PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	DONORS (Donation Network to Optimise Organ Recovery Study): Study protocol to evaluate the implementation of an evidence-based checklist for brain-dead potential organ donor management in intensive care units, a cluster randomised trial
AUTHORS	Westphal, Glauco; Robinson, Caroline; Biasi, Alexandre; Machado, Flávia; Rosa, Regis; Teixeira, Cassiano; de Andrade, Joel; Franke, Cristiano Augusto; Azevedo, Luciano Cesar; Bozza, Fernando; Guterres, Cátia; da Silva, Daiana; Sganzerla, Daniel; do Prado, Débora; Madalena, Itiana; Rohden, Adriane; da Silva, Sabrina; Giordani, Natalia Elis; Andrighetto, Luiza; Benck, Patrícia; Roman, Fernando Roberto; de Melo, Maria de Fátima; Pereira, Thattyane; Grion, Cintia; Diniz, Pedro; Oliveira, João Fernando; Mecatti, Giovana; Alves, Flávio André; Moraes, Rafael Barberena; Nobre, Vandack; Hammes, Luciano; Meade, Maureen; Nothen, Rosana; Falavigna, Maicon

VERSION 1 – REVIEW

REVIEWER	Dr Faissal A M Shaheen Saudi Arabia, Senior consultant physician and nephrologist, Solyman fakeeh hospital
REVIEW RETURNED	02-Jan-2019

GENERAL COMMENTS	No comments excellent paper

REVIEWER	Darren Malinoski Professor of Surgery, Oregon Health & Science University, Portland, Oregon, U.S.A. I currently have grant funding from the Laura and John Arnold Foundation to conduct an RCT examining mild hypothermia and machine perfusion in brain dead kidney donors. I am also an author of several of the referenced papers. None of these are commercial conflicts of interest, but they indicate my published views and perspective.
REVIEW RETURNED	14-Jan-2019

GENERAL COMMENTS	The authors should be commended for undertaking a systematic study surrounding best practices in the care provided to potential brain dead organ donors and their families. General topics that could be explored more fully, either in this publication or when the results of the study are known, are the recent U.S. National Academy of Sciences report on the conduct of deceased organ donation research as well as the general topic of catastrophic brain injury guidelines (CBIGs) and how care is provided in participating ICUs to patients who have a catastrophic/devastating

	(likely non-survivable) brain injury, but have not yet been declared according to neurologic criteria.

REVIEWER	Brett Sampson Flinders Medical Centre, Australia
REVIEW RETURNED	18-Feb-2019

GENERAL COMMENTS	I wish you well in this ambitious trial and look forward to the results.

REVIEWER	Frances Colreavy Department of Intensive Care Medicine, Mater Misercordiae Hospital, Eccles Street, Dublin 7, Ireland
REVIEW RETURNED	22-Mar-2019

GENERAL COMMENTS	1. Checklist 2; The abstract contains one additional secondary outcome compared the OBJECTIVES section. "The total number of cardiac arrests among all potential donors". 2. Checklist 5; Although I have concerns regarding the waiver of consent which is being requested on the basis of "operational and methodological difficulties and a potential negative impact on organ donation", ultimately this will need to be decided by the IRB of each participating hospital. In the event that an individual IRB did not approve the study, the reason for lack of approval at the total number of such sites, would need to be reported an a final manuscript. 3. Checklist 8; In relation to the incidence of cardiac arrest post declaration of brain death I recommend the following 2 references; Benchmarking in organ donation in Spain after brain death in Spain.Lancet 2012, 380:649-650 An exciting new era in donor organ preservation and transplantation:assess, condition and repair. Transplantation 2016, 100: 1801-1802 There are 2 issues that require mention somewhere within this study protocol, although they are not included in the checklist ; consideration of the use of thyroid replacement therapy and consideration of the use of serial echocardiography. The reasons as to their omission in the checklist might be explained. I following 2 references relate to these items. Management of the potential organ donor in the ICU:society of critical care medicine/American College of chest physicians/association of organ procurement organizations consensus statements. Kotloff RM, Blosser S, Fulds GJ et al. Critical Care Medicine 2015, 43: 1291-1325. The use of serial echocardiograms for organ porcurement in brain death. Clin Transplant 2017 31:e 13094

