# Statistical analysis plan for early mobilisation by head-up tilt with stepping versus standard care after severe traumatic brain injury – a randomised clinical feasibility trial

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# Abstract

Background: Early mobilisation on a tilt table with stepping versus standard care may be beneficial for patients with severe brain injury, but data from randomised clinical trials are lacking. Methods: This detailed statistical analysis plan describes the analyses of data collected in a randomised clinical feasibility trial for early mobilisation by head-up tilt with stepping versus standard care after severe traumatic brain injury. Primary feasibility outcomes are the proportion of included participants who were randomised out of all screened patients; the proportion of participants allocated to the experimental intervention who received at least 60% of the planned exercise sessions; and safety outcomes such as adverse events and reactions and serious adverse events and reactions. Exploratory clinical outcomes are suspected unexpected serious adverse reactions; and functional outcomes as assessed by Coma Recovery Scale – Revised at four weeks; Early Functional Ability Scale and Functional Independence Measure at three months. The description includes the statistical analyses including use of multiple imputation and Trial Sequential Analysis. Conclusions: The present statistical analysis plan serves to minimise potential trial reporting bias and selective P hacking and to improve transparency. This trial will inform the feasibility of a potential future multicentre randomised clinical trial. Trial registration: ClinicalTrials.gov identifier: NCT02924649. Registered on 3 October 2016.


# Introduction

The early mobilisation by head-up tilt with stepping versus standard care after severe traumatic brain injury (HUT-TBI) trial is a randomised clinical trial assessing the feasibility of using a tilt-table with integrated stepping for early mobilisation to the upright position in the neuro-intensive care unit [1]. The possible negative effects of bed rest on human physiology have been investigated for decades [2–4]. With the possibility of counteracting the negative effects of prolonged bedrest, it might be beneficial for the patients to undergo early mobilisation whereby they are moved to the upright position using a tilt table. The simultaneous stepping is intended to counteract orthostatic hypotension in the standing position.

Early rehabilitation of patients with severe traumatic brain injury has hitherto been subject to few studies, in which the interventions have been incompletely described [5,6]. Nonetheless, the available studies indicate that early mobilisation may improve functional outcome after traumatic brain injury. However, a large randomised clinical trial, the AVERT trial, showed no benefit of early and intensive mobilisation on functional outcomes measured three months after stroke [7]. Moreover, a systematic review with a meta-analysis found no impact of early active mobilisation and rehabilitation on mortality at discharge from the intensive care unit (ICU) in a large variety of non-neurological ICU patients, although the intervention did increase muscle strength, walking ability, and the number of days alive and out of hospital at six months [8].

The present trial assessed if using a tilt table for early orthostatic exercise was feasible in a group of patients with severe traumatic brain injury [1]. Here we report the statistical analysis plan for the HUT-TBI

trial [1], which has been updated and finalised during the data collection period. Besides the primary outcomes related to feasibility, the analysis plan also addresses the statistical handling of exploratory clinical outcomes and outcomes from sub-studies of cerebral autoregulation and heart rate variability.

# Methods

## Ethical approval

This randomised clinical feasibility trial was approved by the Scientific-Ethics Committee of the Capital Region (H-16041794) and is registered on www.clinicaltrials.gov (ClinicalTrials.gov identifier: NCT02924649); the trial protocol has been published in Trials [1]. The project manager (CGR) is responsible for collecting and storing data and all correspondence. After a patient is found to be eligible for the trial, informed consent from the proxy and a trial guardian (a physician not involved in the trial) is obtained by CGR. The trial is carried out in accordance with the principles of the Helsinki Declaration [9].

## Primary research questions

Is an early head-up tilt protocol feasible in patients with severe traumatic brain injury, in terms of the number of participants who are successfully included, number of exercise sessions performed in the experimental group, and the number of patients with serious adverse events (SAE) and non-serious adverse events (AE) and serious adverse reactions (SAR) and non-serious adverse reactions (AR)?

## Exploratory research questions

- Does early head-up tilt with stepping reduce the number of AE, AR, SAE, and SAR compared with standard care after severe traumatic brain injury?
- Does early head-up tilt with stepping improve the level of consciousness (Coma Recovery Scale – Revised) after four weeks, early functional abilities (Early Functional Ability scale) after three months, or functional independence (Functional Independence Measure) after three months, compared with standard care after severe traumatic brain injury?
- Does head-up tilt with stepping improve the level of consciousness (Coma Recovery Scale – Revised), early functional abilities (Early Functional Ability scale), or functional independence (Functional Independence Measure) after one year compared with standard care in patients with severe traumatic brain injury?

