Health-related quality of life and days alive without life support or out of hospital

Protocol

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Health-related quality of life and days alive without life support or out of hospital: protocol

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Abstract

Background: Mortality is often the primary outcome in randomised clinical trials (RCTs) conducted in critically ill patients. Due to increased awareness on survivors after critical illness and outcomes other than mortality, health-related quality of life (HRQoL) and days alive without life support (DAWOLS) or days alive and out of hospital (DAAOOH) are increasingly being used. DAWOLS and DAAOOH convey more information than mortality, are easier to collect than HRQoL, and are usually assessed at earlier time points, which may be preferable in some situations. However, the associations between DAWOLS-DAAOOH and HRQoL are uncertain.

Methods: We will assess associations between DAWOLS-DAAOOH at day 28 and 90 (independent variables/predictors) and HRQoL assessed using the EuroQol EQ-5D-5L questionnaire (EQ-VAS and EQ-5D-5L index values) at 6 or 12 months (dependent variables) in 2 RCTs: the COVID STEROID 2 RCT conducted in adult patients with COVID-19 and severe hypoxaemia and the HOT-ICU RCT conducted in adult intensive care patients with acute hypoxaemic respiratory failure. We will describe associations using best-fitting fractional polynomial transformations separately in each dataset, with the resulting models presented and assessed in both datasets graphically and using measures of fit and prediction adequacy (i.e., internal performance and external validation). We will use multiple imputation if missingness exceeds 5%.

Discussion: The outlined study will provide important knowledge on the associations between DAWOLS-DAAOOH and HRQoL in adult critically ill patients, which may help researchers and clinical trialists prioritise and select outcomes in future RCTs conducted in this population.
Introduction

All-cause mortality is frequently used as the primary outcome in randomised clinical trials (RCTs) conducted in critically ill patients.\textsuperscript{1,2} While mortality is highly patient-important,\textsuperscript{2} its use comes with limitations\textsuperscript{1,3,4} and dichotomous outcomes generally require large sample sizes.\textsuperscript{5,6} RCTs conducted in critically ill patients are often powered only to detect effects substantially larger than minimally clinically relevant or clinically plausible differences.\textsuperscript{1,7,8} Consequently, RCTs assessing mortality are frequently inconclusive, and the absence of conclusive evidence on clinically relevant effect sizes tends to be misinterpreted as evidence of absence (i.e., no difference).\textsuperscript{9}

While survival is important, it is also central to focus on patients who survive to different health states, some of which may be considered worse than death.\textsuperscript{10} Ultimately, health-related quality of life (HRQoL) may be the most patient-important outcome for intensive care unit (ICU) survivors and is increasingly used in critical care RCTs, usually as a secondary, longer-term outcome.\textsuperscript{2} HRQoL, however, comes with limitations too. First, as a substantial proportion of critically ill patients die, death needs to be considered to avoid potentially misleading results.\textsuperscript{11} Second, loss to follow-up may be related to HRQoL states.\textsuperscript{12} Third, HRQoL is typically assessed after 6 or 12 months to allow patients to recover to a “steady state”. This is sensible, but as follow-up is thus longer than for most other outcomes currently used in critical care, the number of patients lost to follow-up often increases.\textsuperscript{13} Further, the longer time until results are available may be undesirable in pandemics, emergency situations, or adaptive trials, where it leads to slower adaptation.\textsuperscript{14}

RCTs conducted in critically ill patients frequently assess days alive without life support (DAWOLS; including different types of life support such as mechanical ventilation, vasopressor or inotropic therapy, and renal replacement therapy, or combinations of such), and days alive and out of hospital (DAAOOH).\textsuperscript{15,16} Such outcomes have frequently been used as secondary outcomes,\textsuperscript{17-20} but during the coronavirus disease 2019 (COVID-19) pandemic, they have increasingly been used as primary outcomes.\textsuperscript{21,22} These outcomes consider not only survival, but also duration of use of life supportive treatments or hospital stay; thus, they are more granular and convey more information than mortality alone.\textsuperscript{6} These outcomes are likely patient-important as well, as they include mortality, and because the duration of life support or hospital stay is plausibly associated with severity of illness, recovery trajectories and patient preferences. A similar outcome – “days at
home” – has been validated in surgical patients with fewer days at home associated with more post-operative complications.\textsuperscript{23} While DAWOLS and DAAOOH have limitations,\textsuperscript{4,16,24} they are objective and easy to register, convey more information than mortality alone, and are usually assessed after shorter follow-up than HRQoL. Consequently, increased use of these outcomes may be relevant in critical care RCTs. In the outlined study, we aim to assess the associations between DAWOLS-DAAOOH and HRQoL in 2 large, international RCTs conducted in critically ill patients.
Methods