REVIEWER	Dr. Samara Zavalkoff Montreal Children's Hospital- McGill University Health Centre
REVIEW RETURNED	05-Apr-2019

GENERAL COMMENTS	This protocol describes a cluster randomized quality improvement trial to reduce loss of potential organ donors where the main intervention is a clinical checklist. Increasing the donor pool is an improvement societal healthcare need, so this trial is well justified. The protocol is well thought out and detailed with the intention of permitting reproducibility as is required by QI work.

	Modifications to the text would allow further clarify of the protocol for the reader. 1) The primary outcome is stated as “loss of potential donors due to cardiac arrest.” The definition of potential donor would be important to state, as jurisdictions define this differently. This term is used throughout the protocol, but was undefined. As well, “loss” should be defined. Does this mean circulatory death? Will patients who are brain dead undergo CPR to preserve the opportunity to donate in which case loss may mean ischemic injury leading to ineligibility to donate. 2) The term “potential brain-dead donor management” is used throughout the text and can be confusing. As it reads, one might understand that the patient is potentially brain-dead vs what I believe the authors mean which is that the patient is potentially a donor. Suggest revising to “brain-dead, potential donor” 3) In the abstract, under ethics, the authors say a “waiver of prospective informed consent” whereas in the body of the manuscript (line 380-382), they state “a waiver of informed consent.” Based on this inconsistency, I am unclear if the study authors are seeking a waiver of consent for study participation or a deferred consent model. 4) One of the secondary outcomes is number of actual organ donors. Since the sites are randomized and not the patients, there may be non-equal number of patients in both the control and the checklist groups. Therefore, the absolute number of actual organ donors is not directly comparable. Please clarify if this number of organ donors will be indexed to potential donors (which requires definition, see 1) 5) Hospitals with more than ten annual notifications were included, but to meet the required sample size, 19 potential organ donors are required per site (line 238-239). This is almost double. How do the authors reconcile this to be sure power will be achieved? 6) As a quality improvement project, the authors should list their process measures. As the authors mention in their discussion, if there is no effect demonstrated in the intervention group, this may be because of a lack of efficacy of the checklist or due to suboptimal implementation of the intervention. Thus, the authors should report their compliance with the checklist as a process measure. These might be the tertiary objectives, but they should be labelled as process or fidelity measures. As well, are the authors tracking any balancing measures? 7) More details are required to describe checklist application. Will the IHTC or ICU professional apply the checklists in rounds? How will the prompting be done? (eg in person, which member of the medical team will be prompted, will the checklist be paper or electronic?) 8) Monthly reports on performance- who will receive these reports? How will the ICU teams be made aware of their results? 9) How was the checklist developed? Were there (plan-do-study-act) cycles done to develop and improve the checklist intervention? Was the checklist intervention piloted? Is this the

	same checklist that was prospectively studies (reference 12)? There would be justification that this checklist was ready for assessment in a RCT. 10) Questions related to the checklist (supplementary Figure 2) a. “Vasopressin and hydrocortisone were associated”- please clarify. The term associated is unclear here. b. Na <155 – is there a lower limit? c. Mg – is there an upper limit? 11) Table 1 includes strategies to maximize adherence to co-intervention (e.g. family meetings); however, the concept of the family meetings is not introduced in the text until after the table, so this is confusing. Please re-organize. Minor edits 1) Line 115- “aiming” should be replaced by “aimed at” 2) Line 181-183- please state if these exams are spaced in time or concurrent and if spaced, how much time much elapse between them 3) Line 51: a comma is missing between “evidence-based” and “goal-directed” 4) Line 261: “for cardiac arrest” should be replaced by “from cardiac arrest” 5) Line 452- did the authors mean an implementation strategy that may NOT be considered feasible?

