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DONORS (Donation Network to Optimise Organ Recovery Study): Study protocol to evaluate the implementation of an evidence-based checklist for potential brain-dead donor organ management in intensive care units, a cluster randomised trial

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ABSTRACT

Introduction: There is an increasing demand for multi-organ donors for organ transplantation programmes. This study protocol describes the Donation Network to Optimise Organ Recovery Study (DONORS), a planned cluster randomised controlled trial that aims to evaluate the effectiveness of the implementation of an evidence-based goal-directed checklist for potential brain-dead donor management in intensive care units (ICUs) in reducing the loss of potential donors due to cardiac arrest.

Methods and analysis: The study will include ICUs of at least 60 Brazilian sites with an average of >10 annual notifications of valid potential organ donors. Hospitals will be randomly assigned (with a 1:1 allocation ratio) to the intervention group, which will involve the implementation of an evidence-based goal-directed checklist for potential organ donor maintenance, or the control group, which will maintain the usual care practices of the ICU. Team members from all participating ICUs will receive training on how to conduct family interviews for organ donation. The primary outcome will be loss of potential donors due to cardiac arrest. Secondary outcomes will include the number of actual organ donors, the number of organs recovered per actual donor, and the total number of cardiac arrests among all potential organ donors.

Ethics and dissemination: The Institutional Review Board of the Co-ordinating institution and of each participating site must individually approve the study. We will request a waiver of prospective informed consent from substitute decision makers. Study results will be disseminated to the general medical community through publications in peer-reviewed medical journals.

Keywords: brain death, cardiac arrest, organ donation, checklist, quality improvement

Trial registration: ClinicalTrials.gov, NCT03179020, registered 23 March 2017.

Strengths and limitations of this study

- This is the first randomised trial to evaluate whether a goal-directed checklist for the management of potential brain-dead donors may be useful in reducing cardiac arrests and contributing to increase organ availability for transplants.
- The preparation of the goal-directed checklist was preceded by the review of a clinical practice guideline following the Grades of Recommendation Assessment, Development and Evaluation (GRADE) system.
- Brazil is a country with a wide spectrum of demographic and socioeconomic scenarios; the diversity of institutions to be included in DONORS will allow us to provide results in a broad range of demographic and socioeconomic scenarios.
- Main study limitations are the unblinded design and the high heterogeneity of care and outcomes expected among centres in the study.

INTRODUCTION

Organ transplantation is the only treatment option for many patients affected by end-stage organ failure. Despite advances in the field of organ donation, the disparity between the number of patients on transplant waiting lists and the availability of organs for transplantation is increasing. Several parameters determine the availability of suitable organs for donation, and many of these depend on a successful sequence of actions by several healthcare professionals, starting with the identification of a potential multi-organ donor and ending with surgical organ procurement.[1-4] In this process, important factors contributing to the gap between organ supply and demand include failure to identify and report brain death, lack of family consent for organ donation, inaccurate perceptions of contraindications to organ donation, and haemodynamic instability that may compromise the quality of organs or even lead to loss of donors due to cardiac arrest.[1-3] A systematic application of clinical management strategies aiming the haemodynamic stabilisation of brain-dead donors may contribute to an increase in the number of organs for transplantation by improving the quality of organs and reducing the loss of potential donors due to cardiac arrest.[1, 2, 4] In addition, other measures such as optimal ventilatory support and temperature control may improve the quality of organs, resulting in a higher organ recovery rate and better clinical outcomes for transplant recipients.[5, 6]

Checklists have an established role in healthcare to prevent omissions while performing complex procedures. A series of studies have shown that the use of a goal-directed checklist may help the systematic application of clinical guidelines, leading to greater adherence to evidence-based clinical interventions and improving clinical outcomes. Examples include the World Health Organisation (WHO) Surgical Safety Checklist, the Keystone Intensive Care Unit (ICU) Project checklist to prevent catheter-

related bloodstream infection, and clinical checklists to ensure patient safety in the ICU.[7-10]

There is a lack of evidence for the use of checklists regarding the clinical aspects of improving organ availability for transplantation of brain-dead donors. Some observational studies have reported that the application of a goal-directed checklist to guide the management of potential brain-dead organ donors may reduce the rate of cardiac arrest and increase the number of organs recovered per donor. [11-18] However, given the relatively small number of studies, their observational design and inconsistency of findings, this literature cannot yet support the use of a goal-directed checklist in the current management of brain-dead organ donors [19].

Our hypothesis is that supporting the management of potential organ donors with the use of an evidence-based bedside checklist may reduce the loss of potential organ donors due to cardiac arrest and increase the number of donors and organs transplanted per donor. In this protocol, we describe the methods to be used in the Donation Network to Optimise Organ Recovery Study (DONORS).

OBJECTIVES

Primary objective

The primary objective is to evaluate the effectiveness of the implementation of an evidence-based bedside checklist, containing goals and recommendations of care as guidance for the management of potential organ donors, in reducing potential organ donor losses due to cardiac arrest.

Secondary objectives

Secondary objectives are to assess whether the evidence-based goal-directed checklist is effective in (a) increasing the number of actual organ donors and (b) increasing the number of organs recovered per actual donor.

METHODS AND ANALYSIS

The protocol is registered at ClinicalTrials.gov (NCT03179020) and the present manuscript provides additional details regarding study design and methodology.

Study design

DONORS is a parallel cluster randomised controlled trial involving ICUs of Brazilian hospitals. We will randomly assign hospitals to the intervention group, comprising the checklist implementation, or the control group, consisting of usual care in each ICU (Figure 1).

Participants

Cluster eligibility, recruitment and exclusion criteria

We will invite adult ICUs with an average of at least 10 annual notifications of potential organ donors in the prior two years. Information regarding notifications is provided by the Brazilian National Transplant System.

Coronary care units, intermediate care units and emergency departments are not eligible. We will also exclude institutions that already systematically use checklists as guidance for the management of potential organ donors supported by implementation tools, such as guidelines and clinical decision algorithms for bedside use, in print or digital form.

Patient eligibility and exclusion criteria

We will screen and include consecutive potential organ donors, as confirmed by the first clinical examination consistent with having brain death, within the age range of 14 to 90 years. Only ICU patients will be included; potential donors outside the ICU will be included in the study if admitted to ICU within three hours of initial assessment.

Diagnosis of brain death will be made according to the Brazilian Federal Board of Medicine guidance, consisting of: two clinical examinations performed by two different physicians and one apnoea test followed by neuro-imaging (transcranial Doppler, cerebral arteriography, electroencephalography, or brain scintigraphy).[20, 21] We will exclude brain-dead patients who are not candidates for organ donation (Online Supplementary File 1).

Interventions

Checklist for potential brain-dead donor management

The intervention group checklist derives from a clinical practice guideline (CPG) for potential organ 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).[22] The recommendations were developed using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) system.[23] 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.

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 goals and recommendations involve temperature control, mechanical ventilation, haemodynamic control, endocrine and metabolic control, and use of antibiotics and blood products, as required. The full checklist is available in Online Supplementary File 2. Figure 2 describes the logic model for the intervention to be tested in this study.

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 checklist. The same individual will be responsible for prompting the medical team to modify medical management if any inappropriate aspect of care is noted. Table 1 shows the strategies to promote effective implementation of this intervention.

213 **Table 1**. Strategies to maximise adherence to study interventions and co-interventions.

Strategies
1. In-person training of two representatives (study co-ordinators) from each participating site on the conduct of family interviews.
2. Provision of an online course for the training of all intensive care unit (ICU) team members and Intra-Hospital Transplant Co-ordination (IHTC) members on how to prepare for and conduct a family interview. A family interview support guide will also be made available.
3. On-site training of ICU team members and IHTC members of all hospitals in the intervention group. The training aims to provide guidance on the methods for administration of the goal-directed checklist for the management of potential organ donors to as many ICU and IHTC professionals as possible.
4. Production of monthly reports on the performance of each site in relation to patient inclusion and adherence to the checklist goals, grading adherence according to the percentage of goals achieved.
5. The local co-ordinators of the participating sites will be contacted by the study central office co-ordinators whenever there is a failure to adhere to the protocol or to complete the patient's clinical record form.
6. The local co-ordinators of the participating sites will receive, whenever a patient is included, electronic messages to remind them of the need to administer the bedside goal-directed checklist and prompt the medical team on management during the stay of potential organ donors in the ICU.
7. Remote support from the study co-ordinators and central office will be made available to all local co-ordinators for any questions related to the study.

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215 Usual care

ICUs in the control group will continue with their usual management of potential organ donors. They will not be informed of the items assessed in the goal-directed checklist or the strategies to enhance compliance.

Co-interventions

All ICU teams and IHTC members of the participating institutions will receive training in family interviews for organ donation. The training and interview process have been based primarily on the Spanish model of Communication in Critical Situations (Online Supplementary File 3).[23-27] Training consists of two components: (1) face-to-face training of one ICU team representative and one IHTC member of each institution; and (2) provision of an online, self-instructional course for all ICU team members and IHTC members participating in the study (Table 1). These co-interventions aim to standardise ICU strategies in relation to family interviews, reducing variability between participating sites. This is important for the trial due to three main reasons: (a) inadequate interviews may result in a lower rate of effective donation (secondary outcomes of the study), independently of potential donor management; (b) reducing variability between participating sites may have an impact on reducing the intra-cluster correlation of the study, increasing its power; and (c) training strategies might enhance the engagement of the participating sites, especially those in the control group, thereby balancing a potential Hawthorne effect.

Sample size

With 60 ICUs, we will need to include 19 potential organ donors per site (1,140 potential donors) to detect an absolute reduction of donor losses due to cardiac arrests of 10% (from 28% in the control group to 18% in the intervention group),[12]

considering an intra-class correlation coefficient (ICC) of 0.05, power of 80%, and a two-sided alpha level of 5%. 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.

Randomisation

We will randomly assign ICUs to the intervention group or control group with a 1:1 allocation ratio using blocks of variable sizes (2 and 4) and stratified by the estimated annual number of notifications of brain death in each site (sites with ≤ 29 and > 29). ICUs from the same institution are not considered independent clusters to avoid contamination. We will randomise the ICUs consecutively as per the date of authorisation of the principal investigator to implement the study in the institution, obtained after the Institutional Review Board (IRB) approval. To ensure allocation concealment, a statistician from the study co-ordinating office will be responsible for the randomisation process, with all researchers involved in the trial blinded to the allocation sequence.

Outcomes

The primary outcome will be the number of potential organ donor losses due to cardiac arrest, defined as any loss of potential donors for cardiac arrest that occurs after patient enrolment, while the subject remains eligible for organ donation (no contraindications, family approval or waiting family decision for donation). Losses of potential donors due to other factors (e.g., family refusal or contraindication to organ donation after patient inclusion) will not be considered for this outcome.

The secondary outcomes will be:

1) number of actual organ donors, defined as donors for whom the surgical procedure for organ recovery has been initiated (irrespective of organ recovery);

2) number of solid organs recovered per actual donor (ranging from zero to seven organs per donor, as follows: liver; heart; pancreas; two lungs; and two kidneys).