This protocol and statistical analyses plan was prepared according to the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) statement\(^25\) (completed checklist included in the Supplement) and has been submitted and published prior to conduction of the study. An overview of the study and the planned analyses is presented in Figure 1.

Population and data sources

The study will be conducted using data from 2 investigator-initiated, international RCTs conducted in critically ill patients:

- The Higher vs. Lower Doses of Dexamethasone in Patients with COVID-19 and Severe Hypoxaemia (COVID STEROID 2) trial randomised 1000 adults with confirmed COVID-19 and severe hypoxaemia (received 10 litres of oxygen/minute or were mechanically ventilated) to either a higher (12 mg) or a lower (6 mg) dose of dexamethasone daily for up to 10 days.\(^21\) Patients were enrolled from 27 August 2020 to 20 May 2021 at 31 sites (ICUs and medical wards) in Denmark, Sweden, Switzerland and India.

- The Handling Oxygenation Targets in the Intensive Care Unit (HOT-ICU) trial randomised 2928 adult ICU patients requiring at least 10 litres of oxygen/minute or a fraction of inspired oxygen of at least 0.50 in mechanically ventilated patients to either a lower (8 kPa) or a higher (12 kPa) partial pressure of arterial oxygen for a maximum of 90 days while admitted to the ICU, including readmissions.\(^26\) Patients were enrolled from 20 June 2017 to 3 August 2020 in 35 ICUs in Denmark, Switzerland, Finland, the Netherlands, Norway, the United Kingdom and Iceland.

Analyses will be conducted separately in each trial population to assess associations in related but different populations, with secondary external validation in the other trial population.

Outcomes and definitions

**Days alive without life support**

For the purpose of this study, we will use DAWOLS assessed at day 28 and 90, defined as the total number of days within this period where the patient was alive without any use of mechanical ventilation (invasive mechanical ventilation only in the COVID STEROID 2 trial,\(^21\) invasive/non-invasive mechanical ventilation or non-intermittent continuous positive airway pressure in the
HOT-ICU trial\textsuperscript{25}, circulatory support (continuous use of vasopressors or inotropes) or renal replacement therapy (days in-between intermittent renal replacement therapy counted as days receiving life-support); further details are available elsewhere.\textsuperscript{21,26} Of note, the DAWOLS outcome in the HOT-ICU trial was defined as the percentage of DAWOLS divided by the total number of days the patient was alive, although the actual number of days (not as a percentage) was also reported.\textsuperscript{26} This outcome definition is less common than the total number of days, which is recommended elsewhere,\textsuperscript{15,16} and which will be used in the current study. The COVID STEROID 2 trial assessed DAWOLS at both day 28 and day 90.\textsuperscript{21} The HOT-ICU trial assessed DAWOLS at day 90;\textsuperscript{26} in this study, it will be calculated according to 28 days of follow-up as well.

**Days alive and out of hospital**

In this study, we will use DAAOOH assessed at day 28 and 90, defined as the number of days in this period where the patient was alive and discharged from the hospital. As for DAWOLS, the DAAOOH outcome in the HOT-ICU trial were defined as the percentage of days alive,\textsuperscript{26} but the absolute number of days are used for DAAOOH assessments in the current study, which was also presented secondarily in the HOT-ICU trial.\textsuperscript{26} DAAOOH was assessed at day 90 (secondary outcome) in both the COVID STEROID 2 and HOT-ICU trials,\textsuperscript{21,26} but for this study, it will be calculated after 28 days of follow-up as well.