VERSION 1 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

Reviewer: 1
Reviewer Name: Dr Faissal A M Shaheen
Institution and Country: Saudi Arabia, Senior consultant physician and nephrologist, Solyman fakeeh hospital
No comments excellent paper

Reviewer: 2
Reviewer Name: Darren Malinoski
Institution and Country: Professor of Surgery, Oregon Health & Science University, Portland, Oregon, U.S.A.

The authors should be commended for undertaking a systematic study surrounding best practices in the care provided to potential brain dead organ donors and their families. General topics that could be explored more fully, either in this publication or when the results of the study are known, are the recent U.S. National Academy of Sciences report on the conduct of deceased organ donation research as well as the general topic of catastrophic brain injury guidelines (CBIGs) and How care is provided in participating ICUs to patients who have a catastrophic/devastating (likely non-survivable) brain injury, but have not yet been declared according to neurologic criteria.
Authors response: We appreciated the commend and thank for the suggestions. Regarding the document "Opportunities for Organ Donor Intervention Research" we will explore it to support our discussions at the moment of the results report. However, given the relevance of the document, we resorted to it in order to support both the introduction (lines 112 and 138 – marked copy) and the

discussion (line 445 – marked copy) sessions of this manuscript. We also updated the reference numbers after including this suggestion.
Although relevant, unfortunately, it was not possible to obtain sufficiently reliable information about the standard of care in the participating ICUs for patients with CBI before progressing to brain death. Hence, after your comments, we have included it as one of the limitations of our study, (lines 492 to 494 – marked copy) as below: “Finally, a possible variability in the care of patients with catastrophic brain injury (CBI), before its evolution to brain death, may occur among the study centres. On the other hand, the results may contribute as an indirect evidence for the management of patients who have a CBI.”

Reviewer: 3
Reviewer Name: Brett Sampson
I wish you well in this ambitious trial and look forward to the results.
Institution and Country: Flinders Medical Centre, Australia

Reviewer: 4
Reviewer Name: Frances Colreavy
Institution and Country: Department of Intensive Care Medicine, Mater Misercordiae Hospital, Eccles Street, Dublin 7, Ireland

1. Checklist 2; The abstract contains one additional secondary outcome compared the OBJECTIVES section. "The total number of cardiac arrests among all potential donors".
Authors response: Thank you for your careful review. This outcome is not really part of the study's outcomes and has been removed from the abstract.

2. Checklist 5; Although I have concerns regarding the waiver of consent which is being requested on the basis of "operational and methodological difficulties and a potential negative impact on organ donation", ultimately this will need to be decided by the IRB of each participating hospital. In the event that an individual IRB did not approve the study, the reason for lack of approval at the total number of such sites, would need to be reported in a final manuscript.
Authors response: The IRB of each site decides independently for the approval of the study. From the sites initially eligible, two IRBs did not approve the study given the waiver of informed consent. The processes of site selections, the reasons for not inclusions and the reasons for lack of IRB approval, will be reported in the final paper. We also clarify the independent IRB decision in the text of the “Ethics and dissemination” session of the manuscript (line 403 to 404 – marked copy), as follow: “(…) we requested a waiver of informed consent for the IRB of each participating site.”

3. Checklist 8; In relation to the incidence of cardiac arrest post declaration of brain death I recommend the following 2 references;
- Benchmarking in organ donation in Spain after brain death in Spain.Lancet 2012, 380:649-650
- An exciting new era in donor organ preservation and transplantation: assess, condition and repair. Transplantation 2016, 100: 1801-1802
Authors response: Thank you for your kind suggestion. Regarding the first reference, after reading the suggested letter (Lancet 2012, 380:649-650) carefully, we note that although they are talking about the high rates of donation of organs in Spain, the subject "cardiac arrest after the diagnosis of brain death" is not directly addressed. So, we opted to keep the reference already used about this topic (current reference 3), considering that it includes aspects highlighted by the suggested reference.
After reading the second suggested paper with attention, we unfortunately noticed that this is a paper about organ preservation techniques derived from extended criteria donors and donation after circulatory death (DCD) donors, describing “efforts to make untransplantable organs transplantable”. Considering that the care with the different organs after the organ withdrawal is not the scope of our study, we do not use it as reference of the present study.

