long-term cognitive impairment up to years after the ICU stay (1,3–5,12–14).

Treatment of delirium is currently a mix of non-pharmacological and pharmacological approaches. Of non-pharmacological approaches creating a circadian rhythm with mobilisation, noise-reduction and sleep protocol have demonstrated beneficial effects (1). For pharmacological approaches the most frequently treatment is haloperidol although the evidence for the benefits and harms is limited (7).

"Agents Intervening against Delirium in the Intensive Care Unit" trial (AID-ICU-trial).

Pharmacological intervention with haloperidol, a first-generation antipsychotic, continues to be the most frequently used treatment of delirium at ICUs. Thus a recent large cohort study including 1260 patients from 99 mostly European ICU's confirmed that haloperidol was the most frequently used medicine against delirium independent of delirium sub-type (7). Despite limited evidence, various guidelines recommend haloperidol as the first line-agent for treatment of delirium (15).

Haloperidol may, however, be associated with a number of adverse effects, especially cerebral and cardiovascular adverse effects. Furthermore has U.S Food and Drug Administration (FDA) issued a warning for the use of haloperidol to elderly patients with dementia-related psychosis because of an increased risk of death (16). Thus, as of now we do not know if haloperidol for treatment of delirium is beneficial or harmful.

Therefore, the multi-centre randomised, blinded, placebo-controlled trial (RCT) the "Agents Intervening against Delirium in the Intensive Care Unit" trial (AID-ICU) (17) has been initiated aiming at investigating benefits and harms of haloperidol treatment of delirium in adult critically ill patients. The primary outcome of AID-ICU is number of days alive and out of hospital within 90 days (17). Secondary outcomes include one-year mortality, health related quality of life and cognitive function one year after randomisation. AID-ICU is on-going and the results is pending.

Mortality and health related quality of life after critical illness one year after randomization

The definition of Quality of Life (QoL) by World Health Organisation is "*as an individual's perception of their position in life in the context of the culture and value systems in which they live and in relations to their goals, expectations, standards and concerns. It is a broad ranging concept affected in a complex way by the person's physical health, psychological state, level of independence, social relationships, personal beliefs and their relationship to salient features their environment"* (18). As an indicator for and to conceptualise and measure QoL within a given research field, various Health Related Quality of Life (HRQoL) instruments have been developed. These instruments encompasses a multidimensional approach to measure both physical, mental, and social domains; aspects of overall QoL that can be shown to affect health (18–20).

Various generic HRQoL instruments have investigated QoL at short and/or long-term follow-up after critical illness (19,21,22). However 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 (23). Compared to the general population, ICU survivors report a lower HRQoL one year after critical illness (22). ICU survivors experience significant negative changes in health caused by long-term outcomes after critical illness (22–29). Long-term outcomes followed by critical illness have been shown to be associated with both increased morbidity and new/or aggravated physical and psychological disabilities (30). Especially the duration of delirium

in ICU has been found to be independently associated with long-term cognitive impairment(1,4). Delirium is a strong predictor for cognitive impairment up to years after ICU where especially impaired cognitive domains are memory (memory loss), affected executive functions and attention (poor concentration) (1,3–5). Beside the abovementioned impaired cognitive functions, a number of other psychological and mental disabilities including depression and risk of post-traumatic stress syndrome have been reported (31–33). Furthermore recent studies in survivors of critical illness have demonstrated a prolonged or sustained cognitive impairment similar to mild- to moderate traumatic brain injury and mild Alzheimer's disease (1,3,4,10,32,34).

Reported physical impairments include muscle weakness, weight loss, impaired activities of daily living (ADL) (e.g. dressing, eating and bathing) and having difficulties with swallowing (23,31,34–36).

The reported changes are numerous and these impairments and disabilities affect ICU survivors in different ways. Beside physical and psychological impairments, social impairment has been reported which involves reduced ability to resume work, tendency to social isolation and reduced quality of life (23,32,33,37–39). This may lead to e.g. unemployment and changes in socioeconomic status which further may represent a burden to the surrounding i.e. family and society (40).

Measuring health related quality of life in the AID-ICU population and in ICU-survivors with delirium.

Recommended instruments for measuring HRQoL in ICU-survivors include Short Form Health Survey 36(SF-36) and Euroqol (EQ-5D-5L)(24,41). We will use EQ-5D-5L and EQ-VAS (referred to EQ-5D) in the present study (19,42).