**Health-related quality of life**

Both the COVID STEROID 2 and HOT-ICU trials assessed HRQoL using the EuroQol EQ-5D-5L questionnaire,\textsuperscript{27} by either phone or mail.\textsuperscript{21,26} EQ-5D-5L consists of EQ-VAS and five separate dimensions, which may be used to calculate a summarised index value that is frequently used in health economic evaluations.\textsuperscript{27} In the COVID STEROID 2 trial, HRQoL was assessed 6 months after randomisation,\textsuperscript{21} while it was assessed 12 months after randomisation in the HOT-ICU trial.\textsuperscript{26,28}

EQ-VAS is a visual analogue scale ranging from 0 to 100 mm (with 0 and 100 mm representing worst and best imaginable health states, respectively) assessed by the patient.\textsuperscript{27}

The five dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) have five levels of severity each.\textsuperscript{27} The EQ-5D-5L index value is calculated using a value set derived from interview studies of representative populations; index values are anchored at 1 (representing a perfect health state) and 0 (representing a health state as bad as being dead), with states
considered worse than being dead assigned negative values. In this study, index values will be calculated using national EQ-5D-5L value sets as recommended, with the Danish value set used for countries without an available value set, as the majority of patients in both trials were enrolled in Denmark. Additional patients were mostly enrolled in other European countries; however, 38% of patients in the COVID STEROID 2 trial were enrolled in India. At the time of writing, national value sets exist for Denmark, the United Kingdom (England) and the Netherlands; development of value sets for Sweden, Norway and India is ongoing, while no value sets appear to be underway for Switzerland, Finland and Iceland.

Mortality
All-cause mortality assessed at 28 and 90 days after randomisation and at the time of HRQoL assessment (6 or 12 months).

Statistical analyses
All analyses will be conducted separately in the COVID STEROID 2 and HOT-ICU trial populations. Analyses will be conducted using R software (R Core Team, R Foundation for Statistical Computing, Vienna, Austria). Descriptive baseline data (variables listed in Table 1) and outcome data will be presented for all patients and separately for non-survivors at HRQoL follow-up, survivors with available HRQoL data, and survivors with missing HRQoL data in each trial to allow comparison of populations according to survival and respondence status. Data will be summarised using medians with interquartile ranges (IQRs) for numeric values, and absolute and relative frequencies for categorical data.

Primary analyses
The primary analyses will be conducted solely in patients who survived until the time of HRQoL-follow-up. The primary analyses will be conducted for the possible combinations of DAWOLS and DAAOOH assessed at 2 time points (day 28 and 90) as the independent variable (predictor; x) and EQ-VAS and EQ-5D-5L index values as the dependent variable (y).

Relationships will be assessed using an approach based on fractional polynomials. Fractional polynomials are (non-linear) transformations defined using a restricted number of power transformations, which allows model flexibility while being less prone to extreme predictions for low/high values and extrapolated values compared to conventional polynomial transformations.
addition, fractional polynomials are simpler and thus easier to explain and use for prediction in other studies compared to more complex approaches such as splines or non-parametric smoothing functions.\textsuperscript{33,34} We will fit separate models using different possible first-/second-degree fractional polynomial transformations for each association assessed in each dataset (details in the Supplement), followed by selection of the best transformation according to the lowest root mean squared error (RMSE). This approach will be used instead of automated selection,\textsuperscript{33,34} as only a single predictor is assessed and as this approach readily supports multiple imputation, which may be necessary due to missing HRQoL-data.

Full specifications for the selected models will be presented. Fit to data will be assessed using RMSEs and visualised with curves and associated 95\% confidence bands overlain scatter plots of both datasets. Models will be externally validated by assessing RMSEs, calibration-in-the-large (ideally 0, positive/negative values indicate systematic over-/underprediction, respectively) and calibration slopes (assessing systemic over-/underfitting, ideally 1, values <1 / >1 suggest too extreme/too moderate predictions, respectively) in the other trial dataset.\textsuperscript{35}

In addition, Spearman’s non-parametric rank correlation coefficient with 95\% confidence intervals will be presented as relationships are likely to be non-linear but monotonically increasing.

Secondary analyses:

For each of the 5 individual dimensions of EQ-5D-5L, we will graphically and numerically (medians with IQRs) present the distribution of DAWOLS and DAAOOH according to the ratings in each domain. This will be done separately for both follow-up durations (28 and 90 days) in both datasets.

Sensitivity analyses

Two sets of sensitivity analyses including non-survivors will be conducted for the primary analyses. In both sets of sensitivity analyses, patients who died before HRQoL follow-up will be included and assigned 0 for EQ-VAS (lowest possible value) and 0 for the EQ-5D-5L index values.