## Main trial design

The present statistical analysis plan describes our planned analyses for the feasibility trial, investigating head up tilt with stepping versus standard care in patients with severe traumatic brain injury. As described in the published protocol the sample size (n=60)) has been chosen as a realistic number to reach for this feasibility trial [1].

The trial is a randomised clinical feasibility trial with a pragmatic stratification according to the Glasgow Coma Score at inclusion (3-6 compared to 7-10 points). The patients are randomised in a 1:1 ratio by the Copenhagen Trial Unit using a central web-based randomisation system.

Besides standard care, the experimental intervention group receives daily (Monday to Friday) mobilisation on a tilt-table to the standing position for up to 20 minutes per session. This orthostatic exercise continues for four weeks from randomisation or until the patient can stand from a chair or bed with assistance. The tilt-table has a build in stepping device that increases the venous return of blood to the heart and thereby counteracts orthostatic hypotension and increases standing time [10,11]. The control group receives standard care. Standard care is decided in collaboration between doctors, nurses, and physiotherapists and will be monitored

during the trial. Only a small amount of time is used on mobilising the patient to either the edge of the bed or to a wheelchair whilst admitted to the neurologic ICU. The focus of the physiotherapist is on respiratory function and in bed positioning to avoid bedsores.

Additional exploratory physiological outcomes are blood pressure, blood flow velocity of the middle cerebral artery (MCAv), and electrocardiography, which were all measured in the supine position and during head-up tilt at two weeks and four weeks after randomisation. Furthermore, continuous electrocardiography was recorded for up to five days from randomisation in the trial. It is our intention to analyse and publish data on the heart rate variability frequency domain and time domain indices. The statistical analysis plan for these outcomes will be made public in a separate report.

### Primary feasibility outcomes

Our primary feasibility outcomes are as follows:

The lower limit of the confidence interval of the inclusion ratio (the proportion of included participants randomised compared to all eligible patients). For example, if 44 of 60 eligible patients agree to participate, then the proportion will be 73% with a 95% confidence interval (95% CI) between 60% and 84%. The lower limit for this feasibility outcome is set at 60%; if the lower limit of the confidence interval of the gathered data of the HUT-TBI Trial is at 60% or higher, then the trial is considered to be successful in terms of inclusion. This is equivalent to a one-sided test (please see statistical section below).

The lower limit of the confidence interval of the intervention success rate defined as the proportion of participants allocated to the experimental intervention who received at least 60% of the planned exercise sessions. For example, if 21 of 30 participants (70%) randomised to the experimental intervention group receive 60% of the exercise sessions, the lower limit of the confidence interval will be 52%. Accordingly, if the lower limit of the confidence interval of the gathered data of the HUT-TBI Trial is at or above 52%, the trial will be successful in terms of exercise completeness.

Both the inclusion ratio and the intervention success rate limits are arbitrary limits decided together with the clinical staff at the department. It therefore emphasizes clinical reality on the validity of the data.

Our safety outcomes are defined as either proportion of participants with either an SAE, SAR, AE or AR not considered serious [12]. SAEs are defined as any undesirable event that result in death, is life-threatening, requires prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or requires intervention to prevent permanent impairment or damage, whether considered related to the trial intervention or not [12]. AEs are defined as any undesirable event not considered serious occurring to a participant during the trial. The proportion of participants with at least one SAE, SAR, AR, or AE during the intervention period will be compared between the two intervention groups. The proportion of SAE will be assessed through inspection (descriptive analysis) and through statistical analysis (see below).

### Exploratory clinical outcomes

For the exploratory clinical outcomes, we have chosen three outcomes: The Coma Recovery Scale - Revised (CRS-R) [13], the Early Functional Ability scale (EFA) [14,15], and the Functional Independence Measure (FIM) [16,17], all of which are scored at baseline and after four-weeks, three-months and one-year. The CRS-R reflects changes in consciousness and will be analysed at the four-week time point (end of intervention period) comparing the two intervention groups and was scored by assessors blinded to the intervention allocation. The EFA evaluates early functional changes and the FIM evaluates the ability to independently perform functions and activities of daily living. Both will be evaluated at the three-month time point. Secondly, the data for all three exploratory clinical outcomes will be presented as longitudinal data in a figure (error bar plot) showing the mean and the 95% CI for each group. At the one-year follow up, the same three outcome scales are used and supplemented by the Glasgow Outcome Scale – Extended (GOSE); the latter is used routinely at the department for the one-year follow-up.

