PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Feasibility of individualised severe traumatic brain injury management using an automated assessment of optimal cerebral perfusion pressure: the COGiTATE phase II study protocol.
AUTHORS	Beqiri, Erta; Smielewski, Peter; Robba, Chiara; Czosnyka, Marek; Cabeleira, Manuel; Tas, Jeanette; Donnelly, Joseph; Outtrim, Joanne; Hutchinson, Peter; Menon, David; Meyfroidt, Geert; Depreitere, Bart; Aries, Marcel; Ercole, Ari

VERSION 1 – REVIEW

REVIEWER	Craig Anderson The George Institute for Global Health, Sydney, Australia
REVIEW RETURNED	06-May-2019

GENERAL COMMENTS	This manuscript reports the protocol of an ongoing phase II clinical trial to assess the feasibility and safety of an automated individualised titrated according to cerebrovascular perfusion and fixed pressure according to guidelines for intracranial pressure (ICP) monitoring of adults with severe traumatic brain injury (TBI). The rational for this study is well outlined covering the lack of efficacy for TBI and aging populations where tailored ICP monitoring may provide benefits, and where studies to data have been limited by small and retrospective designs. This study is particularly well designed, outlining the interventions, central randomisation, power calculation, analyses and outcome assessments. In particular, the different approaches to surrogate consent and planning for a phase III trial should this study prove positive. I have no substantive criticisms of the manuscript.

REVIEWER	Ken Butcher University of New South Wales, Australia
REVIEW RETURNED	14-May-2019

GENERAL COMMENTS	Assessing the feasibility of individualised severe traumatic brain injury management using an automated assessment of optimal cerebral perfusion pressure: the COGiTATE phase II studyprotocol. This protocol manuscript appears to have been adapted from grant application. The Introduction and justification of the approach are somewhat lengthy because of this. I would suggest a more concise introduction to the clinical problem. The trial has been registered with clinicaltrials.gov.

	Design: Prospective, randomized, controlled, non-blinded trial. It appears the primary endpoint is not evaluated in a blinded manner. The heading 'Objectives' is followed by the description of three 'aims' (one primary and two secondary). There are no explicit hypotheses or hypothesis statements. The aims are not also explicitly or succinctly stated either. The primary endpoint is not explicitly listed either, but rather described in the long description of the objectives/aims. I suggest listing specific aims/objectives (pick one term), without justifying them. List the primary and secondary endpoints. I note that secondary outcomes are listed in box 1, but the primary endpoint is not. If there is a hypothesis, state it after the aims and endpoints. The primary endpoint appears to be the amount of time CPP is within the target range. This is incorrectly described in the first paragraph of the Objectives as: 'This study was powered to target an increase of the monitoring time from 30% to 36% in the intervention group.' The monitoring time is not the primary endpoint, as implied in this sentence. Statistics/Sample Size: In the sample size section, the primary outcome measure is described as 'feasibility', which is not actually an endpoint. A primary endpoint is described in the next paragraph, suggesting outcomes and endpoints have different meanings to the authors. This imprecision with language and terminology is confusing (as it was with Objectives/Aims). In the statistical section, restrict discussion to endpoints. The true primary endpoint is: 'the percentage of time CPP is within a range of 5 mmHg above or below the calculated CPPopt.' There are no published data to support the amount of time CPP is within 5 mmHg of the target CPP, but the authors suggest 30% at pilot data (note the typo in this section 'are have'). The authors hypothesize that their computer algorithm will increase this be 20% (relative) or 6% absolute (36%). The reasons for this are not provided. 1. Why do we expect the algorithm will only increase the amount of time at target by 6%? This seems somewhat low. 2. Is 6% likely to be clinically meaningful? No data are provided to justify this. Please clarify if the endpoint analysis will be blinded, i.e. PROBE design. I think it could be, if evaluators were unaware of which group the patients were randomized to. A statistical analysis plan is not provided. The hypothesis (although not stated) appears to that the CPPopt algorithm (adding the word 'algorithm' would make description of the treatment groups and endpoints clearer) will increase the time at CPPopt by 5%. The statistical test used to assess this should be described. Is this a simple unpaired t-test? Is it expected that the times will be normally distributed? Minor: The number and location of trial centres is not provided. Randomization occurs <24 hours after admission to ICU, rather than 'begins'.

