Health-related quality of life trajectories under different clinical scenarios

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Health-related quality of life (HRQoL) is a patient-important outcome that is increasingly used as a secondary outcome in intensive care unit (ICU) trials. Compared to harder outcomes (e.g., mortality or days alive and out of hospital), which are easy to operationalise, objective and definitive, HRQoL may cover important aspects of clinical improvement in ICU patients that harder outcomes arguably miss. Although its use is growing, HRQoL has at least three challenges. First, HRQoL sampled once at end of follow-up correlates poorly with days alive without outcomes and mortality. Second, ICU survivors seem to quickly converge towards their prior HRQoL level, and cross-sectional data suggest but marginal difference in HRQoL between ICU survivors and the general population. Third, in some of the few ICU trials that do show an effect on HRQoL, the effect is somewhat paradoxical, i.e., a concurrent beneficial effect on mortality and a seeminly negative effect on HRQoL. Thus, the time is now to devise an HRQoL operationalisation to reconcile these paradoxical effects while remaining sensitive to early or accelerated improvement in patients who more quickly reach their eventual HRQoL level.

To this end, we propose the area under the HRQoL trajectory curve (AUTC) as a candidate solution and will undertake a in-silico study to gauge its performance with that of the conventional single-sampling approach currently used in ICU trials, by simulating 100,000 two-arm RCTs with equal, fixed randomisation, under each of multiple clinical scenarios.

We use previously published results to devise a smooth control-group HRQoL trajectory ICU admission and 6-month follow-up, quantifying HRQoL with EQ-5D-5L that ranges from –0.757 (the worst possible HRQoL in the Danish population) over 0 (death) to 1 (best possible HRQoL). The active-arm trajectories are arrived at by way of several simulation parameters, and each combination of these will constitute one clinical scenario; some of these and their effects are illustrated in figure 1. For all patients, we will assume that HRQoL is sampled fortnightly, to strike a good balance between the desire for high temporal resolution and practical considerations; these sampled values will be connected with straight lines to arrive at one stepwise linear HRQoL trajectory per fictive patient in the simulated trials. We will assume a 6-month mortality of 40% in the control arm. Patients who die before end of follow-up are assumed to follow one of four trajetories: constant, linear decline (figure 1D), exponential decay and reflected exponential decay. The day of death with respect to ICU admission is sampled from an empirical quantile function derived from Hofhuis et al. (10.1378/chest.07-1217), scaled to match the 6-month mortality for control-arm and active-arm patients, respectively.

For each clinical scenatio we will compute the following statistics will be calculated: (i) HRQoL in survivors and all patients at end of follow-up (for the all-patient calculation, patients who die before end of follow-up will be assigned HRQoL = 0); (ii) absolute and relative cumulative attained HRQoL; and (iii) type 1 error rate and power for scenarios without and with effect of the intervention, respectively.

We expect to have finalised the analyses by mid-May and, so, to be able to present the results of the analyses at SIM2023.

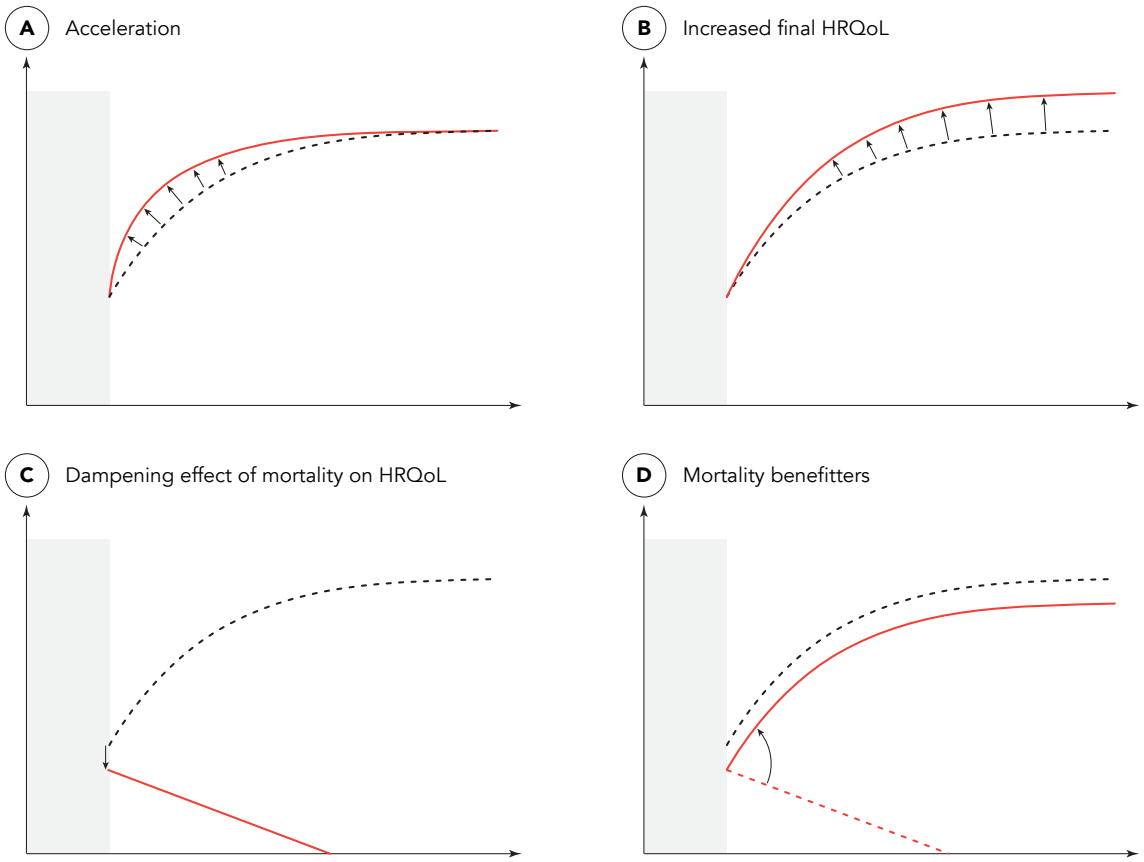

Figure 1: Individual effects of select simulation parameters on the control-group HRQoL trajectory (dashed black curves) to arrive at active-arm group HRQoL trajectory (red solid curves). Follow-up time is plotted on the horisontal axis and HRQoL on the vertical; the grey areas represent ICU stay. A: 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 until the day of death. D: Mortality benefitter (solid red curve) who has a worse HRQoL at index but follows the baseline trajectory; the dashed red line corresponds to the counterfactual scenario in which the patient were not a mortality benefitter and, thus, would have died.