### Exploratory physiological outcomes

For exploratory physiological outcomes we have measured the haemodynamic response to a head-up tilt at baseline, after two weeks, and after four weeks in both groups. From these data we will calculate the cerebral autoregulation index (Mxa) measured by transcranial Doppler ultrasound of the middle cerebral artery at each time point. In short, mean arterial blood pressure and mean MCAv are correlated using a Pearson correlation coefficient. Correlations are calculated during 300 seconds in the supine position (rest) and 300 seconds during head up tilt with 70 degrees head elevation. The Mxa will then principally be considered dichotomously in order to reflect intact cerebral autoregulation of blood flow, with a correlation equal to or below 0.3 or impaired if it is above 0.3 [18]. Data at four weeks will be compared between groups. Secondarily, we will analyse the Mxa as a continuous variable and we will utilise other methods such as the Gosling Pulsatile index, or the cerebrovascular resistance index.

### Statistical analyses

Statistical analysis will be handled using STATA (StataCorp, College Station, Texas, USA).

All baseline characteristics will be presented for each intervention group. Continuous variables will be summarised using means and standard deviations or medians and interquartile range depending on distribution of data. Discrete variables will be presented as frequencies, proportions, and percentages.

Timing of outcome assessments can be found in the published protocol in figure 1 [1].

Regarding the feasibility outcome, we will not adjust for multiplicity since all three outcomes should be achieved for the trial to be considered feasible. That is, the inclusion ratio and exercise success rate should be above the decided limits and the adverse events should not be significantly different in favour of the standard care group. We have decided to use a one-sided test for the feasibility outcomes corresponding to the description above. In these analyses, a significance level of 2.5% will be used.

All our analyses will primarily be intention-to-treat, i.e. all randomised participants will be included in the primary analyses and analysed as randomised. We will secondly perform per protocol analyses including the participants allocated to the intervention who received at least 60% of the planned exercise sessions compared to the patients in the standard care group.

If we do not reach the desired number of participants in the trial, we will consider to analyse our data using Trial Sequential Analysis [19,20]. In this case, we will use the prespecified standard deviations and minimal relevant differences described in supplementary table 1 for continues outcome and the proportion in the control group for dichotomised outcomes. The calculations will be based on an alpha of 5% and a beta of 10%. Trial Sequential Analysis reduces the risk of type I and type II errors due to small sample size and multiple outcome testing [20].

Analysis will start after the last three-month follow-up has been collected and after submission of this statistical analysis plan (end of March 2019). The analysis of the one-year follow-up data will start after data from the last patient has been collected in late December 2019.

### Feasibility outcomes

The first two primary feasibility outcomes will be derived from the trial with the above-mentioned lower limits of the proportions. For the intervention to be feasible, both feasibility outcomes should be achieved, and the early orthostatic intervention group should not have an overrepresentation of SAE, AE, SAR, AR or suspected unexpected serious adverse reactions (SUSAR).

All analysis described below using general linear regression, logistic regression, or mixed-model linear regression will be adjusted for the protocol specified stratification variable (high or low GCS).

We will use inspection of data (descriptive analysis) to evaluate adverse events due to the low power. Secondly, we will use logistic regression to compare the proportions of participants with one or more SAEs, SARs, ARs, and AEs between the two groups [1]. Accordingly, we will use an alpha of 5%. Each patient with at least one SUSAR during the intervention period will be analysed as exploratory feasibility outcome also using logistic regression analysis. Where appropriate, we will present data with a 95% CI.

## Exploratory clinical outcomes

All exploratory clinical outcomes and physiological outcomes are on a continuous interval scale.

The exploratory clinical outcomes will primarily be compared between allocation groups at specified time points. The CRS-R will be analysed at the four-week time point and EFA and FIM will be analysed at the three-month time point using general linear regression analysis. As a sensitivity analysis, longitudinal data will be analysed using mixed model linear regression with each participant as a random effect and the time points as the fixed effect for analysis of longitudinal data over multiple time points.