The tertiary outcomes will include:

1) the proportion of potential donors with adequate respiratory parameters (defined as PaO_2 / FiO_2 ratio ≥ 200);

2) 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);

3) 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);

4) organ dysfunction score, assessed by the Sequential Organ Failure Assessment (SOFA) Score.

Blinding

Due to the nature of the intervention, it will not be possible to blind investigators or healthcare providers in this study. However, we will not disclose details of the content of the checklist to the control group.

Data collection

An ICU healthcare professional or an IHTC member will collect the data, which will be recorded at the patient's bedside using a printed case report form and

subsequently transferred into an electronic data capture system (REDCap, Vanderbilt University, Tennessee, USA).[28] Investigators will receive training for these activities during the study initiation meeting.

Data monitoring

The study statistician will be responsible for reviewing weekly data on all inclusions, checking data consistency, and checking whether all forms have been completed correctly. Clinical research monitors will review all data collected and may require supplementation or correction of inconsistent data according to the Good Clinical Practices (GCP) recommended by the International Council for Harmonisation (ICH).[29] On-site monitoring visits will take place after the fifth patient inclusion in the site and when 100% of the projected number of inclusions for the site has been achieved. Additional monitoring visits will be performed as needed, based on the detection of data inconsistencies, errors in completing the forms, or suspected fraud. Periodic remote follow-up will be performed via telephone or electronic messages with the participating sites according to patient recruitment. The data to be collected from each subject are summarised in Table 2.

Table 2. Data to be entered in the clinical record form of all potential organ donors included in the study.

1. Identification of the potential donor: research centre code and patient's hospital registration number, sex, and date of birth.
2. Screening: inclusion and exclusion criteria for definition of eligibility.
3. History: date and time of hospital admission, date and time of ICU admission, reported and estimated weight, height, SAPS 3 on ICU admission, comorbidities prior to hospitalisation, cause of brain death, date and time of 1st clinical examination for the diagnosis of brain death.
4. Respiratory variables: tidal volume, mL; respiratory rate, mpm; PEEP, cm H_2O; plateau pressure, cm H_2O; peak pressure, cm H_2O (if volume is controlled); FiO_2, %
   Blood gas variables: PaO_2, mm Hg; SaO_2, %; $PaCO_2$, mm Hg; base excess, mmol/dL; PvO_2, mm Hg; SvO_2, %; $PvCO_2$, mm Hg; lactate, mmol/dL.
5. Temperature and haemodynamic variables: temperature, °C; heart rate, bpm; systolic blood pressure, mm Hg; diastolic blood pressure, mm Hg; CVP, mm Hg and/or ΔPp, % and/or ΔSV, % and/or IVCCI, %; cardiac arrhythmias.
6. Diuresis and fluid balance: infused volume; diuresis and fluid balance at different time intervals.
7. Laboratory variables: haemoglobin, g/dL; creatinine, mg/dL; platelets, /mm^3; bilirubin, mg/dL; sodium, mEq/L; potassium, mEq/L; magnesium, mEq/L; phosphorus, mEq/L; calcium, mEq/L.
8. Drug use: noradrenaline; dopamine; vasopressin; desmopressin; corticosteroids; antibiotics.
9. Family interview: time, place and name of the professional communicating the establishment of a brain death protocol to the family; time, place and name of the

professional communicating the death to the family; time, place and name of the professional conducting the family interview with the request for organ donation; experience and qualification of the professional conducting the family interview with the request for organ donation; family authorization for organ donation; loss of potential donor due to family refusal; causes of family refusal.

10. Protocol completion: date and time of 2nd clinical examination for the diagnosis of brain death; date and time of a complementary test for the diagnosis of brain death; complementary test performed for the diagnosis of brain death.
11. Occurrence of cardiac arrest, loss of potential donor due to cardiac arrest, completion of organ harvesting, number and type of organs recovered.

CVP, central venous pressure; ΔPp, pulse pressure respiratory variation; ΔSV, stroke volume respiratory variation; FiO_2, fraction of inspired oxygen; ICU, intensive care unit; PaO_2, arterial partial pressure of oxygen; $PaCO_2$, arterial partial pressure of carbon dioxide; PvO_2, venous partial pressure of oxygen; $PvCO_2$, venous partial pressure of carbon dioxide; PEEP, positive end-expiratory pressure; SAPS 3, Simplified Acute Physiology Score 3; SaO_2, arterial oxygen saturation; SvO_2, venous oxygen saturation; IVCCI, inferior vena cava collapsibility index.

Statistical analysis

We will prepare a detailed statistical analysis plan before data analysis, which is intended to be published or made available online. We will perform the statistical analysis following the intention-to-treat principle, accounting for cluster design, with observations of the ICUs analysed according to the group to which they have been allocated. We will examine the normality of data by visual inspection of histograms and using the Shapiro–Wilk test for normality. Baseline characteristics of both the ICUs and potential organ donors will be presented as frequencies and percentages, means and standard deviation (SD), and medians and interquartile range (IQR), whenever appropriate, for the intervention group and control group.

For the primary outcome, we will calculate hazard ratios (HR) considering the time to the outcome, since patients will be subjected to management at different time intervals in the institutions. Patients will be considered at risk for the occurrence of the outcome of interest while under consideration as potential donors. If the outcome of interest does not occur, patients' follow-up will be considered to have ended at the time their management has been discontinued (family refusal or contraindication to donation). We will conduct predefined subgroup analyses, considering the following variables: age > 60 years; cause of the injury leading to potential brain death (traumatic or non-traumatic); and patient severity on ICU admission defined by the Simplified Acute Physiology Score 3 (SAPS 3) with a cut-off determined by its median. We will conduct sensitivity analyses of adherence to the intervention and of the time interval between the first clinical examination consistent with having brain death and inclusion in the study.

For secondary and tertiary outcomes, we will use models for correlated data, considering the ICU as a cluster and each outcome with its own probability distribution. We will conduct a sensitivity analysis of the outcome 'number of solid organs recovered per actual donor', considering the number of kidneys harvested. We will analyse secondary outcomes by adjusting for multiple hypothesis testing. For all statistical comparisons, we will adopt a statistical significance level of 0.05. An up-to-date version of the R programme (R Development Core Team) will be used to conduct analyses.

Study planning and implementation schedule

We finalised the study design and protocol in March 2016. The National Study Investigators Meetings were held in two parts: 9–10 March 2017 and 8–9 June 2017. At the time of manuscript preparation, 63 ICUs representative of the Brazilian geopolitical

territory are currently recruiting study subjects (Figure 3). On-site training started on June 1, 2017. We expect that the recruitment will be completed in July 2019. The list of sites included is available at ClinicalTrials.gov (NCT03179020).

Organisational aspects of the study

The study is sponsored and co-ordinated by the Moinhos de Vento Hospital, Brazil, in partnership with the Brazilian Ministry of Health through the Programme of Institutional Development of the Brazilian Unified Health System (PROADI-SUS) and in association with the General Co-ordination Office of the National Transplant System (CGSNT) and the Brazilian Research in Intensive Care Network (BRICNet). The study is supported by the AMIB Committee for Organ Donation for Transplant, ABTO, the Spanish National Transplant Organisation (ONT), and the organ procurement organisations (OPOs) of the states of Santa Catarina and Rio Grande do Sul. The study Steering Committee consists of intensivists, transplant co-ordinators and epidemiologists with expertise in conducting multi-centre studies. The committee is involved in the conception and design of the study, supervision of progress and procedures during the study, and writing of the study report and any resulting study manuscript.

Ethics and dissemination

The study was designed in accordance with resolution No. 466/2012 of the Brazilian National Health Council/Ministry of Health, the Declaration of Helsinki, the Document of the Americas, and the ICH/GCP E6(R2) 2016. The study was approved by the IRB of the Co-ordinating Centre (No. 53999616.0.1001.5330) and by the IRB of each participating hospital. Participating in the intervention or control groups does not

imply any risk for the subjects included, since the groups will not be deprived of the application of the most up-to-date recommendations. Because obtaining written informed consent from patients' family members entails operational and methodological difficulties, and would have a potential negative impact on organ donation as well, we will request a waiver of informed consent in accordance with the IRB of each site.

This trial, regardless of the results, will be published in a peer-reviewed medical journal and presented in scientific conferences and scientific meetings involving the representatives of each participating hospital, of each Brazilian state transplant centre, and of the Brazilian Ministry of Health.

DISCUSSION

Despite the existence of CPGs that currently provide recommendations for a 'standard of care' in the management of potential organ donors,[22,28] they are not always implemented, resulting in the risk of loss of specific organs due to management failures or even multiple organ loss due to cardiac arrest of the potential donor.[1-4, 22, 30] CPGs usually do not have an impact on bedside practice in the short term, as they rarely take into account clinical applicability.[31] Therefore, a CPG-based goal-directed checklist associated with a clinician prompting system may be an effective approach to improve physician adherence to CPG recommendations. Physician-centred healthcare can be associated with non-adherence to basic recommendations of care, especially in highly complex processes, such as the management of potential organ donors.[30] In this context, we expect that these organisational adjustments, supported by a checklist-based management strategy, will have a positive impact on organ donation.

Patel et al.[18] published the results of 671 multi-organ donors managed using a goal-directed checklist in the United States. The predetermined goals were met in 45%

of cases prior to organ recovery, and the use of the goal-directed checklist significantly increased the number of organs transplanted per donor.[18] Recently, we published a prospective observational study that involved 27 ICUs in a southern Brazilian state demonstrating that the use of a goal-directed checklist to guide the management of deceased donors reduces potential brain-dead donor losses due to cardiac arrest.[12] Compliance with the checklist increased after the start of the study from 52.1% to 85.8% ($p < 0.001$). The use of the checklist was associated with a lower likelihood of occurrence of cardiac arrest (odds ratio [OR]: 0.30, 95% CI: 0.18-0.49, $p < 0.001$) and an increase in the number of organs recovered per donor.[12] Although these results are encouraging and reproduce the observations of other authors, the observational nature of the studies provides only weak evidence on the subject.[13-18]

The study design and basis for the implementation of DONORS may provide new insights that can help overcome the weaknesses of previous observational studies. The cluster randomisation design will limit selection biases, and we will count on a large number of ICUs, which are responsible for a significant amount of brain death notifications throughout Brazil. The DONORS design will include the evaluation of the effectiveness of a goal-directed checklist strategy in different socioeconomic scenarios in Brazil, allowing us to provide real-world evidence to support the practical clinical applicability of the study findings. Finally, the characteristics of the institutional quality improvement programme of this protocol will allow the potential benefits generated by the proposed study model to be incorporated into ICUs and ultimately transferred to other clinical areas for the care of critically ill patients.

