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Protocol for a Monte Carlo simulation study

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Published in:
Acta Anaesthesiologica Scandinavica

DOI:
10.1111/aas.14324

Publication date:
2023

Document version
Publisher's PDF, also known as Version of record

Document license:
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Citation for published version (APA):
RESEARCH ARTICLE

Health-related quality of life trajectories in critical illness: Protocol for a Monte Carlo simulation study

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Funding information
Novo Nordisk Foundation; Sygeforsikringen “danmark”

Abstract

Background: Health-related quality of life (HRQoL) is a patient-centred outcome increasingly used as a secondary outcome in critical care research. It may cover several important dimensions of clinical status in intensive care unit (ICU) patients that arguably elude other more easily quantified outcomes such as mortality. Poor associations with harder outcomes, conflicting data on HRQoL in critically ill compared to the background population, and paradoxical effects on HRQoL and mortality complicate the current operationalisation in critical care trials. This protocol outlines a simulation study that will gauge if the areas under the HRQoL trajectories could be a viable alternative.

Methods: We will gauge the behaviour of the proposed HRQoL operationalisation through Monte Carlo simulations, under clinical scenarios that reflect a broad critical care population eligible for inclusion in a large pragmatic trial. We will simulate 15,360 clinical scenarios based on a full factorial design with the following seven simulation parameters: number of patients per arm, relative mortality reduction in the interventional arm, acceleration of HRQoL improvement in the interventional arm, the relative improvement in final HRQoL in the interventional arm, dampening effect of mortality on HRQoL values at discharge from the ICU, proportion of so-called mortality beneficiers in the interventional arm and mortality trajectory shape. For each clinical scenario, we will simulate 100,000 two-arm trials with 1:1 randomisation. HRQoL will be sampled fortnightly after ICU discharge. Outcomes will include HRQoL in survivors and all patients at the end of follow-up; mean areas under the HRQoL trajectories in both arms; and mean difference between areas under the HRQoL trajectories and single-sampled HRQoLs at the end of follow-up.

Discussion: In the outlined simulation study, we aim to assess whether the area under the HRQoL trajectory curve could be a candidate for reconciling the seemingly paradoxical effects on improved mortality and reduced HRQoL while remaining sensitive to early or accelerated improvement in patient outcomes. The resultant insights...
1 | INTRODUCTION

Health-related quality of life (HRQoL) is a patient-centred outcome that is increasingly used as a secondary outcome in trials enrolling critically ill patients in the intensive care unit (ICU) although it has been used as a primary outcome. Common and often more easily quantifiable outcomes, such as all-cause mortality or days alive and out of the hospital, are often used as primary outcomes as they are easier to operationalise, more measurable and objective and perhaps more definitive. HRQoL, however, may cover several important dimensions of clinical status in critically ill patients that other such outcomes arguably fail to fully capture.

Indeed, one could speculate that survival alone is not enough: although it is likely the key patient-centred outcome at the time of ICU admission, survival to achieve a reasonable quality of life may be considered to have primacy after ICU and hospital discharge. In line with this, HRQoL is recommended as a core outcome in ICU trials for acute respiratory distress syndrome patients and is expected to be among the platform-wide core outcomes in the Intensive Care Platform Trial (INCEPT). Although subtler aspects of the multiple dimensions of HRQoL may elude low-resolution tools including the 5-level EQ-5D (EQ-5D-5L), such tools are convenient, efficient and have good user characteristics.

Although its use is growing using HRQoL in ICU trials is not without challenges. First, a recent post hoc study of two ICU trials found poor associations between days alive without outcomes and HRQoL when the latter was sampled at the end of follow-up; others are retrospectively looking into this in other trials [ClinicalTrials.gov: NCT04567433]. Second, although some data suggest convergence of ICU survivors’ HRQoL towards their previous level and small differences in HRQoL between ICU survivors and the general population; other studies have arrived at the exact opposite conclusions. Third, as has been observed in a review, in the few ICU trials that have shown an effect on HRQoL, this effect is not necessarily simple to discern: a beneficial effect of an intervention on mortality may cause a seemingly paradoxical negative effect on HRQoL if one only compares HRQoL levels sampled at end of follow-up in survivors (also known as truncation due to death), presumably due to improved survival of patients with poorer HRQoL. The quantitative impact of this paradoxical effect is unknown, however.