EQ-5D has been validated and found reliable for use in intensive care setting (43–45) . EQ-5D is a questionnaire measuring five different domains with each 5 levels (no problem, slight problems, moderate problems, severe problems and extreme problems). The domains are: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The EQ-VAS (Visual Analog Scale) reports the respondents' self-rated health on that particular day on a scale from 0 to 100 (42,46) and can be used a an quantitative measure of health outcome(42).

EQ-5D has been found feasible for patients with impaired cognition (47,48). However if the patient is to challenge with cognitive impairment, Euroqol have also develop a questionnaire where proxies rates the patients HRQoL.
EQ-5D can be administered in different ways e.g. face to face, postal mail and by telephone-interview administration(42,44).

Aims

- To assess the effect of haloperidol vs. placebo on mortality (one-year) in ICU patients with delirium included in the AID-ICU trial one year after inclusion
- To describe the self-reported HRQoL of ICU patients included in the AID-ICU trial one year after inclusion, and assess the effect of haloperidol vs. placebo on HRQoL in adult ICU patients with delirium. Patients dead at one-year follow-up will be assigned a value of zero for the HRQoL.

Outcomes

Primary outcomes:

- Difference in one-year mortality between all the randomised patients in the haloperidol and placebo group of the AID-ICU trial
- HRQoL measured by EQ-5D one-year after randomisation between all the randomised patients in the haloperidol and placebo group of the AID-ICU trial. Patients dead at one-year follow-up will be assigned a value of zero for the HRQoL.

Secondary outcome:

- HRQoL measured by EQ-5D one-year after randomisation between the survivors in the haloperidol and placebo group of the AID-ICU trial.
- The single sub-domains of the EQ-5D one-year after randomisation:
    - Mobility, Self-care, Usual activities, Pain/discomfort, Anxiety/depression and overall health rating (5L) and EQ- VAS.

Method

Study design

This pre-planned follow-up of the population from the AID-ICU trial (49). The trial is designed to assess one-year mortality and long-term health related outcome in ICU patients with delirium allocated to either haloperidol or placebo (0.9% saline).

One-year mortality

The one-year mortality (survival status) will be obtained through National Data Registers or by national and site investigators.

A survival analysis will be performed from randomization to one-year follow-up of the last patient randomised in the AID-ICU trial. There will be conducted a Cox regression with the expression Hazard Ratio (HR) adjusted for the stratification variables of sites and haematological malignancy. With a Kaplan-Meier analysis we can examine mortality in the period following randomization, where date of death is the event and lost to follow-up will be censored from the analysis. Time from follow-up is the underlying time-to-event and death is the event.

EQ-5D

To support a systematic approach that can account for contextual differences in HRQoL the five-level version of the EQ-5D will be used (42). With EQ-5D a health state can be generated with combining one level from each of the 5 domains and as a result of that a 5-digits number describes the participants' health state. Each of the 5 dimensions comprising the EQ-5D descriptive system is divided into 5 levels of perceived problems where the participant is asked to state hers/his health to the appropriate level. Level 1: indicating no problem Level 2: indicating slight problems Level 3: indicating moderate problems Level 4: indicating severe problems Level 5: indicating extreme problems (42).

The responses to the five EQ-5D dimensions (i.e. an EQ-5D health state) can be converted into a single number called an index value. The index value reflects how good or bad the health state is according to the preferences of the general population of a country (42).

Furthermore EQ-5D also includes an EQ-VAS dimension, which is a visual analogue scale where the endpoints are labelled 'The best health you can imagine' and 'The worst health you can imagine'.

Hereby, a quantitative measure reflecting patients' own judgement of health outcome can be extracted (42).

In countries where EQ-5D-5L value sets are not available the index values will be calculated using EQ-5D-3L crosswalk based calculation (50).

Obtaining EQ-5D-5L

Danish surviving participants will be contacted one-year after randomisation ask to participate in the follow-up by telephone by investigators blinded to the trial intervention to ensure compliance to the study. Daily phone-call will be made until response or for a period of 14 days. If no response is obtained, a mail survey will be dispatched.
In case the participant is not cognitively able to participate, we will ask relevant Danish proxies to answer instead (47,48). When using proxies for EQ-5D currently a Danish proxy version (proxy version 1 (paper-ref)) exists. In this version the proxy is asked to rate the patients' health-related quality of life in their (the proxies) opinion.

For the participating foreign countries (Spain, Italy, United Kingdom, Germany, Norway and Finland) the participating sites will use their standard settings to collect EQ-5D data, i.e. either by phone, mail or email contact. In any case, investigators blinded to the trial intervention will do the follow-up.
After obtaining data, these will be entered into the eCRF (electronic case report file) investigators blinded to the trial intervention.