The implementation of a goal-directed checklist for the management of potential donors is a complex intervention, with multiple components. It is important to state that, as in most quality improvement studies, how the intervention is implemented

is crucial to the interpretation of the results. In this respect, through this protocol, we aimed to describe in detail all the interventions and co-interventions proposed in the study in order to allow reproducibility of our procedures in other settings. In addition, the logic model presented in the study (Figure 2) is intended to explore the relationships between the activities proposed in the intervention and the mediators of the effect, such as improved clinical management of potential donors and enhanced communication with the ICU team about the expected outcomes. Also important is that, although the study focuses on assessing short-term outcomes in potential donors (e.g., cardiac arrest and number of organs recovered), potential beneficial outcomes are expected for transplant recipients, such as improved graft function, survival and quality of life.

Our study has some limitations. First, high variability in care and outcomes among institutions is expected. Although the chosen ICC may be considered conservative, there are no estimates in the literature for the proposed intervention, which may result in lack of power if the actual ICC is larger than the estimate. In spite of the procedures to avoid the transfer of information about the checklist to ICUs in the control group, although with low probability this possibility should be considered, thereby exposing the details of the content of the goal-directed checklist for the control group. Furthermore, although stratified randomisation is planned for this study, we must take into consideration the differences in the number of brain death notifications among ICUs, which will recruit patients at different rates, which in turn may generate learning curves that may have an impact on the final cluster randomisation trial results. In order to minimise this problem, we are allowing a maximum of 30 patients to be recruited per each study site; however, some ICUs may recruit a small number of patients. In addition, the trial is testing the effectiveness of the proposed intervention by means of an implementation strategy that may be considered feasible to replicate in other settings.

Inadequate adherence to the checklist may have an impact on the results observed in the intervention group, showing no effect that may be either due to lack of efficacy of the intervention or due to its suboptimal implementation. Another important aspect to highlight is that, although we expect to see an improvement in the quality of organs with the use of the checklist, therefore improving outcomes for organ-transplant recipients, we are limiting the data collection and study procedures to potential donors, not allowing direct assumptions about its possible effects.

CONCLUSIONS

We expect that the results from DONORS will provide information regarding the practical use of checklist-guided management interventions for potential multi-organ donors that may contribute to reducing potential donor losses due to cardiac arrest or other relevant outcomes. At this time, with the increasing demand for organs for transplantation, standardised, evidence-based guidelines that may be adopted globally by ICUs and by transplant co-ordinators are needed to improve the availability and quality of organs available for donation. The evidence generated by this trial will have great potential to contribute positively to the donation of organs.

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Authors' contributions

All authors contributed to the study design and revised this manuscript: GAW, CCR, ABC, FRM, RGR, CT, JA, CAF, LCPA, FAB, CMG, DBS, DS, DZP, ICM, AIR, SSS, NEG, LVA, PSB, FRR, MFRBM, TBP, CMCG, PCD, JFPO, GCM, FACA, RBM, VN, LSH, MOM, RRN, and MF. Additionally, GAW, FRM, and ABC conceived the study, RGR, CT, LCPA, FAB, LSH, and MF also helped with the study design, and GAW drafted the first version of the article. JA, CAF, and RRN, helped with centre recruitment and with the co-intervention aspects. GAW, JA, CMG and DBS co-ordinated educational actions for the intervention. NEG, DS, MF, RGR, CCR, and ABC planned epidemiological and statistical aspects of the study, CMG, ICM, and DZP designed the study manuals and study tools, ICM and CMG led site management, ICM, LAV, CMG, AIR, and SSS visited all sites to provide training, and CCR, ICM, CMG, PSB, and DZP organized the study meetings. All authors read and approved the final manuscript.

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Data sharing

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FIGURE LEGENDS

Figure 1. Study flow diagram.

ICUs, intensive care units; IRB, Institutional Review Board; ITT, intention-to-treat; No., number

Figure 2. Logic model for the checklist intervention.

Figure 3. Geographical distribution of the participating intensive care units in Brazil.

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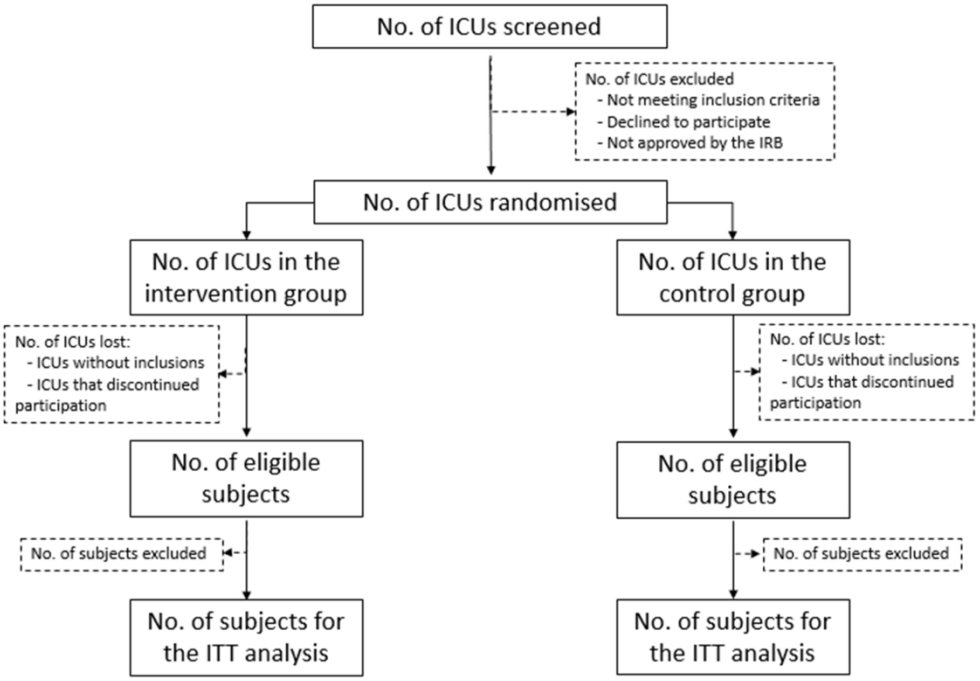

Study flow diagram.
ICUs, intensive care units; IRB, Institutional Review Board; ITT, intention-to-treat; No., number

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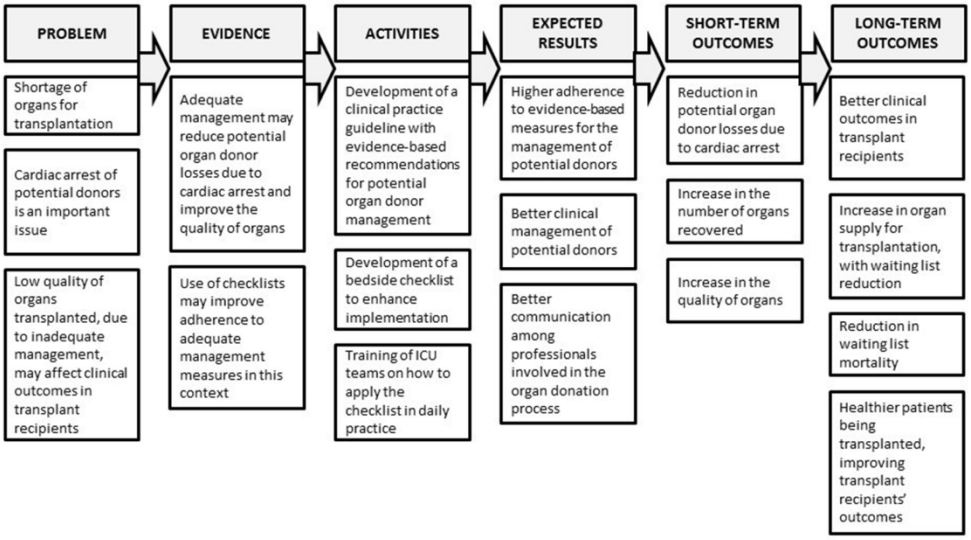

Logic model for the checklist intervention.

Geographical distribution of the participating intensive care units in Brazil.

157x146mm (300 x 300 DPI)

Online Supplementary File 1. Exclusion criteria of potential organ donors from the study.

Age	Infection	History of cancer
Age > 90 years.	HIV, HTLV-I and -II, Uncontrolled sepsis, Acute hepatitis, Malaria, Acute viral infections (e.g., rubella, rabies, West Nile virus, adenovirus, enterovirus, parvovirus, and viral meningoencephalitis or of unknown cause), Cryptococcal meningoencephalitis, Prion diseases, Active tuberculosis with < 2 months of treatment, Bacterial colonisation of the donor without antibiotic treatment options (resistant to all antibiotics).	Metastatic cancer, Breast tumours, Melanoma, Soft-tissue sarcoma, Haematological malignancy, Primary tumours of the central nervous system – Group 3 (anaplastic astrocytoma – grade III, glioblastoma multiforme, medulloblastoma, anaplastic oligodendroglioma – Schmidt C and D, malignant ependymoma, pineoblastoma, anaplastic/malignant meningioma, intracranial sarcoma, germ cell tumour – except well-differentiated teratoma, chordoma, and primary cerebral lymphoma).

Online Supplementary File 2. English translation of the final version of the bedside checklist.

Name: _____

Date and time of 1st clinical examination consistent with brain death: _____/_____/_____ _____:_____

Current date and time: _____/_____/_____ _____:_____

GOALS TO BE ACHIEVED	STATUS			IMMEDIATE ACTIONS WHEN STATUS = "NO"	ACTION TAKEN?	
$SaO_2 \geq 90\%$?	□ Yes	□ No	□ NA	Adjust FiO_2 and/or PEEP to $SaO_2 \geq 90\%$	□ Yes	□ No
Vt of 6 to 8 mL/kg of predicted weight?	□ Yes	□ No	□ NA	Adjust Vt to 6 to 8 mL/kg	□ Yes	□ No
PEEP ≥ 8 cm H_2O?	□ Yes	□ No	□ NA	Adjust PEEP to ≥ 8 cm H_2O	□ Yes	□ No
MAP ≥ 65 mm Hg and good tissue perfusion after a crystalloid bolus?	□ Yes	□ No	□ NA	Continue fluid infusion while there is volume responsiveness (e.g.: ΔPp ≥ 13% / ΔMAP ≥ 8% / ΔSV ≥ 10% / CVP < 8 mm Hg)	□ Yes	□ No
MAP ≥ 65 mm Hg and good tissue perfusion after volume adjustment?	□ Yes	□ No	□ NA	Maintain / initiate noradrenaline (dopamine if bradycardia)	□ Yes	□ No

Vasopressin and hydrocortisone were associated after maintaining / initiating noradrenaline / dopamine?	□ Yes	□ No	□ NA	Associate vasopressin (1 IU bolus + 0.5-2.4 IU / h) and Associate hydrocortisone 100 mg 8/8 h	□ Yes □ Yes	□ No □ No
Diuresis < 4 mL/kg/h?	□ Yes	□ No	□ NA	Assess need for volume replacement Maintain / initiate vasopressin or desmopressin (IV)	□ Yes	□ No
Na^+ < 155 mEq/L?	□ Yes	□ No	□ NA	Correct and order laboratory control in 6 h	□ Yes	□ No
K^+ between 3.5 and 5.5 mEq/L?	□ Yes	□ No	□ NA	Correct and order laboratory control in 6 h	□ Yes	□ No
Mg^{++} > 1.6 mEq/L?	□ Yes	□ No	□ NA	Correct and order laboratory control in 6 h	□ Yes	□ No
Capillary glycaemia < 180 mg/dL?	□ Yes	□ No	□ NA	Insulin IV to maintain glycaemia between 140 and 180 mg/dL	□ Yes	□ No
Haemoglobin ≥ 7 g/dL?	□ Yes	□ No	□ NA	Transfuse red blood cells to Hb ≥ 7g/dL	□ Yes	□ No
Absence of infection?	□ Yes	□ No	□ NA	Initiate / maintain antibiotic therapy	□ Yes	□ No
Proper body temperature? - No vasopressor: Goal: 34-35ºC (after clinical tests)	□ Yes	□ No	□ NA	Get 34 to 35ºC if without vasopressor Get > 35ºC if with vasopressor	□ NA □ NA	□ Yes □ No □ Yes □ No

With vasopressor: > 35ºC

Nurse:_____ **Intensivist:**_____

CVP, central venous pressure; ΔPp, pulse pressure respiratory variation; ΔSV, stroke volume respiratory variation; FiO_2, fraction of inspired oxygen; Hb, haemoglobin; K+, potassium; MAP, mean arterial pressure; Mg++, magnesium; Na+, sodium; PEEP, positive end-expiratory pressure; SaO_2, arterial oxygen saturation; Vt, tidal volume.