The overarching aim of this study is to devise an HRQoL operationalisation that reconciles the paradoxical effects on mortality and HRQoL while remaining sensitive to early or accelerated improvement in patients who more quickly reach their eventual HRQoL levels. Specifically, our objective in this simulation study is to assess whether the area under the HRQoL trajectory curve (AUTC) could be a viable candidate solution for this problem, by comparing its performance with that of the conventional single-sampling approach currently used in ICU trials.

2 | MATERIALS AND METHODS

We will gauge the behaviour of the proposed HRQoL operationalisation through Monte Carlo simulations, under multiple clinical scenarios that reflect our population of interest: a broad ICU population eligible for inclusion in a large pragmatic RCT. This study was designed considering recommendations for statistical simulation studies.

For each of the 15,360 configurations (i.e., each combination of the simulation parameter values listed below), we will simulate 100,000 two-arm trials as done in other recent simulation studies in the realms of intensive care trials and recommended when using simulations to design real clinical trials. Although some of the resultant configurations may be unrealistic, they will nevertheless serve as useful signposts for the interpretation of the more realistic ones. In all simulations, we will assume 1:1 allocation using block randomisation to avoid imbalances in group sizes.

2.1 | HRQoL trajectories

We intend for the results of this simulation study to inform the use of EQ-5D-5L in future ICU trials and, so, have tried to align our design decisions with this tool. Based on EQ-5D-5L index values, the weighted HRQoL value corresponding to perfect health is 1.0, the value corresponding to death is 0.0, and health states worse than death yield weighted HRQoL values below 0.0. EQ-5D-5L index values are computed in a two-step fashion. First, the respondent ranks their state of health in each of five domains (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) using five-level ordinal scales ranging from, essentially, no problem to extremely severe problems. Then, these five health states are combined into a single index value using value sets (typically national, but always population specific). In other HRQoL scales without an explicit value, death is often considered to correspond to the worst possible level of HRQoL. Follow-up will start at randomisation (index, assumed to coincide with ICU admission) with index HRQoL set to 0.0.

All HRQoL trajectories will be derived from a smooth, fixed, control-group HRQoL trajectory connecting the timepoints and HRQoL values in Table 1 with a centripetal Catmull–Rom curve. This “baseline”...
The day of death is sampled from an logNormal(meanlog = log(5), sdlog = log(2) * 1.4826) distribution and, instead, base the distribution directly on real data. Based on the empirical quantile function derived from Meyhoff et al., we can sample days of death without the need for a parametric distribution and, instead, base the distribution directly on real data. This relationship aligns satisfactorily with summary statistics reported by Forster et al. (tabs. 1 and 4).

### Outcomes and synthesis

For each configuration we will have the following estimands:

1. HRQoL in survivors and all patients at the end of follow-up. For the all-patient calculation, patients who die before the end of follow-up will be assigned HRQoL = 0.0 (as per how death is handled by EQ-5D-5L).
2. AUTC in both arms.

3. The mean difference between AUTCs and single-sampled HRQoLs at the end of follow-up with a 95% confidence interval.

The following performance measures (with 95% Monte Carlo confidence intervals) for differences both between AUTCs and single-sampled HRQoLs at the end of follow-up:

<table>
<thead>
<tr>
<th>Study acronym/first author and year</th>
<th>N</th>
<th>Tool</th>
<th>Timing</th>
<th>Results</th>
</tr>
</thead>
</table>
| IMPROVE 
Campos 2022                   | 70 | EQ-5D-3L      | Enrolment and 1 week after ventilator liberation                      | Index values seemingly not used |
|                                    | 139| EQ-5D-3L      | ICU discharge                                                          | −0.1 (−0.1; 0.2)                 |
|                                    |    |               | Hospital discharge                                                     | 0.2 (−0.1; 0.4)                  |
|                                    |    |               | 90 days after enrolment                                                | 0.25 (0.34)                      |
|                                    |    |               | 180 days after enrolment                                               | 0.69 (0.24)                      |
|                                    |    |               | 6 months after enrolment                                               | 0.75 (0.26)                      |
| Nickels 2020                      | 72 | EQ-5D-5L      | 10 days, 3 months and 6 months after enrolment                         | Index values not used            |
| STOP-AKI                           | 227| EQ-5D-5L      | Discharge from ICU or intermediate-care unit                          | Index values seemingly not used |
| Ridley 2018                        | 99 | EQ-5D-3L      | Hospital discharge                                                     | 0.32 (0.36)                      |
|                                    |    |               | 90 days after enrolment                                                | 0.76 (0.23)                      |
|                                    |    |               | 180 days after enrolment                                               | 0.77 (0.24)                      |
|                                    |    |               | 6 months after enrolment                                               | 0.502 (0.347)                    |
|                                    |    |               | 3 months after enrolment                                               | 0.446 (0.324)                    |
|                                    |    |               | After ICU discharge, before hospital discharge                         | 0.512 (0.353)                    |
|                                    |    |               | 6 months after enrolment                                               | 0.565 (0.390)                    |
|                                    |    |               | 12 months after enrolment                                              | 0.565 (0.390)                    |
|                                    |    |               | 3 months after enrolment                                               | 0.502 (0.347)                    |
| EPICC                              | 308| EQ-5D-5L      | 3 months after enrolment                                               | 0.446 (0.324)                    |
| Freeman-Sanderson 2016             | 30 | EQ-5D         | Unclear                                                                | Index values not used            |
| PRaCTical 2009                     | 286| EQ-5D-3L      | After ICU discharge, before hospital discharge                         | 0.49 (0.19; 0.69)                |
|                                    |    |               | 6 months after enrolment                                               | 0.62 (0.3)                      |
|                                    |    |               | 12 months after enrolment                                              | 0.60 (0.3)                      |
| Cohort studies                     |    |               |                                                                        |                                  |
| Cuthbertson 2010                   | 300| EQ-5D-3L      | 12 months after ICU admission                                          | 0.666 (0.280)                    |
|                                    |    |               | 2.5 years after ICU admission                                          | 0.701 (0.281)                    |
|                                    |    |               | 5 years after ICU admission                                            | 0.677 (0.301)                    |
| Cuthbertson 2013                   | 439| EQ-5D-3L      | 3.5 years after ICU admission                                          | 0.64 (0.36)                     |
|                                    |    |               | 5 years after ICU admission                                            | 0.68 (0.32)                     |

aMedian (interquartile range).
bMean (standard error).
cMean (standard deviation).

FIGURE 1 Bee swarm plot of ICU LOS and hospital LOS of 248 ICU patients (both axes are log10-transformed). The blue line shows the estimated linear relationship between log10(ICU LOS) and the median log10 (hospital LOS) and suggests a reasonable approximation to the smoothed relationship illustrated by the dashed line and its 95% confidence band.
**FIGURE 2** Individual effects of select simulation parameters on control-group HRQoL trajectory (dashed black curves). The grey areas represent ICU stay. (A) Acceleration increases the gained HRQoL early on with faster improvement followed by plateauing to converge with the baseline trajectory. (B) The gained HRQoL lies predominantly in the late part of the follow-up period. (C) Mortality dampens the HRQoL at index, and the patient’s trajectory is assumed linear (in this case, but see point 7 in main text for other options) until the day of death. (D) Mortality benefiter (solid red curve) who has a worse HRQoL at index but otherwise follows the control-group trajectory; the dashed red line corresponds to the counterfactual scenario in which the patient were not a mortality benefiter (i.e., had been allocated to the control arm) and, thus, would have died.

**FIGURE 3** Generating the HRQoL trajectory of a single fictive active-arm patient. (A) Pick appropriate group-level HRQoL trajectory to use as the basis. (B) Compute HRQoL value (filled circles) on Days 15 (this patient’s day of ICU discharge), 29, 43, ..., 183. (C) Sample one value $y^*_t = 15$ from a normal distribution with mean $y_t = 15$ and standard deviation calibrated to place 97.5% of the probability density above 0.0, compute relative change as $\frac{y_t = 15}{C_0/C_1} = 1.0$, and multiply this relative change with all original HRQoL values throughout the follow-up period. (D) Enforce valid EQ-5D-5L index values (as per the Danish reference values) and connect with straight lines to arrive at the patient’s final HRQoL trajectory.
1. Bias.
2. Root mean squared error.
3. Coverage of confidence interval.
4. Type 1 error rate and power (\( = 1 \) – Type 2 error rate) for scenarios without and with the effect of the intervention, respectively.