Study population

The follow-up study population will be all a cohort of patients included in the AID-ICU trial with the following inclusion criteria:

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

Exclusion criteria for AID-ICU:

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

Ethical considerations, including consent

According to Danish law (§88) approval for the AID-ICU trial was obtained from the Danish Medicines Agency, the National Committee on Health Research Ethics and the Danish Data Protection Agency. These approvals also included follow-up one year after randomisation. Further details can be obtained in protocol of AID-ICU(17).

At inclusion into of the AID-ICU trial, patients will be incompetent caused by delirium, and the patients will therefore be enrolled after obtaining bystander consent from an independent physician (first guard). Second and third bystander consent will be from the patient's next of kin and a second independent physician will then be obtained. A fourth consent from the individual participant will be obtained, as soon as the patient is able to do so. The consenting party will be provided with written and oral information concerning the AID-ICU. The information also consists of information about withdrawal of consent from the trial at any time. These consents include one-year follow-up. Before one- year follow-up, we will secure the status of the participants' vital status (dead/alive) in order to only contacting living individuals.

The aim of the AID-ICU trial is to investigate harms or benefits with the use of haloperidol for ICU-related delirium. As haloperidol is the most frequently used treatment for delirium in the ICU participants in the AID-ICU trial will not be exposed to any additional risk when treated with haloperidol in the study. Furthermore a detailed escape protocol is present for treating patients with (severe/hyper active) delirium. The AID-ICU trial is dependent on detecting patients with delirium. This will potentially benefit the patients because systematic screening of patients for delirium at this point is often inconsistent (51,52).

Protection of data

This study is based on data from the participants of the AID-ICU trial. At enrolment to the AID-ICU study each participant received a unique trial identification number in the eCRF ensuring anonymity.

All data will be obtained from patient files and national registers and registered in an web-based eCRF. Data are managed electronically in the CRF by trained trial personnel. Data will be handled according to the National Data Protection Agency and protected by the Danish national laws 'Persondataloven' and 'Sundhedsloven'.

Statistical analyses

Descriptive statistics will be performed and include a description of the patients' characteristics at baseline with demography information as well as baseline measurement such as comorbid conditions.

We will perform the primary analyses in the intention-to-treat population.

Analyses:

- The primary analysis exploring the landmark mortality of one-year (every patient in the AID-ICU trial will be followed-up one year from randomization) will be analysed using logistic regression for differences in the binary outcome (alive/dead) and odds ratio will be converted to relative risks. Furthermore will survival data be analysed by using Cox-

regression analysis supplemented with a Kaplan-Meier analysis and log-rank test using information from the total period of follow-up, which is from randomization until one-year from randomization of the last patient.

- The primary analysis for EQ-5D will compare differences in means between the randomised groups using a general linear model adjusted for the stratification variables. Patients dead at one-year follow-up will be assigned a value of zero for the HRQoL. This highly non-normal outcome will then be compared between treatment groups using the novel method of Lange and Kryger Jensen (2018). In brief the probability of having a zero will be modelled using a logistic regression while the mean value among the non-zero values will be modelled using linear regression. A joint test for no treatment effect will be reported. The procedure can accommodate adjustment variables, see elsewhere, and the highly-skewed nature of the data distribution. Furthermore will this analysis also be supplemented with an analysis within the population of 1- year survivors.
- The secondary analyses of single sub-domains of EQ-5D (mobility, self-care, usual activites, pain/discomfort, anxiety/depression and overall health rating (EQ-VAS) will also be performed with the general linear model adjusted for the stratification variables.

For both the survival analysis and EQ-5D we will perform supplementary analyses for the following predefined baseline variables:

- Sites (small sites will be merged and handle according to the AID-ICU protocol)
- Sex
- Age ($\geq$ 69 year- < 69 year)
- Delirium sub-type as hypo-delirium, vs. mixed-delirium vs. hyper-delirium
- Patients with malignancy vs. those without
- One or more risk factors for delirium vs. no risk factors
- SMS score ($\geq$ 25- < 25)

Dead patients and patients with missing values

Deceased patients and patients with missing data will be handled according to the following rules:

- Dead patients will be assigned the 0 value.

- Patients with missing data (patients alive with no response or migrated patients) will be imputed.