Online Supplementary File 3. Family interview support guide.

PREPARING FOR THE FAMILY INTERVIEW	
GROUNDS: Establishing an aid relationship with family members **Triad: Respect, Empathy, and Authenticity**	
READ THE ACTIONS BELOW CAREFULLY BEFORE EACH STEP OF THE FAMILY INTERVIEW	
1. Arranging the location of the interview	□ Well-ventilated place or room □ Restricted access (avoid interferences) □ Enough space and chairs for all participants □ No barriers between interviewer and interviewee (e.g., table, chairs, etc.) □ Facial tissues and water are available □ Phones are turned off
2. Defining the interview participants	□ ICU physician □ Transplant co-ordinator and/or ICU nurse are present □ 1st*/2nd** degree relatives or legally authorised representative*** *1st degree relatives: father, mother, children, full siblings; **2nd degree relatives: grandparents, grandchildren; ***Legally authorised representative: Surrogate/ judicial (documented)[1]
3. Reviewing the components of non-verbal communication	□ Have all family members sitting down □ Leave land-line phones off the hook and turn off mobile phones □ Avoid crossing your arms or legs

	□ Have a trustful look and a serene expression □ Speak in a gentle voice □ Speak in a fine cadence, use pauses □ Tolerate periods of silence □ Give full attention to what family members say, "Listen more and talk less"
4. Reviewing the components of verbal communication	□ Greet everyone and introduce yourself □ Refer to the patient by his/her name □ Find out what the family knows about the case □ Ask family members what they want to know □ Summarise previous clinical data □ Use simple language, avoid unnecessary technical jargon □ Make your message clear, keep it short □ Acknowledge emotions and negative reactions □ Avoid expressions like "do not cry", "keep calm", "I know how you feel"

STEP 1 - FIRST FAMILY CONFERENCE

COMMUNICATING THE ESTABLISHMENT OF A BRAIN DEATH

PROTOCOL – 1st clinical examination

Key points of the first conference	□ **The ICU physician is responsible for** communicating about the possibility of death □ **Communicate the <u>possibility</u> of brain death to the family**

	- **DO NOT** talk about donation - Inform that **further tests** will be performed □ **Review** and **confirm** that the family understands what a suspected death is and that further tests will be performed □ **Make sure** the family knows how to reach you for questions
STEP 2 - SECOND FAMILY CONFERENCE **COMMUNICATING THE BRAIN DEATH – after 2 clinical tests and neuro-imaging evidence**	
Key points of the second conference	□ **The ICU physician is responsible for** communicating about the confirmation of brain death □ **Communicate the confirmation of brain death to the family** - Preferably use the word 'death' instead of the expression 'brain death'. (despite all efforts, unfortunately your loved one died...) □ **DO NOT** talk about donation □ **Wait silently** for the family's reactions and needs □ **Review** and **confirm** that the family understands that the patient is dead □ **Ask the family** if they have any questions
IMPORTANT: "Proceed to STEP 3 only after making sure that the family understands the death"	
STEP 3 - THIRD FAMILY CONFERENCE	

INTERVIEW FOR MULTI-ORGAN DONATION - after the family's understanding of the death	
Key points of the third conference	**Person leading the interview:** □ 1st option: IHTC/OPO member □ 2nd option: ICU physician or nurse **Aspects of the interview** □ Check whether the family **understands** the meaning of the diagnosis of brain death (understands that their loved one is dead) □ Explain to the family that the death occurred under **circumstances that allow them to help** other people by means of organ donation □ Ask the family if their loved one had expressed a wish in life to be an organ donor □ Offer the family, in view of this special situation, the opportunity to discuss about the possibility of organ donation (it is optional) □ **Make sure** the family knows how to reach you for questions
STEP 4 - PLANNING THE APPROACH ACCORDING TO THE FAMILY'S DECISION	
□ **FAMILY CONSENT FOR DONATION** **- Obtain the Family Consent Form**, fully and correctly completed	□ **FAMILY REFUSAL FOR DONATION**

- Complete the death certificate	**- Evaluate the possibility of a rescue interview** for donation after family conflicts have been resolved **- Consider withdrawing therapeutic support** "The physician is legally and ethically entitled to withdraw therapeutic support, including mechanical ventilation, and release the body to the family."[2] - Complete the death certificate

DEATH CERTIFICATE or FORENSIC MEDICAL EXAMINATION

ICU physician's responsibility

□ **NON-VIOLENT DEATH**	□ **VIOLENT DEATH**
- Complete the **"Death Certificate"** including the **date and time of death** and the data of the **last examination performed** (2nd clinical examination) **or** neuro-imaging evidence.	- Complete the **"Forensic Medical Examination Referral Form"** including the **date and time of death** and the data of the **last examination performed** (2nd clinical examination) **or** neuro-imaging evidence. - Request the Forensic Medical Institute for **AUTHORISATION TO REMOVE ORGANS OR TISSUES**

[1] Brazilian Federal Law No. 10211 of March 23, 2001;

[2] Brazilian Federal Board of Medicine – Resolution No. 1826 of December 6, 2007.

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym (yes, Title page)
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry (yes, Abstract and Methods)
	2b	All items from the World Health Organization Trial Registration Data Set (yes)
Protocol version	3	Date and version identifier (not applicable)
Funding	4	Sources and types of financial, material, and other support (yes, Funding statement)
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors (yes, Title page and Authors' contributions)
	5b	Name and contact information for the trial sponsor (yes, Funding statement)
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities (yes, Organisational aspects of the study)
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) (yes, Organisational aspects of the study)
Introduction		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention (yes, Introduction)
	6b	Explanation for choice of comparators (yes, Introduction)

Objectives	7	Specific objectives or hypotheses (yes, Introduction and Objectives)
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) (yes, Methods and analysis)
Methods: Participants, interventions, and outcomes		
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained (yes, Methods and analysis and Study planning and implementation schedule)
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) (yes, Methods and analysis)
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered) (yes, Methods and analysis)
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) (not applicable)
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) (yes, Methods and analysis)
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial (yes, Methods and analysis)
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended (yes, Methods and analysis)
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) (yes, Study planning and implementation schedule and Figure 1)
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations (yes, Methods and analysis)

Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size (yes, Methods and analysis)
Methods: Assignment of interventions (for controlled trials)		
Allocation:		
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions (yes, Methods and analysis)
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned (yes, Methods and analysis)
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions (yes, Methods and analysis)
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how (yes, Methods and analysis)
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial (unblinded study)
Methods: Data collection, management, and analysis		
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol (yes, Methods and analysis – complementary information will be available at the statistical analysis plan paper)
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols (yes, Methods and analysis – complementary information will be available at the statistical analysis plan paper)

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol (yes, Methods and analysis – complementary information will be available at the statistical analysis plan paper)
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol (yes, Methods and analysis – complementary information will be available at the statistical analysis plan paper)
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) (yes, Methods and analysis – complementary information will be available at the statistical analysis plan paper)
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) (yes, Methods and analysis – complementary information will be available at the statistical analysis plan paper)
Methods: Monitoring		
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed (yes, Methods and analysis)
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial (yes, Methods and analysis – complementary information will be available at the statistical analysis plan paper)
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct (yes, Methods and analysis – complementary information will be available at the statistical analysis plan paper)
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor (yes, Methods and analysis – complementary information will be available at the statistical analysis plan paper)
Ethics and dissemination		

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval (yes, Ethics and dissemination)
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) (yes, Ethics and dissemination)
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) (yes, Ethics and dissemination)
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable (not applicable)
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial (yes, Methods and analysis)
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site (conflict of interest forms)
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators (yes, Data sharing)
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation (not applicable)
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions (yes, Ethics and dissemination)
	31b	Authorship eligibility guidelines and any intended use of professional writers (not applicable)
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code (yes, Data sharing)
Appendices		
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates (not applicable)
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable (not applicable)

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

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

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Primary Subject Heading:	Intensive care
Secondary Subject Heading:	Intensive care
Keywords:	brain death, cardiac arrest, organ donation, checklist, quality improvement

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

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ABSTRACT

Introduction: There is an increasing demand for multi-organ donors for organ transplantation programmes. This study protocol describes the Donation Network to Optimise Organ Recovery Study (DONORS), a planned cluster randomised controlled trial that aims to evaluate the effectiveness of the implementation of an evidence-based, goal-directed checklist for brain-dead potential organ donor management in intensive care units (ICUs) in reducing the loss of potential donors due to cardiac arrest.

Methods and analysis: The study will include ICUs of at least 60 Brazilian sites with an average of >10 annual notifications of valid potential organ donors. Hospitals will be randomly assigned (with a 1:1 allocation ratio) to the intervention group, which will involve the implementation of an evidence-based, goal-directed checklist for potential organ donor maintenance, or the control group, which will maintain the usual care practices of the ICU. Team members from all participating ICUs will receive training on how to conduct family interviews for organ donation. The primary outcome will be loss of potential donors due to cardiac arrest. Secondary outcomes will include the number of actual organ donors and the number of organs recovered per actual donor.

Ethics and dissemination: The Institutional Review Board (IRB) of the Co-ordinating centre and of each participating site individually approved the study. We requested a waiver of informed consent for the IRB of each site. Study results will be disseminated to the general medical community through publications in peer-reviewed medical journals.

Keywords: brain death, cardiac arrest, organ donation, checklist, quality improvement

Trial registration: ClinicalTrials.gov, NCT03179020, registered June 7, 2017.