VERSION 1 – AUTHOR RESPONSE

Reviewer comments

Reviewer: 1
This manuscript reports the protocol of an ongoing phase II clinical trial to assess the feasibility and safety of an automated individualised titrated according to cerebrovascular perfusion and fixed pressure according to guidelines for intracranial pressure (ICP) monitoring of adults with severe traumatic brain injury (TBI).
The rational for this study is well outlined covering the lack of efficacy for TBI and aging populations where tailored ICP monitoring may provide benefits, and where studies to data have been limited by small and retrospective designs. This study is particularly well designed, outlining the interventions, central randomisation, power calculation, analyses and outcome assessments. In particular, the different approaches to surrogate consent and planning for a phase III trial should this study prove positive.
I have no substantive criticisms of the manuscript.

Comments of the authors:
We are grateful to the reviewer for their kind words of appreciation of the rational and the design of this study along with the clinical importance of this phase II trial.

Reviewer: 2

1) This protocol manuscript appears to have been adapted from grant application. The Introduction and justification of the approach are somewhat lengthy because of this. I would suggest a more concise introduction to the clinical problem.
Comments of the authors:
We thank the reviewer for this comment. There are indeed similarities with the protocol uploaded on clinicaltrails.gov and the ESICM grant application. We agree with the reviewer about the lengthy reading of the introduction. In the revised manuscript we have now shortened the introduction to make it more concise and pointing to the clinical problem and the related aspects (Introduction, page 2, lines 7-47 and page 3, lines 1-6).

2) The trial has been registered with clinicaltrials.gov.
The reviewer is correct that the trial is registered at clinicaltrials.gov.

3) Design:
a. Prospective, randomized, controlled, non-blinded trial. It appears the primary endpoint is not evaluated in a blinded manner.
Comments of the authors:
This study is a prospective, multicenter, non-blinded, randomized, controlled trial in patients with severe TBI (Design, page 3, line 11-12). ‘Non-blinded’ refers to the treating clinicians, the legally authorized representative of the patient (who is involved in the informed consent procedure), and the local investigators involved in the monitoring set-up.
This cannot be blinded to the treating clinical team for the obvious reason that it is the clinicians need to determine which CPP to follow for the next 4 hours. Furthermore, as an important safeguard the clinicians are asked to evaluate the suggested CPP target in the context of the overall clinical context of the patient, and therefore must be aware of the study randomisation.
However, the primary endpoint will indeed be analysed in a blinded manner to make this as unbiased as possible. We agree with the reviewer that this was not clarified enough in the manuscript. We have now stated this clearly it in the revised manuscript (Statistical analysis, page 7, line 33).

b. The heading ‘Objectives’ is followed by the description of three ‘aims’ (one primary and two secondary). There are no explicit hypotheses or hypothesis statements. The aims are not also explicitly or succinctly stated either. The primary endpoint is not explicitly listed either, but rather described in the long description of the objectives/aims. I suggest listing specific aims/objectives (pick one term), without justifying them. List the primary and secondary endpoints. I note that secondary outcomes are listed in box 1, but the primary endpoint is not. If there is a hypothesis, state it after the aims and endpoints.

Comments of the authors:
We agree with the reviewer that the objectives, endpoints and hypothesis of the study were not as explicitly and succinctly stated in the manuscript as they might have been. We also agree that the applied terminology might have been confusing.
We modified the section ‘Objectives’ (Design, paragraph Objectives, page 3) as follows:
- Terminology: we chose ‘objective’ and we did not use ‘aims’ in the sections where an explicit listing was required (Design, paragraph Objectives, page 3, lines 22-24);
- We carefully listed the objectives and the primary endpoints in this section (Design, paragraph Objectives, page 3, lines 22-26), without justifying them. Instead, we added a section ‘Outcome measures’ (Design, paragraph outcome measures, page 5, lines 7-37) where we describe and justify the endpoints for completeness.
- The safety and physiology variables that will be evaluated for the secondary endpoint are mentioned in the paragraph ‘Objectives’ (Design, paragraph Objectives, line 26) and listed in detail in box 1, as was done in the original version of the manuscript.
- We stated the hypothesis of the study after the objectives and endpoints (Design, paragraph Objectives, page 3, lines 27-29,) as follows: ‘The main hypothesis of COGiTATE are: 1) in the intervention group the percentage of the monitored time with measured CPP within a range of 5 mmHg above or below CPPopt will reach 36%; 2) the difference between the two groups regarding the daily TIL score will be lower or equal to 3.
We think that these modifications improve the Objective section considerably.

