S2 Appendix: Original analysis plan and modifications following comments from editors and reviewers

Manuscript: Temporal profile of intracranial pressure and cerebrovascular reactivity in severe traumatic brain injury and association with fatal outcome: an observational study.

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Main objective: To investigate the associations of the temporal profile of ICP and PRx to TBI specific mortality.

Participants: All sTBI participants with high resolution ICP and ABP recordings (n=601) will be included.

- For the outcomes analyses of TBI specific mortality, patients dying from non-neurological cases and non-functional survivors will be excluded, leaving 556 patients in the main analyses.

Exposure: Periods of raised ICPs and cerebrovascular dysregulation are captured with computerised continues monitoring.

Outcomes: Time and cause of death and contributing factors to mortality were determined by review of hospital records or by acquisition of death certificate or autopsy reports.

- Fatal outcome and functional survivors:

  o Fatal outcome: Cause-specific mortality will be categorised in two groups: those that died due to neurological causes (non-survivable TBI or brain death) and patients with a fatal outcome who died from non-neurological causes (i.e. respiratory failure, sepsis, myocardial infarction).

  o Functional Survivors: Survivors are defined as those alive at six months post-injury. Functional survivors are defined as those surviving the injury with severe disability, moderate disability, or good recovery at six months post-injury. Hence, patients in a vegetative state are excluded from further outcome analysis, as those are non-functional survivors, and are known to be atypical in their characteristics.

Statistical analyses: Mixed effects models.

- To assess the difference in brain physiological parameter and their trajectories between those with a fatal outcome and functional survivors, a linear mixed-effects model (LMEM) with a between-subjects factor (group: fatal vs. non-fatal), a within-subject factor (time: T_{24} to T_{240}) and the interaction between these two with patient ID as a random effect. Best model fit will be based on the Akaike Information Criterion.

- A generalized linear mixed model (GLMM) will be used to examine the effect of ICP and PRx on the probability [odds ratio (OR)] of having fatal outcome over time, using repeated

measures of these parameters over the first 240 hours post-injury. The model also included the same fixed and random effects and interactions term as the LMEM model.

- To test how well ICP and PRx could distinguish between fatal outcome and functional survivors during different time points (T_{24}-T_{240}), the area under the receiver operating characteristic curve (ROC AUC) will be calculated and compared.

Covariates: Selected based on literature and a priori knowledge about our data (resulting from previous work examining the association of ICP, PRx and outcome):

- Age as a continues variables

- Sex

- Best-pre-intubation GCS (3-15) as an ordinal scale

- Primary injury type (Diffuse vs. Mass lesion)

- Surgical interventions (none, craniotomy, primary DC, and secondary DC)

- DC as an adaptive intervention parameter.

Sensitivity analyses: In order to examine the potential influence of selection bias, it is important to check if the cohort is not 'expiring' because of mortality taken place at particular time-points. The peak incidence of death at any time point and the proportionality of the number of deaths to the survivors will be tested at every time point (T_{24} - T_{240}).

Subgroup analyses: In this study no subgroup analyses are specified. However, several studies have been planned to identify potential effect modifiers of the time-course of ICP and PRx.

Modification based on the comments from editors and reviewers: Following the suggestion of reviewers, we performed the mixed effect model analyses, additionally adjusting for the year of admission.