Each outcome, with the corresponding minimal relevant difference, standard deviation and power level can be found in Supplementary table 1. The one-year follow up data for CRS-R, EFA, and FIM will be analysed in the same way. Furthermore, for the one-year analysis the Glasgow outcome scale extended will be compared between groups using general linear regression and adjusting for stratification-specific variables.

In case the regression models described above (linear regression and mixed model) cannot be fitted due to breach of their underlying assumptions (e.g. skewed distribution of data/residuals), non-parametric methods (e.g. Van Elteren test) taking the stratified randomisation into account will be employed. Analysis will in all cases be conducted at the prespecified time points as stipulated above. As described in our protocol, we have still reported that all results will be interpreted as hypothesis generating.

## Exploratory physiological outcomes

The exploratory physiological outcomes measuring cerebral autoregulation will be compared at the 4-week time point (or end of intervention). To do this, we will use logistic regression with the Mxa as a binary outcome (above 0.3), as the dependent variable and with further adjustment for age and sex. The Mxa will also be tested as a continuous variable (ranging from -1 to 1) using mixed-model linear regression and Fischer's Z transformation with each participant as a random effect for analysis of longitudinal data over multiple time points. The latter is used as a sensitivity analysis. The same approach will be used for the Gosling Pulsatile index and the cerebrovascular resistance index.

## Missing data

Trials conducted in the ICU are at high risk of missing data alone on the account of the patient´s condition [21]. If data are missing, we will consider using multiple imputation according to the recommendations by Jakobsen and colleagues [22]. These recommendations states that up to 40% of missing data can be imputed, but the method of choice depends on the outcomes, whether the dependent variable has missing data only at baseline, etc. [22]. If multiple imputation is used the following variables will be incorporated in the analysis: baseline value of the dependent variable, stratification variable (GCS), end of post traumatic amnesia, and days to first mobilisation. For all continuous clinical outcomes, we will analyse survivors, and in a sensitivity analysis impute the lowest possible value for participants who died or dropped out as well as the best possible value. We will present the results of both analyses.

## Trial status and profile

The inclusion period ended in December 2018 with only 38 patients included during a two-year period. End of the three-month follow-up period will be in March 2019 and the one-year follow up will be in December 2019. Flow of patients will be presented in a CONSORT diagram as reported in the protocol [1]. We will report the number of screened patients, the number of included patients, and the main reason for exclusion of eligible patients. Furthermore, we will present the number of patients who died within the four-week intervention period, within the first three months from randomisation, and within the first year.

## Publication strategy

We plan to publish the following papers:

- The primary feasibility outcomes and the analyses of the exploratory clinical outcomes will be published separately to establish feasibility of the intervention and the sample size of a larger multicentre study (publication I).
- Analysis of the exploratory outcomes with the focus of investigating a specific physiological effect on cerebral autoregulation after a series of orthostatic exercises during head up tilt (publication II).

## Presentation of results in tables and figures

Publication I: The CONSORT flow chart diagram will be presented as Figure 1 (not shown here). To assess the balance of our randomisation, description of baseline characteristics will be presented in a table (Table 1). Variables will be summarized as either frequencies and percentages or as continues or ordinal variables as mean with standard deviations (SD) or median and interquartile range (IQR) (see Appendix 1).

The primary feasibility outcome will be presented in Table 2 and Table 3. The first table will consist of the proportion of patients included in the trial as well as the number of patients who successfully received more than 60% of the intended interventions. Table 3 will present and describe the AE seen during the intervention period as well as the logistic regression analysis.

The exploratory clinical outcome will be presented in a figure showing each outcome over the four time points, with the absolute numbers of each outcome at each time point in a Supplementary table 2. Furthermore, the longitudinal analysis will be presented in a figure showing each time point with confidence intervals (not illustrated).

Publication II: The second publication will present Table 1 as a demographic table. The results from the haemodynamic measurements (heart rate, mean arterial pressure and MCAv) will be presented in a figure with included table (Figure 1). The figure will consist of three graphs (A, B and C) with data summarized beneath, showing Δ-values between supine position and during head up tilt at baseline, after 2 weeks and after 4 weeks. As supplementary material we will present a spaghetti-plot of each of the above variables in supine and in standing (Supplementary figure 3, not shown here). Table 4 shows the Mxa values in

supine and in standing for both groups at the end of the intervention period. Alongside this, a Figure 3 (not shown here) will illustrate the time line for Mxa, with Mxa on the y-axis and time on the x-axis, showing a mean with confidence intervals for each time point (baseline, 2 weeks, 4 weeks). Figure 2A will illustrate Mxa in the supine and Figure 2B in standing. Lastly, a Table 5 will show the frequency of intact cerebral autoregulation in the two groups with *P*-values indicating group differences.