Strengths and limitations of this study

- This is the first randomised trial to evaluate whether a goal-directed checklist for the management of brain-dead potential organ donors may be useful in reducing cardiac arrests and contributing to increase organ availability for transplants.
- The preparation of the goal-directed checklist was preceded by the review of a clinical practice guideline following the Grades of Recommendation Assessment, Development and Evaluation (GRADE) system.
- Brazil is a country with a wide spectrum of demographic and socioeconomic scenarios; the diversity of institutions to be included in DONORS will allow us to provide results in a broad range of demographic and socioeconomic scenarios.
- Main study limitations are the unblinded design and the high heterogeneity of care and outcomes expected among centres in the study.

INTRODUCTION

Organ transplantation is the only treatment option for many patients affected by end-stage organ failure. Despite advances in the field of organ donation, the disparity between the number of patients on transplant waiting lists and the availability of organs for transplantation is increasing. Several parameters determine the availability of suitable organs for donation, and many of these depend on a successful sequence of actions by several healthcare professionals, starting with the identification of a potential multi-organ donor and ending with surgical organ procurement.[1-5] In this process, important factors contributing to the gap between organ supply and demand include failure to identify and report brain death, lack of family consent for organ donation, inaccurate perceptions of contraindications to organ donation, and haemodynamic instability that may compromise the quality of organs or even lead to loss of donors due to cardiac arrest.[1-3] A systematic application of clinical management strategies aimed at the haemodynamic stabilisation of brain-dead donors may contribute to an increase in the number of organs for transplantation by improving the quality of organs and reducing the loss of potential donors due to cardiac arrest.[1, 2, 4] In addition, other measures such as optimal ventilatory support and temperature control may improve the quality of organs, resulting in a higher organ recovery rate and better clinical outcomes for transplant recipients.[6, 7]

Checklists have an established role in healthcare to prevent omissions while performing complex procedures. A series of studies have shown that the use of a goal-directed checklist may help the systematic application of clinical guidelines, leading to greater adherence to evidence-based clinical interventions and improving clinical outcomes. Examples include the World Health Organisation (WHO) Surgical Safety Checklist, the Keystone Intensive Care Unit (ICU) Project checklist to prevent catheter-

related bloodstream infection, and clinical checklists to ensure patient safety in the ICU.[8-11]

There is a lack of evidence for the use of checklists regarding the clinical aspects of improving organ availability for transplantation of brain-dead donors. Some observational studies have reported that the application of a goal-directed checklist to guide the management of brain-dead potential organ donors may reduce the rate of cardiac arrest and increase the number of organs recovered per donor. [12-19] However, given the relatively small number of studies, their observational design and inconsistency of findings, often related with barriers to carrying out studies in this scenario [5], this literature cannot yet support the use of a goal-directed checklist in the current management of brain-dead potential organ donors [20].

Our hypothesis is that supporting the management of potential organ donors with the use of an evidence-based bedside checklist may reduce the loss of potential organ donors due to cardiac arrest and increase the number of donors and organs transplanted per donor. In this protocol, we describe the methods to be used in the Donation Network to Optimise Organ Recovery Study (DONORS).

OBJECTIVES

Primary objective

The primary objective is to evaluate the effectiveness of the implementation of an evidence-based bedside checklist, containing goals and recommendations of care as guidance for the management of brain-dead potential organ donors, in reducing potential organ donor losses due to cardiac arrest.

Secondary objectives

Secondary objectives are to assess whether the evidence-based, goal-directed checklist is effective in (a) increasing the number of actual organ donors and (b) increasing the number of organs recovered per actual donor.

METHODS AND ANALYSIS

The protocol is registered at ClinicalTrials.gov (NCT03179020) and the present manuscript provides additional details regarding study design and methodology. The items from the Word Health Organization trial registration data set are described in the Online Supplementary File 1.

Study design

DONORS is a parallel cluster randomised controlled trial involving ICUs of Brazilian hospitals. We will randomly assign hospitals to the intervention group, comprising the checklist implementation, or the control group, consisting of usual care in each ICU (Figure 1).

Participants

Cluster eligibility, recruitment and exclusion criteria

We will invite adult ICUs with an average of at least 10 annual notifications of potential organ donors in the prior two years. Information regarding notifications is provided by the Brazilian National Transplant System.

Coronary care units, intermediate care units and emergency departments are not eligible. We will also exclude institutions that already systematically use checklists as guidance for the management of potential organ donors supported by implementation

tools, such as guidelines and clinical decision algorithms for bedside use, in print or digital form.

Patient eligibility and exclusion criteria

We will screen and include consecutive brain-dead potential organ donors, as confirmed by the first clinical examination consistent with having brain death, within the age range of 14 to 90 years. Only ICU patients will be included; potential donors outside the ICU will be included in the study if admitted to ICU within three hours of initial assessment.

Diagnosis of brain death will be made according to the Brazilian Federal Board of Medicine guidance, consisting of: two clinical examinations performed by two different physicians, in an interval of at least 1 hour between the examinations, and one apnoea test followed by neuro-imaging (transcranial Doppler, cerebral arteriography, electroencephalography, or brain scintigraphy).[21, 22] We will exclude brain-dead patients who are not candidates for organ donation (Online Supplementary File 2).

Interventions

Checklist for brain-dead potential organ donors management

After a preliminary prospective study [13] that found a positive impact of a clinical goal-directed protocol on reducing irreversible cardiac arrests in brain-dead potential organ donors, an updated checklist was generated after drawing up a clinical practice guideline (CPG) for brain-dead potential organ 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 four 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 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. 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.

Usual care

ICUs in the control group will continue with their usual management of potential organ donors. They will not be informed of the items assessed in the goal-directed checklist or the strategies to enhance compliance.

Co-interventions

All ICU teams and IHTC members of the participating institutions will receive training in family interviews for organ donation. The training and interview process have been based primarily on the Spanish model of Communication in Critical Situations (Online Supplementary File 4).[27-31] Training consists of two components: (1) face-to-face training of one ICU team representative and one IHTC member of each institution; and (2) provision of an online, self-instructional course for all ICU team members and IHTC members participating in the study (Table 1). These co-interventions aim to standardise ICU strategies in relation to family interviews, reducing variability between participating sites. This is important for the trial due to three main reasons: (a) inadequate interviews may result in a lower rate of effective donation (secondary outcomes of the study), independently of potential donor management; (b) reducing variability between participating sites may have an impact on reducing the intra-cluster correlation of the study, increasing its power; and (c) training strategies might enhance the engagement of the participating sites, especially those in the control group, thereby balancing a potential Hawthorne effect. Table 1 shows the strategies to promote effective implementation of intervention and co-intervention.

Table 1. Strategies to maximise adherence to study interventions and co-interventions.

Strategies
1. In-person training of two representatives (study co-ordinators) from each participating site on the conduct of family interviews.
2. Provision of an online course for the training of all intensive care unit (ICU) team members and Intra-Hospital Transplant Co-ordination (IHTC) members on how to prepare for and conduct a family interview. A family interview support guide will also be made available.
3. On-site training of ICU team members and IHTC members of all hospitals in the intervention group. The training aims to provide guidance on the methods for administration of the goal-directed checklist for the management of potential organ donors to as many ICU and IHTC professionals as possible.
4. 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.
5. The local co-ordinators of the participating sites will be contacted by the study central office co-ordinators whenever there is a failure to adhere to the protocol or to complete the patient's clinical record form.
6. The local co-ordinators of the participating sites will receive, whenever a patient is included, electronic messages to remind them of the need to administer the bedside goal-directed checklist and prompt the medical team on management during the stay of potential organ donors in the ICU.
7. Remote support from the study co-ordinators and central office will be made available to all local co-ordinators for any questions related to the study.

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Sample size

With 60 ICUs, we will need to include 19 brain-dead potential organ donors per site (1,140 potential donors) to detect an absolute reduction of donor losses due to cardiac arrests of 10% (from 28% in the control group to 18% in the intervention group)[13], considering an intra-class correlation coefficient (ICC) of 0.05, power of 80%, and a two-sided alpha level of 5%. 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.

Randomisation

We will randomly assign ICUs to the intervention group or control group with a 1:1 allocation ratio using blocks of variable sizes (2 and 4) and stratified by the estimated annual number of notifications of brain death in each site (sites with ≤ 29 and > 29). ICUs from the same institution are not considered independent clusters to avoid contamination. We will randomise the ICUs consecutively as per the date of authorisation of the principal investigator to implement the study in the institution, obtained after the Institutional Review Board (IRB) approval. To ensure allocation concealment, a statistician from the study co-ordinating office will be responsible for the randomisation process, with all researchers involved in the trial blinded to the allocation sequence.

Outcomes

The primary outcome will be the number of brain-dead potential organ donor losses due to cardiac arrest, defined as any loss of brain-dead potential organ donors

from irreversible or unreversed cardiac arrest that occurs after patient enrolment, while the subject remains eligible for organ donation (no contraindications, family approval or waiting family decision for donation). Losses of potential donors due to other factors (e.g., family refusal or contraindication to organ donation after patient inclusion) will not be considered for this outcome.

The secondary outcomes will be:

1) number of actual organ donors, indexed to brain-dead potential donors, defined as donors for whom the surgical procedure for organ recovery has been initiated (irrespective of organ recovery)[3];

2) number of solid organs recovered per actual donor (ranging from zero to seven organs per donor, as follows: liver; heart; pancreas; two lungs; and two kidneys).

The tertiary outcomes will include:

1) the proportion of potential donors with adequate respiratory parameters (defined as PaO_2 / FiO_2 ratio ≥ 200);

2) 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);

3) 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);

4) organ dysfunction score, assessed by the Sequential Organ Failure Assessment (SOFA) Score.

Blinding

Due to the nature of the intervention, it will not be possible to blind investigators or healthcare providers in this study. However, we will not disclose details of the content of the checklist to the control group.

Data collection

An ICU healthcare professional or an IHTC member will collect the data, which will be recorded at the patient's bedside using a printed case report form and subsequently transferred into an electronic data capture system (REDCap, Vanderbilt University, Tennessee, USA).[32] Investigators will receive training for these activities during the study initiation meeting.

Data monitoring

The study statistician will be responsible for reviewing weekly data on all inclusions, checking data consistency, and checking whether all forms have been completed correctly. Clinical research monitors will review all data collected and may require supplementation or correction of inconsistent data according to the Good Clinical Practices (GCP) recommended by the International Council for Harmonisation (ICH).[33] On-site monitoring visits will take place after the fifth patient inclusion in the site and when 100% of the projected number of inclusions for the site has been achieved. Additional monitoring visits will be performed as needed, based on the detection of data inconsistencies, errors in completing the forms, or suspected fraud. Periodic remote follow-up will be performed via telephone or electronic messages with the participating sites according to patient recruitment. The data to be collected from each subject are summarised in Table 2.

322 **Table 2**. Data to be entered in the clinical record form of all potential organ donors
323 included in the study.