There are 2 issues that require mention somewhere within this study protocol, although they are not included in the checklist;
Issue 1. Thyroid replacement. The reasons to its omission in the checklist might be explained.
Authors response: This is a very interesting topic. Alterations in the thyroid axis are common after brain death. Based on this, and in some observational studies, consensus guidelines (Critical Care Medicine 2015, 43: 1291-1325) have recommended to consider thyroid hormone replacement in hemodynamically unstable donors. However, the apparent benefit of systematic thyroid hormone replacement was not confirmed by RCTs, which could not find any impact on donor hemodynamics or number of procured organs. Additionally, two following meta-analyses (listed below) did not confirm the cardiovascular benefits associated with supplementation of these hormones: 1) Macdonald PS, Aneman A, Bhonagiri D et al. A systematic review and meta-analysis of clinical trials of thyroid hormone administration to brain dead potential organ donors. Crit Care Med 2012;40:1635-44; and, 2) Rech TH, Moraes RB, Crispin D, et al. Management of the brain-dead organ donor: a systematic review and meta-analysis. Transplantation 2013;95:966. Considering the aforementioned, we decided not to include the thyroid replacement in the checklist. We included this clarification in the "Interventions" session (lines 210 to 217 – marked copy) of the manuscript as follow (text inclusions are underlined): "The checklist was designed to address CPG goals and recommendations that involve temperature control, mechanical ventilation, haemodynamic control, metabolic control, use of antibiotics and blood products, as required, and hormone administration (hydrocortisone, vasopressin and/or desmopressin, insulin). Thyroid hormone was not recommended due to lack of evidence to confirm the benefit of its use. [25,26]"

Issue 2. Serial echocardiography. The reasons for its omission in the checklist might be explained. The use of serial echocardiograms for organ procurement in brain death. Clin Transplant 2017 31:e 13094
Authors response: Regarding serial echocardiography: It is known that left ventricular systolic dysfunction (LVSD) accounts for the non-acceptance of hearts for transplantation. It is also known that some hours may be necessary to the cardiac function recovery after the autonomic storm. Some authors have reported that many dysfunctional hearts have an improvement in their function and can be used for transplants without an increase in recipient mortality. Despite serial echocardiographic monitoring is a promising tool to assess potential recovery in neurogenic stunned myocardium and guide continued support in potential donors, there are only a few observational studies about this subject: J Am Coll Cardiol. 2017 Sep 5;70(10):1248-1258; Clin Transplant. 2017 Nov;31(11); Clin Transplant. 2017 May;31(5). Taking together the fact that the systematic echocardiographic monitoring would not be feasible in all the participating hospitals, we did not consider the use of this mode of monitoring.

Reviewer: 5
Reviewer Name: Dr. Samara Zavalkoff
Institution and Country: Montreal Children's Hospital- McGill University Health Centre

This protocol describes a cluster randomized quality improvement trial to reduce loss of potential organ donors where the main intervention is a clinical checklist. Increasing the donor pool is an improvement societal healthcare need, so this trial is well justified.
The protocol is well thought out and detailed with the intention of permitting reproducibility as is required by QI work.
Modifications to the text would allow further clarify of the protocol for the reader.