c. The primary endpoint appears to be the amount of time CPP is within the target range. This is incorrectly described in the first paragraph of the Objectives as: ‘This study was powered to target an increase of the monitoring time from 30% to 36% in the intervention group.’ The monitoring time is not the primary endpoint, as implied in this sentence.
Comments of the authors:
We thank the reviewer as we noticed that the formulation of the primary endpoint was actually incorrectly stated. The primary endpoint should have read ‘the percentage of time CPP is within a range of 5 mmHg above or below the calculated CPPopt’. We have corrected this.
In addition, the percentage of time is actually restricted to the time the neuro-monitoring is available. Therefore, we have more accurately restated the primary endpoint as ‘the percentage of monitored time with measured CPP within a range of 5 mmHg above or below CPPopt’.
In the revised manuscript different sections were changed accordingly: the section Objectives (Design, paragraph objectives, page 3, lines 3-4), ‘Outcome measures’ (Design, paragraph Outcome measures, page 4, lines 1-12) and ‘Sample size’ (Sample Size, page 6, lines 6-7).

4) Statistics/Sample Size:
a. In the sample size section, the primary outcome measure is described as ‘feasibility’, which is not actually an endpoint. A primary endpoint is described in the next paragraph, suggesting outcomes and endpoints have different meanings to the authors. This imprecision with language and terminology is confusing (as it was with Objectives/Aims). In the statistical section, restrict discussion to endpoints. The true primary endpoint is: ‘the percentage of time CPP is within a range of 5 mmHg above or below the calculated CPPopt.’
Comments of the authors:

We thank the reviewer to improve the terminology in the manuscript. The study concerns a phase II or feasibility study. The primary endpoint/outcome is the percentage of monitored time with measured CPP within a range of 5 mmHg above or below CPPopt. In the Sample size section (Sample size, page 6, line 31 and 36-45) we modified the phrasing accordingly to have consistent terminology.

b. There are no published data to support the amount of time CPP is within 5 mmHg of the target CPP, but the authors suggest 30% at pilot data (note the typo in this section 'are have'). The authors hypothesize that their computer algorithm will increase this be 20% (relative) or 6% absolute (36%). The reasons for this are not provided. 1. Why do we expect the algorithm will only increase the amount of time at target by 6%? This seems somewhat low. 2. Is 6% likely to be clinically meaningful? No data are provided to justify this.
Comments of the authors:
We agree with the reviewer that this section could be better justified since we considered this very carefully when designing the study. In particular:
i. There are no published data to support the amount of time CPP is within 5 mmHg of the target CPP, but the authors suggest 30% at pilot data.
As this is the first intervention study in this area we had to fall back on retrospective [recent and therefore unpublished] data and certain assumptions. The figure of 30% was chosen from retrospective analysis of unpublished data in two centres (Groningen and Cambridge) where TBI patients were not treated according autoregulation guided CPP management. This data suggests that patients in any case spent 30% or so of their time within these limits and therefore we aim to increase this in our intervention group. The two pilot prospective studies mentioned in the Introduction (Introduction, page 2, lines 37-39, reference 14 and 15) refers to centres treating their TBI patients with their own locally developed approach to autoregulation CPP targets without increases in mortality rate.
In the revised manuscript we clarified where the percentage of 30% comes from for the power calculation. In the revised manuscript the sentence now reads 'Retrospective analysis in unpublished data showed that on average patients spent a mean (+SD) of 30% (+8%) of their monitored time with measured CPP within 5 mmHg of CPPopt.' (Sample size, page 6, lines 38-40).

ii. …note the typo in this section 'are have'

We have corrected the typo.

iii. The authors hypothesize that their computer algorithm will increase this be 20% (relative) or 6% absolute (36%).
The reviewer points towards an important issue. There is a misunderstanding in the terminology we used which we will adapt. We don't hypothesize that our computer algorithm will increase the percentage of time from 30 to 36%. The customized computer algorithm is meant to support the clinicians in the intervention arm to make decisions regarding a 4 hourly set CPP target.
We hypothesized that by requesting the clinical team, at 4 hourly reviews, to follow actively the CPPopt target (provided by the computer algorithm) we would be able to increase the percentage of monitored time with measured CPP within a range of 5 mmHg above or below CPPopt from 30 to 36% (20% relative increase).
This clarification is now reflected in the manuscript in the Outcome measures section (Design, paragraph outcome measures, page 5, lines 8-20)

iv. The reasons for this are not provided. 1. Why do we expect the algorithm will only increase the amount of time at target by 6%? This seems somewhat low. 2. Is 6% likely to be clinically meaningful? No data are provided to justify this.