1. Identification of the potential donor: research centre code and patient's hospital registration number, sex, and date of birth.
2. Screening: inclusion and exclusion criteria for definition of eligibility.
3. History: date and time of hospital admission, date and time of ICU admission, reported and estimated weight, height, SAPS 3 on ICU admission, comorbidities prior to hospitalisation, cause of brain death, date and time of 1st clinical examination for the diagnosis of brain death.
4. Respiratory variables: tidal volume, mL; respiratory rate, mpm; PEEP, cm H_2O; plateau pressure, cm H_2O; peak pressure, cm H_2O (if volume is controlled); FiO_2, % Blood gas variables: PaO_2, mm Hg; SaO_2, %; $PaCO_2$, mm Hg; base excess, mmol/dL; PvO_2, mm Hg; SvO_2, %; $PvCO_2$, mm Hg; lactate, mmol/dL.
5. Temperature and haemodynamic variables: temperature, °C; heart rate, bpm; systolic blood pressure, mm Hg; diastolic blood pressure, mm Hg; CVP, mm Hg and/or ΔPp, % and/or ΔSV, % and/or IVCCI, %; cardiac arrhythmias.
6. Diuresis and fluid balance: infused volume; diuresis and fluid balance at different time intervals.
7. Laboratory variables: haemoglobin, g/dL; creatinine, mg/dL; platelets, /mm^3; bilirubin, mg/dL; sodium, mEq/L; potassium, mEq/L; magnesium, mEq/L; phosphorus, mEq/L; calcium, mEq/L.
8. Drug use: noradrenaline; dopamine; vasopressin; desmopressin; corticosteroids; antibiotics.
9. Family interview: time, place and name of the professional communicating the establishment of a brain death protocol to the family; time, place and name of the

professional communicating the death to the family; time, place and name of the professional conducting the family interview with the request for organ donation; experience and qualification of the professional conducting the family interview with the request for organ donation; family authorization for organ donation; loss of potential donor due to family refusal; causes of family refusal.

10. Protocol completion: date and time of 2nd clinical examination for the diagnosis of brain death; date and time of a complementary test for the diagnosis of brain death; complementary test performed for the diagnosis of brain death.
11. Occurrence of cardiac arrest, loss of potential donor due to cardiac arrest, completion of organ harvesting, number and type of organs recovered.

CVP, central venous pressure; ΔPp, pulse pressure respiratory variation; ΔSV, stroke volume respiratory variation; FiO_2, fraction of inspired oxygen; ICU, intensive care unit; PaO_2, arterial partial pressure of oxygen; $PaCO_2$, arterial partial pressure of carbon dioxide; PvO_2, venous partial pressure of oxygen; $PvCO_2$, venous partial pressure of carbon dioxide; PEEP, positive end-expiratory pressure; SAPS 3, Simplified Acute Physiology Score 3; SaO_2, arterial oxygen saturation; SvO_2, venous oxygen saturation; IVCCI, inferior vena cava collapsibility index.

Statistical analysis

We will prepare a detailed statistical analysis plan before data analysis, which is intended to be published or made available online. We will perform the statistical analysis following the intention-to-treat principle, accounting for cluster design, with observations of the ICUs analysed according to the group to which they have been allocated. We will examine the normality of data by visual inspection of histograms and using the Shapiro–Wilk test for normality. Baseline characteristics of both the ICUs and potential organ donors will be presented as frequencies and percentages, means and standard deviation (SD), and medians and interquartile range (IQR), whenever appropriate, for the intervention group and control group.

For the primary outcome, we will calculate hazard ratios (HR) considering the time to the outcome, since patients will be subjected to management at different time intervals in the institutions. Patients will be considered at risk for the occurrence of the outcome of interest while under consideration as potential donors. If the outcome of interest does not occur, patients' follow-up will be considered to have ended at the time their management has been discontinued (family refusal or contraindication to donation). We will conduct predefined subgroup analyses, considering the following variables: age > 60 years; cause of the injury leading to potential brain death (traumatic or non-traumatic); and patient severity on ICU admission defined by the Simplified Acute Physiology Score 3 (SAPS 3) with a cut-off determined by its median. We will conduct sensitivity analyses of adherence to the intervention (compliance with checklist proposed measures) and of the time interval between the first clinical examination consistent with having brain death and inclusion in the study.

For secondary and tertiary outcomes, we will use models for correlated data, considering the ICU as a cluster and each outcome with its own probability distribution. We will conduct a sensitivity analysis of the outcome 'number of solid organs recovered per actual donor', considering the number of kidneys harvested. We will analyse secondary outcomes by adjusting for multiple hypothesis testing. For all statistical comparisons, we will adopt a statistical significance level of 0.05. An up-to-date version of the R programme (R Development Core Team) will be used to conduct analyses.

Study planning and implementation schedule

We finalised the study design and protocol in March 2016. The National Study Investigators Meetings were held in two parts: 9–10 March 2017 and 8–9 June 2017. At the time of manuscript preparation, 63 ICUs representative of the Brazilian geopolitical

territory are currently recruiting study subjects (Figure 3). On-site training started on June 1, 2017. We expect that the recruitment will be completed in December 2019. The list of sites included is available at ClinicalTrials.gov (NCT03179020).

Organisational aspects of the study

The study is sponsored and co-ordinated by the Moinhos de Vento Hospital, Brazil, in partnership with the Brazilian Ministry of Health through the Programme of Institutional Development of the Brazilian Unified Health System (PROADI-SUS) and in association with the General Co-ordination Office of the National Transplant System (CGSNT) and the Brazilian Research in Intensive Care Network (BRICNet). The study is supported by the AMIB Committee for Organ Donation for Transplant, ABTO, the Spanish National Transplant Organisation (ONT), and the organ procurement organisations (OPOs) of the states of Santa Catarina and Rio Grande do Sul. The study Steering Committee consists of intensivists, transplant co-ordinators and epidemiologists with expertise in conducting multi-centre studies. The committee is involved in the conception and design of the study, supervision of progress and procedures during the study, and writing of the study report and any resulting study manuscript.

Ethics and dissemination

The study was designed in accordance with resolution No. 466/2012 of the Brazilian National Health Council/Ministry of Health, the Declaration of Helsinki, the Document of the Americas, and the ICH/GCP E6(R2) 2016 [33]. The study was approved by the IRB of the Co-ordinating Centre (No. 53999616.0.1001.5330) and by the IRB of each participating site (Online Supplementary File 5). Participating in the

intervention or control groups does not imply any risk for the subjects included, since the groups will not be deprived of the application of the most up-to-date recommendations. Because obtaining written informed consent from patients' family members entails operational and methodological difficulties, and would have a potential negative impact on organ donation as well, we requested a waiver of informed consent for the IRB of each participating site.

This trial, regardless of the results, will be published in a peer-reviewed medical journal and presented in scientific conferences and scientific meetings involving the representatives of each participating hospital, of each Brazilian state transplant centre, and of the Brazilian Ministry of Health.

Patient and Public Involvement

Considering the characteristics of the study population, the patients were not directly involved in the research question, study design, study participants recruitment and study conduction.

DISCUSSION

Despite the existence of CPGs that currently provide recommendations for a 'standard of care' in the management of potential organ donors,[23,29] they are not always implemented, resulting in the risk of loss of specific organs due to management failures or even multiple organ loss due to cardiac arrest of the potential donor.[1-4, 23, 34] CPGs usually do not have an impact on bedside practice in the short term, as they rarely take into account clinical applicability.[35] Therefore, a CPG-based goal-directed checklist associated with a clinician prompting system may be an effective approach to improve physician adherence to CPG recommendations. Physician-centred healthcare

can be associated with non-adherence to basic recommendations of care, especially in highly complex processes, such as the management of potential organ donors.[34] In this context, we expect that these organisational adjustments, supported by a checklist-based management strategy, will have a positive impact on organ donation.

Patel et al.[19] published the results of 671 multi-organ donors managed using a goal-directed checklist in the United States. The predetermined goals were met in 45% of cases prior to organ recovery, and the use of the goal-directed checklist significantly increased the number of organs transplanted per donor.[19] Recently, we published a prospective observational study that involved 27 ICUs in a southern Brazilian state demonstrating that the use of a goal-directed checklist to guide the management of deceased donors reduces brain-dead potential organ donor losses due to cardiac arrest.[13] Compliance with the checklist increased after the start of the study from 52.1% to 85.8% ($p < 0.001$). The use of the checklist was associated with a lower likelihood of occurrence of cardiac arrest (odds ratio [OR]: 0.30, 95% CI: 0.18-0.49, $p < 0.001$) and an increase in the number of organs recovered per donor.[13] Although these results are encouraging and reproduce the observations of other authors, the observational nature of the studies provides only weak evidence on the subject.[14-19]

The study design and basis for the implementation of DONORS may provide new insights that can help overcome the weaknesses of previous observational studies, often related with barriers to conduct studies in deceased organ donors.[5] The cluster randomisation design will limit selection biases, and we will count on a large number of ICUs, which are responsible for a significant amount of brain death notifications throughout Brazil. The DONORS design will include the evaluation of the effectiveness of a goal-directed checklist strategy in different socioeconomic scenarios in Brazil, allowing us to provide real-world evidence to support the practical clinical applicability

of the study findings. In addition, the trial is testing the effectiveness of the proposed intervention by means of an implementation strategy that may be considered feasible to replicate in different settings. Finally, the characteristics of the institutional quality improvement programme of this protocol will allow the potential benefits generated by the proposed study model to be incorporated into ICUs and ultimately transferred to other clinical areas for the care of critically ill patients.

The implementation of a goal-directed checklist for the management of potential donors is a complex intervention, with multiple components. It is important to state that, as in most quality improvement studies, how the intervention is implemented is crucial to the interpretation of the results. In this respect, through this protocol, we aimed to describe in detail all the interventions and co-interventions proposed in the study in order to allow reproducibility of our procedures in other settings. In addition, the logic model presented in the study (Figure 2) is intended to explore the relationships between the activities proposed in the intervention and the mediators of the effect, such as improved clinical management of potential donors and enhanced communication with the ICU team about the expected outcomes. Also important is that, although the study focuses on assessing short-term outcomes in potential donors (e.g., cardiac arrest and number of organs recovered), potential beneficial outcomes are expected for transplant recipients, such as improved graft function, survival and quality of life.

Our study has some limitations. First, high variability in care and outcomes among institutions is expected. Although the chosen ICC may be considered conservative, there are no estimates in the literature for the proposed intervention, which may result in lack of power if the actual ICC is larger than the estimate. In spite of the procedures to avoid the transfer of information about the checklist to ICUs in the control group, although with low probability this possibility should be considered,

thereby exposing the details of the content of the goal-directed checklist for the control group. Furthermore, although stratified randomisation is planned for this study, we must take into consideration the differences in the number of brain death notifications among ICUs, which will recruit patients at different rates, which in turn may generate learning curves that may have an impact on the final cluster randomisation trial results. In order to minimise this problem, we are allowing a maximum of 30 patients to be recruited per each study site; however, some ICUs may recruit a small number of patients. Inadequate adherence to the checklist may have an impact on the results observed in the intervention group, showing no effect that may be either due to lack of efficacy of the intervention or due to its suboptimal implementation. Another important aspect to highlight is that, although we expect to see an improvement in the quality of organs with the use of the checklist, therefore improving outcomes for organ-transplant recipients, we are limiting the data collection and study procedures to potential donors, not allowing direct assumptions about its possible effects. 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 sites. On the other hand, the results may contribute as an indirect evidence for the management of patients who have a CBI.