1) The primary outcome is stated as "loss of potential donors due to cardiac arrest." The definition of potential donor would be important to state, as jurisdictions define this differently. This term is used throughout the protocol, but was undefined. As well, "loss" should be defined. Does this mean

circulatory death? Will patients who are brain dead undergo CPR to preserve the opportunity to donate in which case loss may mean ischemic injury leading to ineligibility to donate.
Authors response: Thank you very much for your valuable contribution. Regarding the term “potential donor”: Indeed, the definition of potential donors throughout the protocol are dubious. Hence, we replaced the term “potential donor” by “brain-dead potential organ donor”. The term “loss of brain-dead, potential organ donor by cardiac arrest” means that the brain-dead potential donors was affected by an irreversible or unreversed cardiac arrest. We tried to make it clearer throughout the text, and we included this clarification in the “Outcomes” session (line 281 – marked copy).

2) The term “potential brain-dead donor management” is used throughout the text and can be confusing. As it reads, one might understand that the patient is potentially brain-dead vs what I believe the authors mean which is that the patient is potentially a donor. Suggest revising to “brain-dead, potential donor”
Authors response: We totally agree, that the term used may lead to double interpretation. So, as stated in the first question, the term “potential brain-dead donor” was replaced by “brain-dead potential organ donor” throughout the text.

3) In the abstract, under ethics, the authors say a “waiver of prospective informed consent” whereas in the body of the manuscript (line 380-382), they state “a waiver of informed consent.” Based on this inconsistency, I am unclear if the study authors are seeking a waiver of consent for study participation or a deferred consent model.
Authors response: In order to make it clearer, we changed the sentence in the abstract (line 86 – marked copy) to: “We requested a waiver of informed consent for the IRB of each site.”

4) One of the secondary outcomes is number of actual organ donors. Since the sites are randomized and not the patients, there may be non-equal number of patients in both the control and the checklist groups. Therefore, the absolute number of actual organ donors is not directly comparable. Please clarify if this number of organ donors will be indexed to potential donors (which requires definition, see 1)
Authors response: The number of actual organ donors will be indexed to brain-dead, potential donors. We make it clearer in the text (line 287 – marked copy) as follows (text inclusions are underlined): “1) number of actual organ donors indexed to brain-dead potential donors, defined as brain-dead, potential donors for whom the surgical procedure for organ recovery has been initiated (…);”. The definition of “actual donors” is supported by the reference number 3.

5) Hospitals with more than ten annual notifications were included, but to meet the required sample size, 19 potential organ donors are required per site (line 238-239). This is almost double. How do the authors reconcile this to be sure power will be achieved?
Authors response: For the sample size estimate, we performed a simplification, using a fixed cluster size (n=19) and, as well stated in the question, the power would reduce if we have a variation in the cluster sizes. In order to prevent important power loss, we fixed maximum number of subjects per cluster in 30 and we estimate recruiting at least 1,200 participants (instead of 1,140). We acknowledged it in the manuscript at the end of sample size section (lines 261 to 264 – marked copy): “Therefore, considering a possible variation in cluster size and its impact on statistical power, we intend to include a minimum of 60 ICUs with at least 1,200 potential organ donors, not allowing more than 30 participants in each cluster.” Furthermore, due to other uncertainties related to sample size estimate (e.g. rate of events, ICC) we included in this trial 63 clusters and expect to include around 1,350 subjects.

6) As a quality improvement project, the authors should list their process measures. As the authors mention in their discussion, if there is no effect demonstrated in the intervention group, this may be because of a lack of efficacy of the checklist or due to suboptimal implementation of the intervention.