# Discussion

This statistical analysis plan for the feasibility trial of conducting early orthostatic exercise in patients with severe traumatic brain injury is published to minimise outcome reporting bias and data-driven results. From the total data gathered in the trial, the primary outcomes are feasibility outcomes, but we have also described assessments of our exploratory outcomes.

Our statistical analysis plan is based on considerations to secure unbiased data handling and analyses without getting inspired by the collected data, i.e. *P*-hacking [19].

The use of Trial Sequential analysis for the exploratory clinical outcomes will help establish sample size estimation for a larger trial. One objective of the present trial would direct which outcome to choose. Assessing the functional outcome in patients with severe traumatic brain injury over the course of illness is challenging, since they may present with a reduced level of consciousness in the early stage but may eventually return to work. Hence, the scale must encompass many outcomes. The alternative would be to use a scale such as the Glasgow Outcome Scale Extended. This scale is cruder and its validaty while the patient is admitted to a hospital department may be limited. For future trials our trial results may inspire the initial sample size calculation, which can then be adjusted as data from more trials are added.

Our statistical analysis plan has some limitations. Due to shortage of time we decided to divide the physiological outcomes from the feasibility and clinical explorative outcomes. It does however have the advantage to clearly separate these outcomes, as the first are more important for the decision of preparing and conducting a definitive randomised clinical trial, whereas the latter are more explorative in nature. Furthermore, multiple imputation for missing data assumes that these are missing at random; however, this assumption may be incorrect. For example, data completeness may differ between patients in the intervention and the standard care group.

# Conclusions

The HUT-TBI trial investigates the feasibility of early orthostatic exercise versus usual care. With the present pre-specified statistical analysis plan, we hope to minimise analytic bias. On the larger scale, we hope that the feasibility outcomes and the exploratory outcomes may inform and enable generation of hypotheses for a larger multicentre trial investigating benefits and harms of early orthostatic exercise.

# Abbreviations

AE: adverse event; AR: adverse reaction; CG: Control group; 95% CI: 95% confidence interval; CRS-R: Coma Recovery Scale – Revised; CVRI: Cerebrovascular Resistance Index; EFA: Early Functional Ability; EOE: Early orthostatic exercise; FIM: Functional Independence Measure; GCS: Glasgow coma scale; GPI: Gosling's Pulsatile Index; HR: heart rate; ICU: Intensive care unit; MAP: Mean arterial pressure; MCAv: Middle cerebral artery blood flow velocity; Mxa: cerebral autoregulation index; SAE: serious adverse event; SAR: serious adverse reaction; SD: standard deviation; SUSAR: suspected unexpected adverse reaction;

# Declarations


### Acknowledgements

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### Availability of data and materials

The datasets analysed during the current study are not publicly available due to the small sample size, but are available from the corresponding author on request.

### Authors' contributions

All authors were involved in the conception of the statistical analysis plan. CGR drafted the statistical analysis plan. CGR, JCJ, CO, JM and KM provided input for drafting and finalising the statistical analysis plan. JCJ acted as senior statistician and CO as co-statistician. JCJ and CO did the analysis independently. KM is the chief investigator of the trial. All authors read and approved the manuscript for publication.

### Consent for publication

Not applicable.

### Competing interests

The authors declare that they have no known competing interests.

Data management plan and standard operating procedure

The data management plan and standard operating procedure are kept at the Copenhagen Trial Unit.