CONCLUSIONS

We expect that the results from DONORS will provide information regarding the practical use of checklist-guided management interventions for potential multi-organ donors that may contribute to reducing potential donor losses due to cardiac arrest or other relevant outcomes. At this time, with the increasing demand for organs for transplantation, standardised, evidence-based guidelines that may be adopted globally by ICUs and by transplant co-ordinators are needed to improve the availability and

quality of organs available for donation. The evidence generated by this trial will have great potential to contribute positively to the donation of organs.

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Authors' contributions

All authors contributed to the study design and revised this manuscript: GAW, CCR, ABC, FRM, RGR, CT, JA, CAF, LCPA, FAB, CMG, DBS, DS, DZP, ICM, AIR, SSS, NEG, LVA, PSB, FRR, MFRBM, TBP, CMCG, PCD, JFPO, GCM, FACA, RBM, VN, LSH, MOM, RRN, and MF. Additionally, GAW, FRM, and ABC conceived the study, RGR, CT, LCPA, FAB, LSH, and MF also helped with the study design, and GAW drafted the first version of the article. JA, CAF, and RRN, helped with centre recruitment and with the co-intervention aspects. GAW, JA, CMG and DBS co-ordinated educational actions for the intervention. NEG, DS, MF, RGR, CCR, and ABC planned epidemiological and statistical aspects of the study, CMG, ICM, and DZP designed the study manuals and study tools, ICM and CMG led site management, ICM, LAV, CMG, AIR, and SSS visited all sites to provide training, and CCR, ICM, CMG, PSB, and DZP organized the study meetings. All authors read and approved the final manuscript.

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Data sharing

The datasets used and/or analysed during the current study will be available from the corresponding author on reasonable request.

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FIGURE LEGENDS

Figure 1. Study flow diagram.

IRB, Institutional Review Board; No., number

Figure 2. Logic model for the checklist intervention.

Figure 3. Geographical distribution of the participating intensive care units in Brazil. (map base copyright obtained from www.gettyimages.pt).

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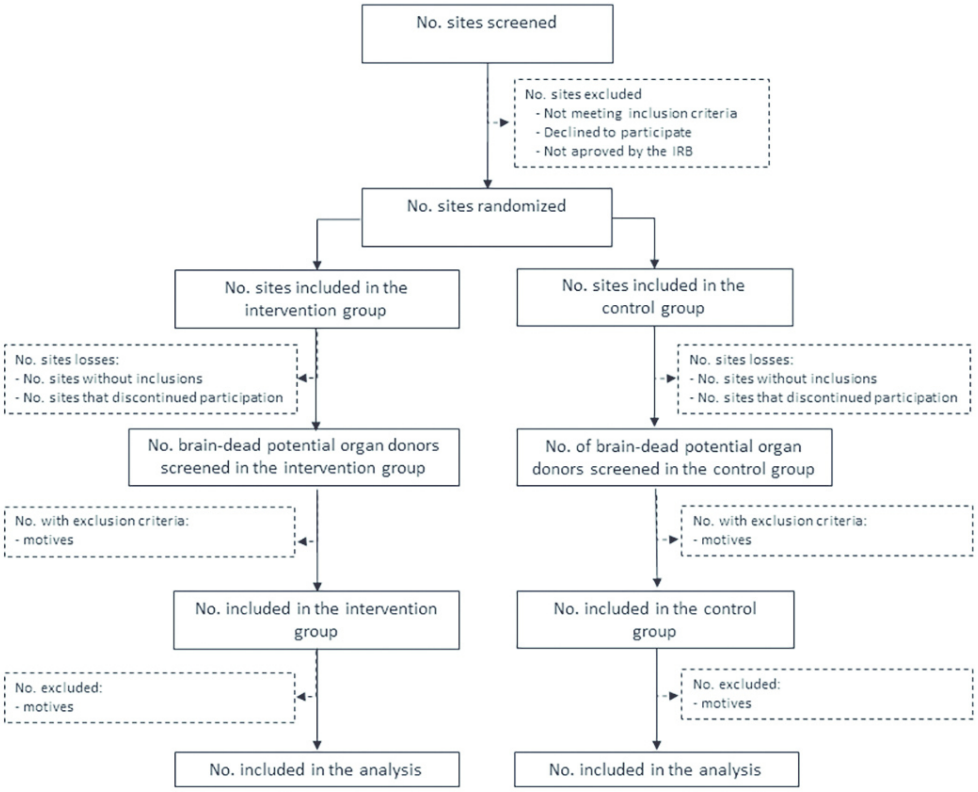

Study flow diagram.
IRB, Institutional Review Board; No., number

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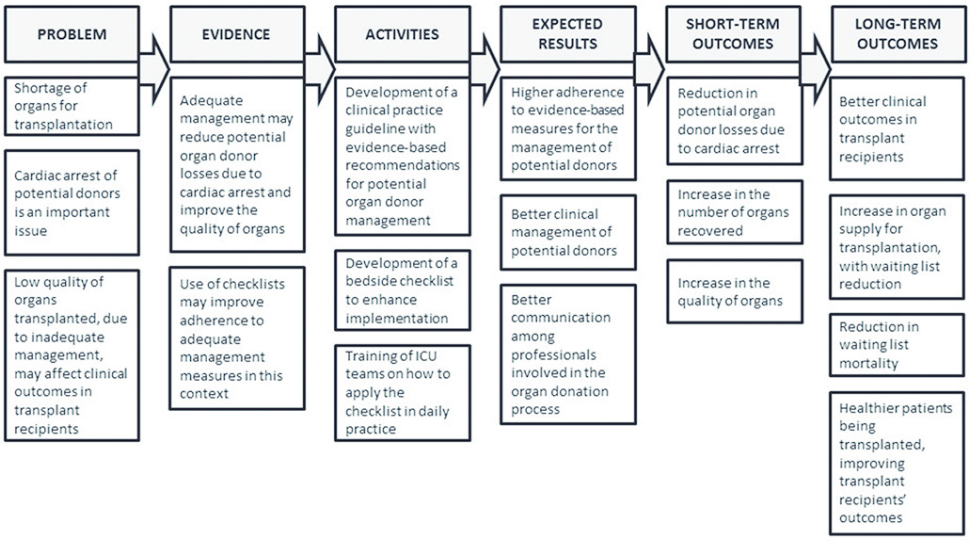

Logic model for the checklist intervention.

90x90mm (300 x 300 DPI)

Geographical distribution of the participating intensive care units in Brazil.
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90x90mm (300 x 300 DPI)

Online Supplementary File 1. Items from the World Health Organisation Trial Registration Data Set.

DATA CATEGORY	INFORMATION
Primary registry and trial identifying number	ClinicalTrials.gov NCT03179020
Registry name	Donation Network to Optimize Organ Recovery Study (DONORS)
Date of registration in primary registry	June 7, 2017
Secondary identifying numbers	CAAE 53999616.0.1001.5330
Source of monetary or material support	The present study was funded by the Brazilian Ministry of Health through the Programme of Institutional Development of the Brazilian Unified Health System (PROADI-SUS).
Primary sponsor	Brazilian Ministry of Health
Secondary sponsor	Brazilian Ministry of Health
Contact for public queries	Glauco Westphal, MD, PHD: Rua Ramiro Barcelos, 910. Postal code: 90035-001 - Porto Alegre, RS, Brazil. E-MAIL: glauco.ww@gmail.com Tel.: +55-51-3314.3385
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Public title	Donation Network to Optimise Organ Recovery Study (DONORS)
Scientific title	Implementation of an evidence-based checklist for potential brain-dead donor organ management in intensive care units (ICUs): a cluster randomised trial
Countries of recruitment	Brazil
Health conditions or problems studied	Brain death Organ donation
Interventions	1) Active comparator: management of the potential donor guided by the use of an evidence-based checklist. This checklist is based on main recommendations of the Brazilian guideline for the management of potential multiple organ donors. 2) Control comparator: management of the potential donor according to usual care.
Key inclusion and exclusion criteria	1) For ICUs Inclusion criteria: adult ICUs reporting at least 10 valid potential donors (without clinical contraindications for donation) per year. Exclusion criteria: coronary care units, intermediate care units, emergency departments, ICUs that already use checklists for the management of potential donors.

	2) For potential donors Inclusion criteria: age of 14 years or older, suspected brain death after the first clinical test. Exclusion criteria: age > 90 years, HIV, metastatic cancer, uncontrolled sepsis, acute hepatitis, malaria, acute viral infections, cryptococcal meningoencephalitis and prion diseases, active tuberculosis treated for <2 months, colonisation of the donor by bacteria without any option of antibiotic treatment, history of breast tumour, melanoma, soft tissue sarcoma or haematologic neoplasia, WHO Group 3 primary tumours.
Study type	Interventional Allocation: randomized Intervention model: parallel Masking: open label Primary purpose: prevention
Date of first enrolment	20th June 2017
Target sample size	1200 potential donors
Recruitment status	Recruiting
Primary outcome	Losses of potential donors due to cardiac arrest
Key secondary outcomes	Proportion of effective organ donors, number of organs recovered per effective donor

Online Supplementary File 2. Exclusion criteria of brain-dead potential organ donors from the study.

Age	Infection	History of cancer
Age > 90 years.	HIV, HTLV-I and II, Uncontrolled sepsis, Acute hepatitis, Malaria, Acute viral infections (e.g., rubella, rabies, West Nile virus, adenovirus, enterovirus, parvovirus, and viral meningoencephalitis or of unknown cause), Cryptococcal meningoencephalitis, Prion diseases, Active tuberculosis with < 2 months of treatment, Bacterial colonisation of the donor without antibiotic treatment options (resistant to all antibiotics).	Metastatic cancer, Breast tumours, Melanoma, Soft-tissue sarcoma, Haematological malignancy, Primary tumours of the central nervous system – Group 3 (anaplastic astrocytoma – grade III, glioblastoma multiforme, medulloblastoma, anaplastic oligodendroglioma – Schmidt C and D, malignant ependymoma, pineoblastoma, anaplastic/malignant meningioma, intracranial sarcoma, germ cell tumour – except well-differentiated teratoma, chordoma, and primary cerebral lymphoma).

Online Supplementary File 3. English translation of the final version of the bedside checklist.