HRQoL data may be missing in patients who are alive one year after randomisation (non-responders). If data in the questionnaires completed by Danish survivors are missing exclusively for the outcome of HRQoL, in less than 5% of patients, or data are missing completely at random (MCAR), with Littles test negative (P>0.05), we will not impute missing data. If data are missing for outcomes and adjusting covariates in more than 5% of the patients missing, data will be imputed using multiple imputation (MI) assuming data missing at random (MAR), 50 imputed datasets will be generated. If MI is considered necessary aggregated analysis of the imputed datasets will be calculated. However, assuming data missing not at random (MNAR) we will conduct analyses in best-worse and worse best scenarios where data from missing response from survivors will be imputed using the mean plus minus 1 SD of the HRQoL in patients with complete data (40).

If the distribution of HRQoL deviates substantially from the normal distribution the primary analysis will be adjusted for the stratification variable of sites using Van Elterens test for differences of medians between groups. If the distribution of HRQoL comes close to a normal distribution or if the distribution of the Log transformed data comes close to a normal distribution we perform multiple linear regression adjusted for both the stratification variable of sites and haematological malignancy and we will supplement the primary analysis adjusted exclusively for stratification variables with an analysis adjusted for both the stratification variables and the predefined covariates of age, SMS score, malignancy, and type of admission. We will provide 95% confidence intervals between means (if data are nearly normally distributed) or otherwise between medians (by bootstrapping) and a P-value less than 0.05 will be considered statistically significant.

Financing

Funding for this follow-up study will be provided by Department of Anaesthesiology and Intensive Care Zealand University Hospital, Køge. Furthermore will funding be sought to cover additional

costs. Costs of the AID-ICU trial is partly covered by Innovationsfonden and Regionernes Medicinpulje. Further funding may appear.

Publication

Changes in order of authors may appear.

- Camilla Bekker Mortensen
- Lone Musaeus Poulsen
- Nina Christina Andersen-Ranberg
- Stine Estrup
- Anders Perner
- AID-ICU sites national investigators
- X?
- X?
- Jørn Wetterslev
- Theis Lange
- Bjørn Ebdrup
- Ingrid Egerod
- Karin Samuelson
- Ole Mathiesen

References:

1. Pandharipande PP, Girard TD, Jackson JC, Morandi A, Thompson JL, Pun BT, m.fl. Long-term cognitive impairment after critical illness. N Engl J Med. 3. oktober 2013;369(14):1306–16.
2. Pandharipande P, Cotton BA, Shintani A, Thompson J, Pun BT, Morris JA, m.fl. PREVALENCE AND RISK FACTORS FOR DEVELOPMENT OF DELIRIUM IN SURGICAL AND TRAUMA ICU PATIENTS. J Trauma. juli 2008;65(1):34–41.
3. Pandharipande PP, Ely EW, Arora RC, Balas MC, Boustani MA, La Calle GH, m.fl. The intensive care delirium research agenda: a multinational, interprofessional perspective. Intensive Care Med. september 2017;43(9):1329–39.
4. Girard TD, Jackson JC, Pandharipande PP, Pun BT, Thompson JL, Shintani AK, m.fl. Delirium as a predictor of long-term cognitive impairment in survivors of critical illness. Crit Care Med. juli 2010;38(7):1513–20.
5. Patel MB, Morandi A, Pandharipande PP. What's new in post-ICU cognitive impairment? Intensive Care Med. april 2015;41(4):708–11.
6. Morandi A, Jackson JC, Ely EW. Delirium in the intensive care unit. Int Rev Psychiatry Abingdon Engl. februar 2009;21(1):43–58.
7. Collet MO, Caballero J, Sonneville R, Bozza FA, Nydahl P, Schandl A, m.fl. Prevalence and risk factors related to haloperidol use for delirium in adult intensive care patients: the multinational AID-ICU inception cohort study. Intensive Care Med. 16. maj 2018;
8. Ely E, 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. 5. december 2001;286(21):2703–10.
9. The DSM-5 criteria, level of arousal and delirium diagnosis: inclusiveness is safer. BMC Med. 25. september 2014;12:141.
10. Morandi A, Pandharipande PP, Jackson JC, Bellelli G, Trabucchi M, Ely EW. Understanding terminology of delirium and long-term cognitive impairment in critically ill patients. Best Pract Res Clin Anaesthesiol. september 2012;26(3):267–76.
11. Hayhurst CJ, Pandharipande PP, Hughes CG. Intensive Care Unit DeliriumA Review of Diagnosis, Prevention, and Treatment. Anesthesiol J Am Soc Anesthesiol. 1. december 2016;125(6):1229–41.
12. Ely EW, Shintani A, Truman B, Speroff T, Gordon SM, Harrell FE, m.fl. Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit. JAMA. 14. april 2004;291(14):1753–62.
13. Milbrandt EB, Deppen S, Harrison PL, Shintani AK, Speroff T, Stiles RA, m.fl. Costs associated with delirium in mechanically ventilated patients. Crit Care Med. april 2004;32(4):955–62.
14. Thomason JWW, Shintani A, Peterson JF, Pun BT, Jackson JC, Ely EW. Intensive care unit delirium is an independent predictor of longer hospital stay: a prospective analysis of 261 non-ventilated patients. Crit Care Lond Engl. august 2005;9(4):R375-381.
15. Page VJ, Ely EW, Gates S, Zhao XB, Alce T, Shintani A, m.fl. 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. september 2013;1(7):515–23.
16. Haloperidol - FDA prescribing information, side effects and uses [Internet]. [henvist 9. marts 2018]. Tilgængelig hos: https://www.drugs.com/pro/haloperidol.html

