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

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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 benefiters 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
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 recent 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 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”
TABLE 1  Values for control-group trajectories.

<table>
<thead>
<tr>
<th>Timing</th>
<th>t (Days)</th>
<th>HRQoL in control group</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICU admission</td>
<td>= 0</td>
<td>0.00</td>
</tr>
<tr>
<td>ICU discharge</td>
<td>~ logNormal(meanlog = log(5), sdlg = log(2) × 1.4826)</td>
<td>0.10</td>
</tr>
<tr>
<td>Hospital discharge</td>
<td>= (day of ICU discharge)/0.518 × 9.310</td>
<td>0.30</td>
</tr>
<tr>
<td>90 days</td>
<td>= 90</td>
<td>0.68</td>
</tr>
<tr>
<td>End of follow-up</td>
<td>= ceiling[(180 – day of ICU discharge)/14) × 14 + day of ICU discharge</td>
<td>0.75</td>
</tr>
</tbody>
</table>

Note: Equality sign means that value is fixed, tilde (~) means a stochastic value following the indicated distribution. Abbreviation: HRQoL, health-related quality of life.

trajectory will be the same in all scenarios and all trials, but patients assigned to those control groups will have their own derived trajectories as detailed below. This operationalisation is inspired by the mean of the MOS 36-Item Short-Form Health Survey (SF-36)21 in Hoffhuis et al. (tab. 2),19 but because that study’s patient population appears disparate from our target population, we instead base our EQ-5D-5L index values on published results from ICU trials and cohort studies as well as 1-year follow-up data from the Conservative versus Liberal Approach to fluid therapy of Septic Shock in Intensive Care (CLASSIC) trial22,23 (see Table 2).

Length of ICU stay (ICU LOS) will be assumed to follow a log-normal distribution with parameters based on the ICU LOS values reported by Meyhoff et al.32: the median ICU LOS was 5 days, and the difference between the first quartile and the median was 2 days. We use the latter as a crude estimate of the median absolute deviance and scale by 1.4826 to approximate the properties of the standard deviation of a Gaussian variable.33

The relationship between ICU LOS and hospital LOS is based on data on 248 patients admitted in the final quarter of 2022 to the department of AG, BSKH, MBNK, MHM and AP (Figure 1). The coefficients were estimated with median regression with the following R code: quantreg::rq(log10(hospital_los) ~ log10(icu_los), tau = 0.5). This relationship aligns satisfactorily with summary statistics reported by Forster et al. (tabs. 1 and 4).24 We follow patients until at least 180 days after ICU admission, with the exact day of final follow-up given by the equation in Table 1.

We will use the following simulation parameters to transform the trajectories in each clinical scenario (Figure 2 illustrates the isolated effects of select simulation parameters on the HRQoL trajectory):

1. Number of patients per arm: 100, 500, 1000 and 2000.
2. Relative mortality reduction in the interventional arm: 0%, 2.5%, 5%, 10% and 20%. These values are aligned with and appropriate for the clinical domain of the author group (intensive care).
3. Acceleration in the interventional arm (Figure 2A): 0%, 2%, 5% and 10%.
4. The relative improvement in final HRQoL in the interventional arm (Figure 2B): 0%, 10% and 20%.
5. The dampening effect of mortality on HRQoL values at ICU discharge in patients who die at some point between ICU discharge and the end of follow-up (Figure 2C): 0%, 10%, 20% and 50%.
6. The proportion of mortality benefactors in interventional arm (Figure 2D): 0%, 5%, 10% and 15%. This proportion of patients in the active arm will survive until the end of follow-up but with worse HRQoL starting points and flatter trajectories (using the dampening parameter above); inspired by Colantuoni et al.15
7. Mortality trajectory shape, starting on the day of ICU discharge: constant until the day of death, linear trend until the day of death, exponential decay, “reflected exponential decay.”

The active-arm trajectory in a given clinical scenario will come about by applying the following simulation parameters to the control-group trajectory: mortality dampening, the relative improvement in final HRQoL and HRQoL improvement acceleration in the active. Each simulated patient’s HRQoL trajectory is stepwise linear and will come about through the process illustrated in Figure 3. Although their being stepwise linear may overestimate or underestimate the AUTCs slightly, depending on the direction and acceleration/deceleration, we found it the least bad approach for three reasons: the difference is unlikely to be substantial, it can reasonably be assumed invariant to group assignment, and smoothing would introduce untestable assumptions about the data-generating process.