Thus, the authors should report their compliance with the checklist as a process measure. These might be the tertiary objectives, but they should be labelled as process or fidelity measures. As well, are the authors tracking any balancing measures?
Authors response: We will perform a sensitivity analysis according to compliance to the checklist. We signalized this aspect in the manuscript (line 359 – marked copy), as follow (text inclusions are underlined): “We will conduct sensitivity analyses of adherence to the intervention (compliance with checklist proposed measures)”. Details on how we will evaluate checklist adherence will be described in the statistical analysis plan and it will involve the proportion of goals achieved. These fidelity measures will be assessed only for the intervention group, not being possible to be labelled as outcomes. Although our tertiary outcomes are not process indicators, they are surrogate outcomes that are related to adequate management results. The “the proportion of potential donors with adequate respiratory parameters (defined as PaO2 / FiO2 ratio ≥ 200)” are directly linked with ventilatory goals of the checklist; the proportion of potential donors with adequate body temperature (defined as body temperature between 34°C and 35°C if haemodynamically stable and > 35°C if mean arterial pressure [MAP] < 65 mm Hg or use of noradrenaline or dopamine) are directly related with temperature and perfusion goals of the checklist; the proportion of potential donors with adequate circulatory parameters (inadequate parameters defined as MAP < 65 mm Hg or dose of noradrenaline ≥ 0.1 mc/kg/min or dose of dopamine ≥ 15 mcg/kg/min) are directly related with haemodynamic goals; the organ dysfunction score, assessed by the Sequential Organ Failure Assessment (SOFA) Score are related with overall quality of the clinical management. Finally, occasional imbalances between groups will be assessed comparing baseline characteristics of subjects. Dummy tables will be published in the statistical analysis plan.

7) More details are required to describe checklist application. Will the IHTC or ICU professional apply the checklists in rounds? How will the prompting be done? (eg in person, which member of the medical team will be prompted, will the checklist be paper or electronic?)
Authors response: Thank you very much for your questions in this subject. We split the comments and tried to be clearer in these aspects, as follows:

Will the IHTC or ICU professional apply the checklists in rounds?
Authors response: In order to make it clearer, we rewrote the phrase that describes this aspect in the text (line 225 to 226 – marked copy), as follows (text changes are underlined): “The checklist will be bedside applied immediately after the time of potential donor inclusion in the study and repeated every six hours until organ recovery or loss of the potential donor.”

How will the prompting be done? (eg in person, which member of the medical team will be prompted, will the checklist be paper or electronic?)
Authors response: We rewrote the description of this aspect in the text (lines 224 to 228 – marked copy), as follows (text changes are underlined): “A member of the Intra-Hospital Transplant Co-ordination (IHTC) or a designated ICU nurse will apply the paper-based checklist at the bedside. The same professional will be responsible for personally prompting the medical staff member responsible for the care of this specific subject, with the purpose to modify the medical management if any inappropriate aspect of care is noted.”

8 Monthly reports on performance- who will receive these reports? How will the ICU teams be made aware of their results?

-who will receive these reports?
Authors response: Monthly reports in the form of a newsletter will send by electronic message to all members of the health team. In order to clarify we rewrote the item 4 in the Table 1, about what comprise the newsletter, as follows: “Monthly reports with the number of potential donors screened and included will send by electronic message, in the form of a newsletter, to all members of the health

team comprising of professionals from the ICU and IHTC." This adjustment will also respond the next question.

How will the ICU teams be made aware of their results?
Authors response: In the newsletter the teams will receive a list with the number of brain-dead, potential donors screened and included. The study management team compares the actual inclusions to the estimated number for each centre, as well as comparing the number of reports of brain death reported to the corresponding OPOs. Teams are also made aware via telephone contact or electronic messages regarding possible differences between the number of notifications for the OPO and the number of inclusions in the study.