17. AID-ICU Trial [Internet]. CRIC - Centre for Research in Intensive Care. Tilgængelig hos: http://www.cric.nu/
18. World Health Organization, others. WHOQOL: measuring quality of life. 1997 [henvist 11. februar 2016]; Tilgængelig hos: http://apps.who.int/iris/handle/10665/63482
19. Badia X, Diaz-Prieto A, Gorriz MT, Herdman M, Torrado H, Farrero E, m.fl. Using the EuroQol-5D to measure changes in quality of life 12 months after discharge from an intensive care unit. Intensive Care Med. december 2001;27(12):1901–7.
20. Karimi M, Brazier J. Health, Health-Related Quality of Life, and Quality of Life: What is the Difference? PharmacoEconomics. juli 2016;34(7):645–9.
21. Hofhuis JG, van Stel HF, Schrijvers AJ, Rommes JH, Bakker J, Spronk PE. Health-related quality of life in critically ill patients: how to score and what is the clinical impact?: Curr Opin Crit Care. oktober 2009;15(5):425–30.
22. Flaatten H, Kvåle R. Survival and quality of life 12 years after ICU. A comparison with the general Norwegian population. Intensive Care Med. juni 2001;27(6):1005–11.
23. Hodgson CL, Udy AA, Bailey M, Barrett J, Bellomo R, Bucknall T, m.fl. The impact of disability in survivors of critical illness. Intensive Care Med. juli 2017;43(7):992–1001.
24. Angus DC, Carlet J, 2002 Brussels Roundtable Participants. Surviving intensive care: a report from the 2002 Brussels Roundtable. Intensive Care Med. marts 2003;29(3):368–77.
25. Dowdy DW, Eid MP, Sedrakyan A, Mendez-Tellez PA, Pronovost PJ, Herridge MS, m.fl. Quality of life in adult survivors of critical illness: A systematic review of the literature. Intensive Care Med. maj 2005;31(5):611–20.
26. Kvåle R, Flaatten H. [Outcome after intensive care]. Tidsskr Den Nor Laegeforening Tidsskr Prakt Med Ny Raekke. 14. januar 2010;130(1):44–6.
27. Hofhuis JGM, van Stel HF, Schrijvers AJP, Rommes JH, Spronk PE. Changes of Health-Related Quality of Life in Critically Ill Octogenarians. Chest. december 2011;140(6):1473–83.
28. 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. januar 2012;40(1):112–8.
29. Duggan MC, Wang L, Wilson JE, Dittus RS, Ely EW, Jackson JC. The relationship between executive dysfunction, depression, and mental health-related quality of life in survivors of critical illness: Results from the BRAIN-ICU investigation. J Crit Care. 2017;37:72–9.
30. Paratz JD, Kenardy J, Mitchell G, Comans T, Coyer F, Thomas P, m.fl. 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.
31. Broomhead Lr, Brett SJ. Clinical review: Intensive care follow-up – what has it told us? Crit Care. oktober 2002;6(5):411.
32. Jackson JC, Pandharipande PP, Girard TD, Brummel NE, Thompson JL, Hughes CG, m.fl. Depression, post-traumatic stress disorder, and functional disability in survivors of critical illness in the BRAIN-ICU study: a longitudinal cohort study. Lancet Respir Med. maj 2014;2(5):369–79.
33. Eddleston JM, White P, Guthrie E. Survival, morbidity, and quality of life after discharge from intensive care. Crit Care Med. 2000;28(7):2293–2299.
34. Iwashyna TJ, Ely EW, Smith DM, Langa KM. Long-term cognitive impairment and