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# Tables

### Table 1. Baseline characteristics of included patients

| | Early orthostatic exercise (n=) | Control intervention (n=) |
|---|---|---|
| Age (years) | | |
| Male – n (%) | | |
| GCS at inclusion – median (IQR)<br>• Low GCS (3-6) – n (%)<br>• High GCS (7-10) – n (%) | | |
| Brain injury – n (%)<br>• aSDH<br>• EDH<br>• Cont.<br>• Etc. | | |
| Mechanism of injury – n (%)<br>• Fall<br>• Traffic (car)<br>• Traffic (bike)<br>• Etc. | | |
| Secondary injury – n (%)<br>• Type of injury<br>• Etc. | | |
| Neurosurgical procedures performed – n (%)<br>• Type of procedure<br>• Etc. | | |
| GCS at admission – median (IQR) | | |
| Days from injury to randomisation – mean ±SD | | |
| Sedated at time of intervention – n (%) | | |
| RASS at inclusion – median (IQR) | | |
| IQR: Interquartile range; n: number; aSDH: Acute subdural haematoma; EDH: Epidural haematoma; Cont.: Contusion; SD: Standard deviation; GCS: Glasgow coma score; RASS: Richmond agitation sedation scale. | | |

**Table 2. Characteristics of feasibility outcome**

| | n/N (%) with 95% confidence interval |
|---|---|
| Included patients per eligible patient | |
| Proportion of patients with more than 60% completed exercises | |

**Table 3. Adverse events and reactions**

| Patients experiencing at least one: | Early orthostatic exercise (n=) | Control intervention (n=) |
|---|---|---|
| AE - n (%) | | |
| SAE- n (%) | | |
| AR- n (%) | | |
| SAR- n (%) | | |
| SUSAR- n (%) | | |
| | Adjusted Odds ratio (95% CI)* | |
| Treatment (Control intervention reference) | | |
| n: Number; AE: Adverse event; SAE: Serious adverse event; AR: Adverse reaction; SAR: Serious adverse reaction; SUSAR: Suspected unexpected serious adverse reaction; 95% CI: 95% confidence interval. Logistic regression analysis comparing the odds ratio of getting an adverse event, serious adverse event or reaction between the intervention groups when adjusting for stratification variable. | | |

**Table 4. Exploratory physiological outcome on autoregulation of cerebral blood flow after 4 weeks inclusion.**

| | Control intervention (n=) | Early orthostatic exercise (n=) | Adjusted analysis† | | Unadjusted analysis | |
|---|---|---|---|---|---|---|
| | | | Regression coefficient (95% CI) | *P* | Regression coefficient (95% CI) | *P* |
| Mxa (supine) *Mean (±SD)* | | | | | | |
| Mxa (70 degrees) *Mean (±SD)* | | | | | | |
| GPI *Mean (±SD)* | | | | | | |
| RI *Mean (±SD)* | | | | | | |
| Mxa: mean flow index of cerebral autoregulation; GPI: Gosling's Pulsatile Index; CVRI: Cerebrovascular Resistance Index; 95% CI: 95% Confidence interval; † Adjusted for stratification variable (GCS) | | | | | | |

**Table 5. Intact cerebral autoregulation at end of intervention.**

| | Early orthostatic exercise (n=) | Control intervention (n=) | Adjusted analysis† | | Unadjusted analysis | |
|---|---|---|---|---|---|---|
| | | | Regression coefficient (95% CI) | *P* | Regression coefficient (95% CI) | *P* |
| Intact cerebral autoregulation (Mxa supine) | | | | | | |
| Intact cerebral autoregulation (Mxa tilt) | | | | | | |
| CI 95%: 95% confidence interval; Mxa: cerebral autoregulation index; † Adjusted for stratification variable (GCS) | | | | | | |

# Additional File Legends

**Supplementary table 1.**

CRS-R: Coma Recovery Scale – Revised; EFA: Early Functional Ability scale; FIM: Functional independence measure.

* The standard deviation of the CRS-R was estimated from the change value of two studies and used to estimate the minimal relevant difference (SD/2) [23,24]

** The standard deviation of the EFA score was estimated from two observational studies investigating patients with brain injury approximately 1.5 months after injury and used to estimate the minimal relevant difference (SD/2) [25,26]

*** The FIM standard deviation and minimal relevant difference has been investigated in two studies on patients with brain injury [16,17]

**Supplementary table 2. Exploratory clinical outcome for baseline, end of intervention, three-months and one-year.**

CRS-R: Coma Recovery Scale – Revised; EFA: Early Functional Ability; FIM: Functional Independence Measure.

**Supplementary figure 1**

Spaghetti plot showing 6 graphs with each patient represented by a line for baseline, 2 weeks and 4 weeks measures. Graph 1 and 2 shows heart rate for control group and experimental group. Graph 3 and 4 shows mean arterial pressure for control group and experimental group. Graph 5 and 6 shows mean middle cerebral artery blood flow for control group and experimental group (not illustrated).