In the first set of sensitivity analyses, patients who died on or before day 28 or 90 (maximum follow-up duration for DAWOLS and DAAOOH) will be assigned 0 days (worst possible value) for DAWOLS and DAAOOH, even if the patient had some days alive and without life support/out of
hospital. This is frequently recommended and done in trials using this outcome to ensure that
death is the worst possible outcome in the analyses.\textsuperscript{15,16}

In the second set of sensitivity analyses, the actual values for DAWOLS and DAAOOH will be used
without penalising death, reflecting the definition used in the primary analyses of the COVID
STEROID 2 trial.\textsuperscript{21}

Finally, a third set of sensitivity analyses will be conducted for the primary analyses of EQ-5D-5L
index values using the Danish value set\textsuperscript{10} for all patients regardless of country of enrolment.

\textbf{Sample size considerations}
This study uses a convenience sample including all patients who survived until HRQoL-follow-up
from the COVID STEROID 2 and HOT-ICU trials in the primary analyses and all patients including
non-survivors in the sensitivity analyses. No formal sample size calculation has been performed,
but we consider both trial datasets large enough to adequately assess the associations of interest.

\textbf{Missing data handling}
The proportion of missing data for the variables of interest will be presented. If the proportion of
patients with missing data for either HRQoL, DAWOLS-DAAOOH, or mortality exceeds 5% in either
trial, we will multiply impute missing data using chained equations, the predictive mean matching
method for numeric data (DAWOLS, DAAOOH and EQ-VAS), binary logistic regression for binary
data (mortality), and ordinal logistic regression for ordinal data (individual EQ-5D-5L domains)
using the \textit{mice} R package.\textsuperscript{36,37}

For each trial, 25 complete datasets will be imputed, with subsequent calculation of EQ-5D-5L
index values. In addition to the outcome variables discussed above, the baseline variables listed in
\textbf{Table 1} will be included in the imputation models.

If multiple imputation is used, no complete case analysis will be conducted. Rubin’s rules will be
used to combine results, where applicable after appropriate transformation.\textsuperscript{38} Descriptive data will
be calculated using all imputed, pooled datasets and RMSEs will be calculated using the pooled
model coefficients on all imputed, pooled datasets.

\textbf{Ethics and dissemination}
Both trials were approved by all relevant authorities and ethics committees as reported
elsewhere.\textsuperscript{21,26} No further approvals were necessary for this secondary study. The results of this study will be reported in an international peer-reviewed journal regardless of the findings, and the reporting will adhere to the STROBE statement. \textsuperscript{25}
Discussion

The outlined study will provide important information on the associations between DAWOLS-DAAOOH and HRQoL in adult critically ill patients. This may inform outcome selection in future RCTs conducted in this population, enabling focus also on survivors after critical illness.

The outlined study comes with strengths. First, while both the COVID STEROID 2 and HOT-ICU trials have completed inclusion at the time of writing, this protocol has been finalised and published prior to end of follow-up for HRQoL in the COVID STEROID 2 trial and before publication of the HOT-ICU HRQoL results. Second, sensitivity analyses will be conducted, ensuring that associations are assessed under different assumptions, including using different HRQoL value sets and inclusion of non-survivors, considering both the actual number of days and with death considered the worst possible outcome (zero days), reflecting the different definitions used in different trials. Third, the use of 2 comparable but different RCT populations enables generalisation to a broader patient population and allows assessment of consistency of findings between trials. Finally, we will assess the associations between DAWOLS-DAAOOH and long-term HRQoL with 2 different and commonly used durations of follow-up, thus possibly providing data on which of these 2 follow-up times may be most relevant from a HRQoL-focused point of view.