2.2  | Mortality

We will assume a 6-month mortality of 40% in the control arm, aligned with what may be expected in the clinical domain of the authors (intensive care) and the kinds of clinical trials expected to leverage the results of this simulation study.32 The day of death is sampled from an empirical quantile function derived from Meyhoff et al.32 scaled to match a 6-month mortality of 40% for control-arm patients and 40% times the relative mortality reduction in interventional-arm patients.

Sampling from this distribution is a two-step process: pick a random number between 0% and 100%, then find the horizontal axis value where a horizontal line corresponding to that value intersects the empirical cumulative density function curve (shown in Figure 4). No intersection corresponds to censoring, and these patients are considered to survive beyond the follow-up period. Using this empirical quantile function, we can sample days of death without the need for a parametric distribution and, instead, base the distribution directly on real data.

2.3  | 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).
TABLE 2  Recent RCTs with in-ICU interventions and select studies, collecting EQ-5D data at various points in time after inclusion.

<table>
<thead>
<tr>
<th>Study acronym/first author and year</th>
<th>N</th>
<th>Tool</th>
<th>HRQoL assessment</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMPROVE 2022</td>
<td>70</td>
<td>EQ-5D-3L</td>
<td>Enrolment and 1 week after ventilator liberation</td>
<td>Index values seemingly not used</td>
</tr>
<tr>
<td>Campos 2022</td>
<td>139</td>
<td>EQ-5D-3L</td>
<td>ICU discharge</td>
<td>−0.1 (−0.1; 0.2)</td>
</tr>
<tr>
<td>Nickels 2020</td>
<td>72</td>
<td>EQ-5D-5L</td>
<td>10 days, 3 months and 6 months after enrolment</td>
<td>Index values seemingly not used</td>
</tr>
<tr>
<td>STOP-AKI</td>
<td>227</td>
<td>EQ-5D-5L</td>
<td>Discharge from ICU or intermediate-care unit</td>
<td>Index values seemingly not used</td>
</tr>
<tr>
<td>Ridley 2018</td>
<td>99</td>
<td>EQ-5D-3L</td>
<td>Hospital discharge</td>
<td>0.2 (−0.1; 0.4)</td>
</tr>
<tr>
<td>EPICC</td>
<td>308</td>
<td>EQ-5D-5L</td>
<td>Hospital discharge</td>
<td>0.25 (0.34)</td>
</tr>
<tr>
<td>Freeman-Sanderson 2016</td>
<td>30</td>
<td>EQ-5D</td>
<td>3 months after enrolment</td>
<td>0.32 (0.36)</td>
</tr>
<tr>
<td>PRaCTICaL 2009 1</td>
<td>286</td>
<td>EQ-5D-3L</td>
<td>Index values not used</td>
<td>0.25 (0.34)</td>
</tr>
<tr>
<td>Cuthbertson 2010 13</td>
<td>300</td>
<td>EQ-5D-3L</td>
<td>12 months after ICU admission</td>
<td>0.49 (0.19; 0.69)</td>
</tr>
<tr>
<td>Cuthbertson 2013 31</td>
<td>439</td>
<td>EQ-5D-3L</td>
<td>2.5 years after ICU admission</td>
<td>0.66 (0.28)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>5 years after ICU admission</td>
<td>0.70 (0.28)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3.5 years after ICU admission</td>
<td>0.67 (0.30)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>5 years after ICU admission</td>
<td>0.64 (0.36)</td>
</tr>
</tbody>
</table>

# Median (interquartile range).
# Mean (standard error).
# Mean (standard deviation).

FIGURE 1  Beeswarm 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.

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.
**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 \( \text{abs}(y^*_t - y_{t-15}) / \text{abs}(y_t - y_{t-15}) = 1.0 \) 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). 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, prior publication of this protocol, the large number of clinical scenarios 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. 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 unlikely 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.

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