We choose for this small improvement because (1) this is the first prospective study, (2) we don't know the exact adherence or compliance to the protocol as the clinical team will take the whole clinical condition into account (this account for both arms of the study) and (3) we don't know how the set targets affects the CPPopt calculation (this also accounts for both study arms). This increase is comparable to the typical differences seen between good/poor outcomes in unpublished retrospective data.
The question of whether our pragmatic choice of 6% minimum increase in the target adherence is clinically meaningful will need to be addressed in the future study as it is beyond the scope of this feasibility project.
This clarification is now reflected in the manuscript in the Outcome measures section (Design, paragraph outcome measures, page 5, lines 8-20)

c. Please clarify if the endpoint analysis will be blinded, i.e. PROBE design. I think it could be, if evaluators were unaware of which group the patients were randomized to.

Comments of the authors:
Indeed, we intend to do this: The endpoint analysis will be blinded given the evaluators will not be aware of the group the patients were randomized to. In the revised manuscript this is specified in the statistical section (Statistical analysis, page 7, line 33).

d. A statistical analysis plan is not provided. The hypothesis (although not stated) appears to that the CPPopt algorithm (adding the word 'algorithm' would make description of the treatment groups and endpoints clearer) will increase the time at CPPopt by 5%. The statistical test used to assess this should be described. Is this a simple unpaired t-test? Is it expected that the times will be normally distributed?

Comments of the authors:
We agree with the reviewer that the statistical plan was not fully provided.
- The hypothesis (although not stated) appears to that the CPPopt algorithm (adding the word 'algorithm' would make description of the treatment groups and endpoints clearer) will increase the time at CPPopt by 5%.

In the revised manuscript the hypothesis is now stated in the section 'Objectives' (Design, paragraph Objectives, page 3, lines 27-29), after the objectives and the endpoints are listed:
'The main hypothesis of COGiTATE are: 1) in the intervention group the percentage of the monitored time with measured CPP within a range of 5 mmHg above or below CPPopt will reach 36%; 2) the difference in between groups in daily TIL score will be lower or equal to 3.'

- The statistical test used to assess this should be described. Is this a simple unpaired t-test? Is it expected that the times will be normally distributed?

The statistical test used to assess the hypothesis is indeed a simple student's t-test. We expect the times to be distributed from an approximately normal distribution. If this is not the case, we will use a non-parametric test. Simulations suggest that in this eventuality our power calculation will still remain approximately appropriate with the margin of extra patients chosen. We have now stated this in the section 'Statistical analysis' (Statistical analysis, page 7, lines 36-39), as follows:
The two groups will be compared with a students' t-test (or a non-parametric equivalent in the event of a significant departure the normal distribution). Multivariable linear models will be used to control for the covariates center, age, GCS after resuscitation, pupil reactivity, presence of extracranial injury and primary craniotomy.'

5) Minor:
a. The number and location of trial centres is not provided.

Comments of the authors:
We specified the number and the location of the trial centers in the section Design (Design, page 3, lines 11-14): '…Three tertiary centres are involved at the start of the study: Maastricht University Medical Center, Maastricht (The Netherlands), Cambridge University Hospitals NHS Foundation Trust, Cambridge (UK), and University Hospitals Leuven, Leuven (Belgium)….'

b. Randomization occurs <24 hours after admission to ICU, rather than 'begins'.

Comments of the authors:
We thank the reviewer for pointing this out. We have changed the relevant sentence accordingly (Study population, page 5, line 44)
FORMATTING AMENDMENTS (if any)
Required amendments will be listed here; please include these changes in your revised version:

Comments of the authors:
We understand that no formatting amendments are required.

ADDITIONAL CHANGES
1) We modified the title of the manuscript from 'Assessing the feasibility of individualised severe traumatic brain injury management using an automated assessment of optimal cerebral perfusion pressure: the COGiTATE phase II study protocol.' to 'Feasibility of individualised severe traumatic brain injury management using an automated assessment of optimal cerebral perfusion pressure: the COGiTATE phase II study protocol.' (Title, page 1, lines 1-2).

2) We added the paragraph 'Patient and Public Involvement' in the 'Methods and Analysis' section as required by the editorial office (Patient and Public Involvement, page 8, lines 4-9).

VERSION 2 – REVIEW

REVIEWER	Craig Anderson The George Institute for Global Health Australia
REVIEW RETURNED	29-Jul-2019

GENERAL COMMENTS	The authors have addressed Reviewer comments

REVIEWER	Ken Butcher University of New South Wales Australia
REVIEW RETURNED	20-Aug-2019

GENERAL COMMENTS	Much improved and my concerns were all addressed.