The statistics will be computed under three assumptions about when HRQoL sampling can start:

1. On the day of ICU discharge (so, while still admitted to the hospital).
2. On the day of hospital discharge.
3. 90 days after randomisation.

The main analysis will include all patients, but a secondary analysis will compute the outcome metrics in survivors only (to mimic what is frequently done currently\(^2\)). Comparisons will be qualitative/descriptive.

### 2.4 | Ethics and reporting

Ethical approval is unnecessary as we will use simulated data only. Results will be reported descriptively and submitted to an international, peer-reviewed journal regardless of the findings, accompanied by the full analytical code to ensure transparency and facilitate reproducibility. Any deviation from this protocol and statistical analysis plan will be reported and motivated.

### 3 | DISCUSSION

In the outlined simulation study, we aim to assess whether the AUTC could be a candidate for reconciling the seemingly paradoxical effects on improved mortality and reduced HRQoL while remaining sensitive to early or accelerated improvement in patients. Conceivably, using temporal data on HRQoL trajectories could supersede the conventional single-sampling approach in capturing and quantifying beneficial effects on HRQoL. Repeated collection of HRQoL data, however, would require more human and financial resources, and survey fatigue might introduce problematic missingness. Thus, to be sensible, the added benefit of repeated HRQoL sampling would need to balance and hopefully outweigh, these challenges. Because so little data are available on shorter-term HRQoL trajectories in ICU patients, a simulation study is a good starting point owing to its very low cost and in-silico nature.

The outlined study has several strengths: it adheres to relevant recommendations in the field of statistical simulation studies,\(^16\) prior publication of this protocol, the large number of clinical scenarios (15,360) covering the spectrum between trivial and unlikely scenarios, as well as our simulating 100,000 trials for each scenario as recommended when using simulations to design real RCTs.\(^35\) Furthermore, to the best of our knowledge, this is the first in-silico study to extensively study the behaviour of HRQoL trajectories in ICU patients.

Our study will have limitations as well. First, simulated clinical scenarios are necessarily simplifications, and so the results are unlikely to generalise perfectly to the real clinical context. The well-defined simulated clinical scenarios, however, give us full control of the system’s behaviour, which in turn enables us to discern patterns and trace their origin. Second, and related, our operationalisation of the simulation parameters could be incorrect; for example, accelerated improvement in HRQoL might not materialise in the way we simulate. Because our focus is the AUTC, however, such slight misspecification would likely distort the results enough to nullify them. Third, due to the relative lack of shorter-term HRQoL data from real ICU populations, we had to piece together the HRQoL trajectories combining the data that are, nonetheless, available with reasonable heuristics. Although the latter are based on vast experience with HRQoL as an outcome in ICU trials, in the author group, they could be challenged.

### 4 | CONCLUSION

The outlined simulation study aims to assess if areas under patient-level HRQoL trajectory curves capture subtle improvements in HRQoL that elude one-off HRQoL sampling at the end of follow-up. If so, the resultant insights will hopefully inform subsequent...
methodological work on prudent collection and statistical analysis of such data from real ICU patients.

**AUTHOR CONTRIBUTIONS**

Conception: BSKH. Study design: All authors. Writing, original draft: BSKH. Writing, critical review: All authors. All authors approved the final version of the manuscript. Funders played no role in designing this study.

**ACKNOWLEDGEMENTS**

The authors would like to express their gratitude to Esben Mar Gregers Jensen for his help in extracting the admission and discharge data used in Figure 1. The Department of Intensive Care at Rigshospitalet has received funding for other research projects from the Novo Nordisk Foundation, Sygeforsikringen “danmark” and has conducted contract research for AM-Pharma.

The authors declare no conflict of interest.

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