# Figures

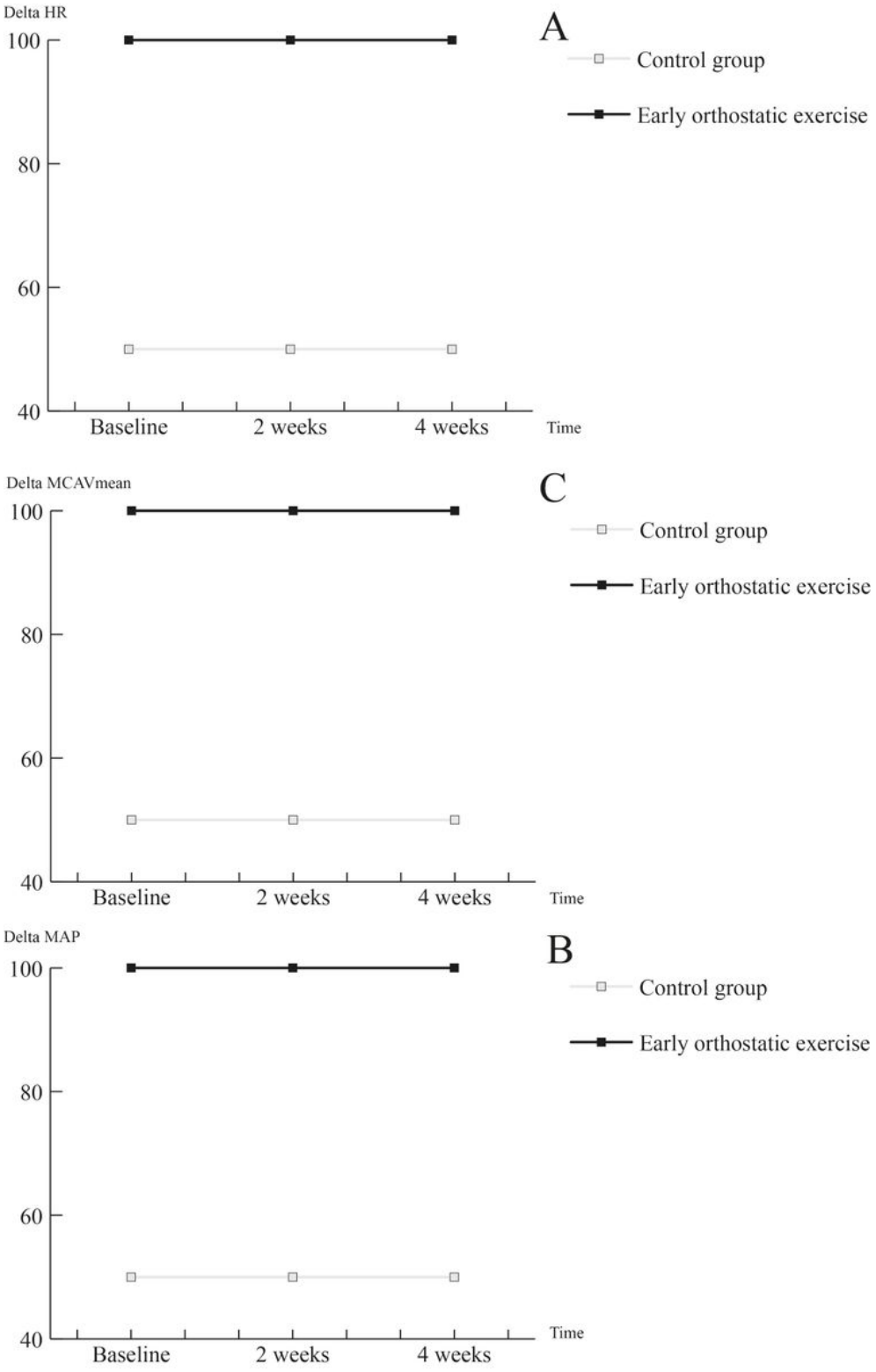


**Figure 1**

A, B, and C including table. Haemodynamic change from supine position to head up tilt. HR: Heart rate; CG: Control group; EOE: Early orthostatic exercise; MAP: Mean arterial pressure; MCAVmean: Mean middle cerebral artery blood flow velocity.

# Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- 20190514Checklist.docx
- 20191204Supplementarytable1.docx
- 20191209Supplementarytable2.docx