The study comes with limitations, too. First, there may be moderate missingness for HRQoL outcomes, as is commonly the case. As missing HRQoL data are unlikely to be missing-completely-at-random, non-negligible missingness will be handled using multiple imputation to limit the risk of bias and loss of power. We will assume that data are missing-at-random, and that missing HRQoL data can be acceptably imputed using available baseline data; even if data are not-missing-at-random, multiple imputation may be preferred to complete case analysis. Second, we do not plan to assess the associations between DAWOLS-DAAOOH and HRQoL separately in the 2 treatment arms in each RCT, as we do not expect the interventions assessed to substantially affect the associations between DAWOLS-DAAOOH and HRQoL. Third, HRQoL is assessed at different time points in the 2 trials, which may affect the external validation (primarily regarding calibration-in-the-large). Despite this limitation, we consider external validation important to assess extent of overfitting and the generalisability of the results. Fourth, EQ-5D-5L value sets do not currently exist for all involved countries. We will use the Danish value set for countries without national...
sets as most patients were included in Denmark. The Danish value set is likely reasonable for the other European countries due to cultural similarities, but probably less so for India. However, as no other value set deemed more appropriate for India is currently available, the Danish value set will be used for consistency if the Indian value set has not been published when the analyses are conducted.

Finally, it is important to acknowledge that DAWOLS and DAAOOH come with advantages and disadvantages compared to other outcomes, including all-cause mortality and HRQoL. If DAWOLS and DAAOOH are found to be adequately associated with HRQoL, this may support increased use, while lack of sufficient associations will not necessarily disqualify the use of these outcomes in RCTs.

In conclusion, the outlined study will provide important knowledge on the associations between DAWOLS-DAAOOH and HRQoL in adult critically ill patients, which may help researchers and trialists select and prioritise outcomes in future RCTs conducted in this patient population.
**Authors’ contributions:** Conception: AG and MHM. Study design: AG, OLS, AKGJ, BSR, and MHM. Drafting of the protocol: AG. Revision of the protocol for critically important intellectual content and approval of the final version: all authors. AG, OLS, MWM, TLK, EC, MNK, TS, AP, BSR, and MHM were involved in the conduct of the COVID STEROID trial and/or the HOT-ICU trial.

**Conflicts of interest:** The Department of Intensive Care at Rigshospitalet has received funding for other research projects from the Novo Nordisk Foundation, Pfizer, Ferring and Fresenius Kabi, and conducts contract research for AM-Pharma (the REVIVAL trial).

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**Supplement:** additional description of the fractional polynomials approach used and completed STROBE checklist.
References


11. Colantuoni E, Li X, Hashem MD, Girard TD, Scharfestein DO, Needham DM. A structured methodology review showed analyses of functional outcomes are frequently limited to

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22. The Writing Committee for the REMAP-CAP Investigators. Effect of Hydrocortisone on


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### Tables and figures

#### Table 1. Baseline variables assessed

<table>
<thead>
<tr>
<th>Baseline variable</th>
<th>COVID STEROID 2</th>
<th>HOT-ICU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Country of enrolment</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Age</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Sex</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Place of enrolment (intensive care unit [ICU] vs. non-ICU)</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Admission type (medical vs. surgical, including both elective and emergency surgery)</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Respiratory support (invasive mechanical ventilation vs. non-invasive ventilation or continuous positive airway pressure vs. open system)</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Use of vasopressors or inotropes</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Ischaemic heart disease or heart failure</td>
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<td>X</td>
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<td>Diabetes mellitus</td>
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<td>X</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
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<td>X</td>
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<tr>
<td>Immunosuppressive therapy within three months of randomisation or chronic use of corticosteroids</td>
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<td>Active metastatic or haematologic cancer</td>
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</tr>
<tr>
<td>Sequential [Sepsis-related] Organ Failure Assessment (SOFA) score</td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

Baseline variables presented for all patients and for non-survivors, survivors with available health-related quality of life data and survivors without health-related quality of life data in each trial. These variables will also be included in the imputation models if multiple imputation is used.
Overview of the outlined study. First, the COVID STEROID 2 and HOT-ICU trial datasets are depicted, with potential missing values indicated by “?” . Second, multiple imputation (MI) will be conducted (25 times, separately in each database – this step will be omitted if total missingness is below 5%), followed by separate analysis in each imputed dataset. Third, results for the multiply imputed datasets from each trial are pooled, and the best fitting model is selected, with other models disregarded. Fourth, the best model from each dataset is assessed internally (in the same trial as it was developed) and externally (in the other trial) and results presented. For the fourth step, multiply imputed data will similarly be used if missingness exceeds 5%, with separate analysis in each imputed dataset followed by pooling of the final results.
COVID STEROID 2

HOT-ICU