functional disability among survivors of severe sepsis. JAMA. 27. oktober 2010;304(16):1787–94.
35. Prescott HC, Angus DC. Enhancing Recovery From Sepsis: A Review. JAMA. 02 2018;319(1):62–75.
36. Brodsky MB, Huang M, Shanholtz C, Mendez-Tellez PA, Palmer JB, Colantuoni E, m.fl. Recovery from Dysphagia Symptoms after Oral Endotracheal Intubation in Acute Respiratory Distress Syndrome Survivors. A 5-Year Longitudinal Study. Ann Am Thorac Soc. marts 2017;14(3):376–83.
37. Hofhuis JGM, Spronk PE, van Stel HF, Schrijvers GJP, Rommes JH, Bakker J. The impact of critical illness on perceived health-related quality of life during ICU treatment, hospital stay, and after hospital discharge: a long-term follow-up study. Chest. februar 2008;133(2):377–85.
38. Bein T, Hackner K, Zou T, Schultes S, Bösch T, Schlitt HJ, m.fl. Socioeconomic status, severity of disease and level of family members' care in adult surgical intensive care patients: the prospective ECSSTASI study. Intensive Care Med. april 2012;38(4):612–9.
39. Duggan MC, Wang L, Wilson JE, Dittus RS, Ely EW, Jackson JC. The relationship between executive dysfunction, depression, and mental health-related quality of life in survivors of critical illness: Results from the BRAIN-ICU investigation. J Crit Care. februar 2017;37:72–9.
40. Jakobsen JC, Gluud C, Wetterslev J, Winkel P. When and how should multiple imputation be used for handling missing data in randomised clinical trials - a practical guide with flowcharts. BMC Med Res Methodol. 6. december 2017;17(1):162.
41. Oeyen SG, Vandijck DM, Benoit DD, Annemans L, Decruyenaere JM. Quality of life after intensive care: a systematic review of the literature. Crit Care Med. december 2010;38(12):2386–400.
42. van Reenen, Mandy JB. EQ-5D-5L User guide Basic information on how to use the EQ-5D-5L instrument. 2015.
43. Robinson KA, Davis WE, Dinglas VD, Mendez-Tellez PA, Rabiee A, Sukrithan V, m.fl. A systematic review finds limited data on measurement properties of instruments measuring outcomes in adult intensive care unit survivors. J Clin Epidemiol. februar 2017;82:37–46.
44. Kaarlola A, Pettilä V, Kekki P. Performance of two measures of general health-related quality of life, the EQ-5D and the RAND-36 among critically ill patients. Intensive Care Med. 1. december 2004;30(12):2245–52.
45. Khoudri I, Belayachi J, Dendane T, Abidi K, Madani N, Zekraoui A, m.fl. Measuring quality of life after intensive care using the Arabic version for Morocco of the EuroQol 5 Dimensions. BMC Res Notes. 22. januar 2012;5(1):56.
46. Herdman M, Gudex C, Lloyd A, Janssen M, Kind P, Parkin D, m.fl. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res Int J Qual Life Asp Treat Care Rehabil. december 2011;20(10):1727–36.
47. Hounsome N, Orrell M, Edwards RT. EQ-5D as a quality of life measure in people with dementia and their carers: evidence and key issues. Value Health J Int Soc Pharmacoeconomics Outcomes Res. april 2011;14(2):390–9.
48. Orgeta V, Edwards RT, Hounsome B, Orrell M, Woods B. The use of the EQ-5D as a measure of health-related quality of life in people with dementia and their carers. Qual Life Res Int J Qual Life Asp Treat Care Rehabil. februar 2015;24(2):315–24.
50. van Hout B, Janssen MF, Feng Y-S, Kohlmann T, Busschbach J, Golicki D, m.fl.

Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. Value Health J Int Soc Pharmacoeconomics Outcomes Res. august 2012;15(5):708–15.
51. Rowley-Conwy G. Barriers to delirium assessment in the intensive care unit: A literature review. Intensive Crit Care Nurs. februar 2018;44:99–104.
52. Neto AS, Nassar AP, Cardoso SO, Manetta JA, Pereira VGM, Espósito DC, m.fl. Delirium screening in critically ill patients: a systematic review and meta-analysis. Crit Care Med. juni 2012;40(6):1946–51.