9) How was the checklist developed? Were there (plan-do-study-act) cycles done to develop and improve the checklist intervention? Was the checklist intervention piloted? Is this the same checklist that was prospectively studies (reference 12)? There would be justification that this checklist was ready for assessment in a RCT.
Authors response: We tried to clarify these subjects taking account your considerations, and changing the "Intervention" session of the manuscript (line 196 to 228), as follows (text changes are underlined):
"After a preliminary prospective study [13] that found a positive impact of a clinical goal-directed protocol on reducing cardiac arrests in brain-dead, potential donors, an updated checklist was generated after drawing up a clinical practice guideline (CPG) for brain-dead, potential donor management. The CPG recommendations were developed from July 2016 to March 2017, as a joint initiative of the Brazilian Ministry of Health, Brazilian Association of Intensive Care Medicine (AMIB), and Brazilian Association of Organ Transplantation (ABTO).[23] The recommendations were developed using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) system.[24] The following criteria were considered in the decision-making process: the risks and benefits of interventions; the quality of evidence for risks and benefits; resource use and costs; and acceptability by healthcare professionals.
The checklist was designed to address CPG goals and recommendations that involve temperature control, mechanical ventilation, haemodynamic control, endocrine and metabolic control, and use of antibiotics and blood products, as required, and hormone administration (hydrocortisone, vasopressin and/or desmopressin, insulin). Thyroid hormone was not recommended due to lack of evidence to confirm the benefit of its use.[25,26] We tested the checklist in 4 ICUs with high volume in brain death notifications that participated in the preliminary study [13] and make minimal adjustments suggested by the professionals that tested the tool. The full checklist is available in Online Supplementary File 3. Figure 2 describes the logic model for the intervention to be tested in this study. We will provide on-site training in each ICU for healthcare professionals to inform how to implement the checklist and how to apply the intended recommendations.
The checklist application protocol will be activated at the time of potential donor inclusion in the study and repeated every six hours until organ recovery or loss of the potential donor. A member of the Intra-Hospital Transplant Co-ordination (IHTC) or a designated ICU professional will apply the paper-based checklist at the bedside. The same individual will be responsible for personally prompting the medical team to modify medical management if any inappropriate aspect of care is noted."

10) Questions related to the checklist (supplementary Figure 2)
a. "Vasopressin and hydrocortisone were associated"- please clarify. The term associated is unclear here.
Authors response: We replaced the expression "associate vasopressin" by "add vasopressin" so as well the expression "associate hydrocortisone" was replaced by "add hydrocortisone". Changes were made in the "Online Supplementary File 3".

b. Na <155 – is there a lower limit?

Authors response: Due to the presence of diabetes insipidus and / or infusions of hyperosmolar solutions (mannitol and hypertonic sodium solution) during the treatment of neurocritical patients, hypernatremia is the metabolic disorder most commonly observed when these patients progress to brain-dead. This is a commonly used therapeutic goal in this setting, without considering a lower limit for sodium levels.

c. Mg – is there an upper limit?
Authors response: Polyuria can also result in other electrolyte disorders such as hypomagnesemia. Hypermagnesemia is quite uncommon in critical patients and is not a concern that requires monitoring during maintenance of the brain-dead potential organ donor. For this reason, we do not consider an upper limit in the monitoring of this electrolyte.

11) Table 1 includes strategies to maximize adherence to co-intervention (e.g. family meetings); however, the concept of the family meetings is not introduced in the text until after the table, so this is confusing. Please re-organize.
Authors response: In order to re-organize the information presented in Table 1, we changed the mention of this table to the final of the co-intervention paragraph (line 251 – marked copy), and show the table after the co-intervention session (line 254 – marked copy).

Minor edits
1) Line 115- “aiming” should be replaced by “aimed at”.
Authors response: Replaced (line 118 – marked copy).

2) Line 181-183- please state if these exams are spaced in time or concurrent and if spaced, how much time much elapse between them.
Authors response: We rewrote the text (line 189 – marked copy) as follows (text inclusions are underlined): “(…) two clinical examinations performed by two different physicians, in an interval of at least 1 hour between the examinations, and one apnoea test (…)”

3) Line 151: a comma is missing between “evidence-based” and “goal-directed”.
Authors response: The comma was included.

4) Line 261: “for cardiac arrest” should be replaced by “from cardiac arrest”.
Authors response: Replaced (line 281 – marked copy).

5) Line 452- did the authors mean an implementation strategy that may NOT be considered feasible?
Authors response: Thank you again for your attention. There was a mistake in inserting this phrase into the study's limitations paragraph. The sentence was moved to the third paragraph of the discussion (lines 451 to 453 – marked copy).