Name: _____

Date and time of 1st clinical examination consistent with brain death: _____/_____/_____ _____:_____

Current date and time: _____/_____/_____ _____:_____

GOALS TO BE ACHIEVED	STATUS			IMMEDIATE ACTIONS WHEN STATUS = "NO"	ACTION TAKEN?	
$SaO_2 \geq 90\%$?	□ Yes	□ No	□ NA	Adjust FiO_2 and/or PEEP to $SaO_2 \geq 90\%$	□ Yes	□ No
Vt of 6 to 8 mL/kg of predicted weight?	□ Yes	□ No	□ NA	Adjust Vt to 6 to 8 mL/kg	□ Yes	□ No
PEEP ≥ 8 cm H_2O?	□ Yes	□ No	□ NA	Adjust PEEP to ≥ 8 cm H_2O	□ Yes	□ No
MAP ≥ 65 mmHg and good tissue perfusion after crystalloid bolus?	□ Yes	□ No	□ NA	Continue fluid infusion while there is volume responsiveness (ex.: ΔPp ≥ 13% / ΔMAP ≥ 8% / ΔSV ≥ 10% / CVP < 8 mmHg)	□ Yes	□ No
MAP ≥ 65 mmHg and good tissue perfusion after volume adjustment?	□ Yes	□ No	□ NA	Maintain / initiate noradrenaline (dopamine if bradycardia)	□ Yes	□ No

Vasopressin and hydrocortisone were associated after maintaining / initiating noradrenaline / dopamine?	□ Yes	□ No	□ NA	Add vasopressin (1 IU bolus + 0.5-2.4 IU / h) and Add hydrocortisone 100 mg 8/8 h	□ Yes □ Yes	□ No □ No
Diuresis < 4 mL/kg/h?	□ Yes	□ No	□ NA	Assess need for volume replacement Maintain / initiate vasopressin or desmopressin (IV)	□ Yes	□ No
Na^+ < 155 mEq/L?	□ Yes	□ No	□ NA	Correct and order laboratory control in 6 h	□ Yes	□ No
K^+ between 3.5 and 5.5 mEq/L?	□ Yes	□ No	□ NA	Correct and order laboratory control in 6 h	□ Yes	□ No
Mg^{++} > 1.6 mEq/L?	□ Yes	□ No	□ NA	Correct and order laboratory control in 6 h	□ Yes	□ No
Capillary glycaemia < 180 mg/dL?	□ Yes	□ No	□ NA	Insulin IV to maintain glycaemia between 140 and 180 mg/dL	□ Yes	□ No
Haemoglobin ≥ 7 g/dL?	□ Yes	□ No	□ NA	Transfuse red blood cells to Hb ≥ 7g/dL	□ Yes	□ No
Absence of infection?	□ Yes	□ No	□ NA	Initiate / maintain antibiotic therapy	□ Yes	□ No
Proper body temperature? - No vasopressor: Goal: 34-35ºC (after clinical tests)	□ Yes	□ No	□ NA	Get 34 to 35ºC if without vasopressor Get > 35ºC if with vasopressor	□ NA □ NA	□ Yes □ No □ Yes □ No

With vasopressor: > 35ºC

Nurse:_____ **Intensivist:**_____

CVP, central venous pressure; ΔPp, pulse pressure respiratory variation; ΔSV, stroke volume respiratory variation; FiO_2, fraction of inspired oxygen; Hb, haemoglobin; K+, potassium; MAP, mean arterial pressure; Mg++, magnesium; Na+, sodium; PEEP, positive end-expiratory pressure; SaO_2, arterial oxygen saturation; Vt, tidal volume.

Online Supplementary File 4. Family interview support guide.

PREPARING FOR THE FAMILY INTERVIEW	
GROUNDS: Establishing an aid relationship with family members **Triad: Respect, Empathy, and Authenticity**	
READ THE ACTIONS BELOW CAREFULLY BEFORE EACH STEP OF THE FAMILY INTERVIEW	
1. Arranging the location of the interview	□ Well-ventilated place or room □ Restricted access (avoid interferences) □ Enough space and chairs for all participants □ No barriers between interviewer and interviewee (e.g., table, chairs, etc.) □ Facial tissues and water are available □ Phones are turned off
2. Defining the interview participants	□ ICU physician □ Transplant co-ordinator and/or ICU nurse are present □ 1st*/2nd** degree relatives or legally authorised representative*** *1st degree relatives: father, mother, children, full siblings; **2nd degree relatives: grandparents, grandchildren; ***Legally authorised representative: Surrogate/ judicial (documented)[1]
3. Reviewing the components of non-verbal communication	□ Have all family members sitting down □ Leave land-line phones off the hook and turn off mobile phones □ Avoid crossing your arms or legs

	□ Have a trustful look and a serene expression □ Speak in a gentle voice □ Speak in a fine cadence, use pauses □ Tolerate periods of silence □ Give full attention to what family members say, "Listen more and talk less"
4. Reviewing the components of verbal communication	□ Greet everyone and introduce yourself □ Refer to the patient by his/her name □ Find out what the family knows about the case □ Ask family members what they want to know □ Summarise previous clinical data □ Use simple language, avoid unnecessary technical jargon □ Make your message clear, keep it short □ Acknowledge emotions and negative reactions □ Avoid expressions like "do not cry", "keep calm", "I know how you feel"

STEP 1 - FIRST FAMILY CONFERENCE

COMMUNICATING THE ESTABLISHMENT OF A BRAIN DEATH PROTOCOL – 1st clinical examination

Key points of the first conference	□ **The ICU physician is responsible for** communicating about the possibility of death □ **Communicate the <u>possibility</u> of brain death to the family**

	- **DO NOT** talk about donation - Inform that **further tests** will be performed □ **Review** and **confirm** that the family understands what a suspected death is and that further tests will be performed □ **Make sure** the family knows how to reach you for questions
STEP 2 - SECOND FAMILY CONFERENCE **COMMUNICATING THE BRAIN DEATH – after 2 clinical tests and neuro-imaging evidence**	
Key points of the second conference	□ **The ICU physician is responsible for** communicating about the confirmation of brain death □ **Communicate the confirmation of brain death to the family** - Preferably use the word 'death' instead of the expression 'brain death'. (despite all efforts, unfortunately your loved one died...) □ **DO NOT** talk about donation □ **Wait silently** for the family's reactions and needs □ **Review** and **confirm** that the family understands that the patient is dead □ **Ask the family** if they have any questions
IMPORTANT: "Proceed to STEP 3 only after making sure that the family understands the death"	
STEP 3 - THIRD FAMILY CONFERENCE	

INTERVIEW FOR MULTI-ORGAN DONATION - after the family's understanding of the death	
Key points of the third conference	**Person leading the interview:** □ 1st option: IHTC/OPO member □ 2nd option: ICU physician or nurse **Aspects of the interview** □ Check whether the family **understands** the meaning of the diagnosis of brain death (understands that their loved one is dead) □ Explain to the family that the death occurred under **circumstances that allow them to help** other people by means of organ donation □ Ask the family if their loved one had expressed a wish in life to be an organ donor □ Offer the family, in view of this special situation, the opportunity to discuss about the possibility of organ donation (it is optional) □ **Make sure** the family knows how to reach you for questions
STEP 4 - PLANNING THE APPROACH ACCORDING TO THE FAMILY'S DECISION	
□ **FAMILY CONSENT FOR DONATION** **- Obtain the Family Consent Form**, fully and correctly completed	□ **FAMILY REFUSAL FOR DONATION**

- Complete the death certificate	**- Evaluate the possibility of a rescue interview** for donation after family conflicts have been resolved **- Consider withdrawing therapeutic support** "The physician is legally and ethically entitled to withdraw therapeutic support, including mechanical ventilation, and release the body to the family."[2] - Complete the death certificate

DEATH CERTIFICATE or FORENSIC MEDICAL EXAMINATION

ICU physician's responsibility

□ **NON-VIOLENT DEATH**	□ **VIOLENT DEATH**
- Complete the **"Death Certificate"** including the **date and time of death** and the data of the **last examination performed** (2nd clinical examination) **or** neuro-imaging evidence.	- Complete the **"Forensic Medical Examination Referral Form"** including the **date and time of death** and the data of the **last examination performed** (2nd clinical examination) **or** neuro-imaging evidence. - Request the Forensic Medical Institute for **AUTHORISATION TO REMOVE ORGANS OR TISSUES**

[1] Brazilian Federal Law No. 10211 of March 23, 2001;

[2] Brazilian Federal Board of Medicine – Resolution No. 1826 of December 6, 2007.

Online Supplementary File 5. Sites and Institutional Review Board approval number.

SITE (Brazilian city, estate)		INSTITUTIONAL REVIEW BOARD	APPROVAL NUMBER
Co-ordinating centre: Hospital Moinhos de Vento –(Porto Alegre, Rio Grande do Sul)		HOSPITAL MOINHOS DE VENTO – HMV	53999616.0.1001.5330
1	Hospital Alberto Urquiza Wanderley (João Pessoa, Paraíba)	HOSPITAL MOINHOS DE VENTO – HMV	53999616.0.2031.5330
2	Hospital Beneficência Portuguesa de São Paulo (São Paulo, São Paulo)	HOSPITAL BENEFICÊNCIA PORTUGUESA DE SÃO PAULO	53999616.0.2037.5483
3	Hospital Bom Jesus de Ponta Grossa (Ponta Grossa, Paraná)	CENTRO DE ENSINO SUPERIOR DOS CAMPOS GERAIS - CESCAGE/PR	53999616.0.2061.5215
4	Hospital Bom Jesus de Toledo (Toledo, Paraná)	HOSPITAL MOINHOS DE VENTO – HMV	53999616.0.2063.5330
5	Hospital Bruno Born (Lajeado, Rio Grande do Sul)	CENTRO UNIVERSITÁRIO UNIVATES	53999616.0.2027.5310
6	Casa de Saúde de Santos (Santos, São Paulo)	HOSPITAL GUILHERME ALVARO	53999616.0.2020.5448
7	Hospital Cristo Redentor (Porto Alegre, Rio Grande do Sul)	HOSPITAL NOSSA SENHORA DA CONCEIÇÃO - GRUPO HOSPITALAR CONCEIÇÃO	53999616.0.2035.5530
8	Hospital da Restauração (Recife, Pernambuco)	HOSPITAL DA RESTAURAÇÃO	53999616.0.2055.5198
9	Hospital das Clínicas de Botucatu (Botucatu, São Paulo)	UNESP -FACULDADE DE MEDICINA DE BOTUCATU	53999616.0.2017.5411
10	Hospital das Clínicas da Faculdade de Medicina de Ribeirão Preto – USP (Ribeirão Preto, São Paulo)	USP - HOSPITAL DAS CLÍNICAS DA FACULDADE DE MEDICINA DE RIBEIRÃO	53999616.0.2036.5440
11	Hospital das Clínicas de Minas Gerais (Belo Horizonte, Minas Gerais)	UNIVERSIDADE FEDERAL DE MINAS GERAIS	53999616.0.2041.5149
12	Hospital das Clínicas de Rio Branco (Rio Branco, Acre)	HOSPITAL DAS CLÍNICAS DO ACRE - HCA/FUNDHACRE	53999616.0.2070.5009
13	Hospital de Base de São José do Rio Preto (São José do Rio Preto, São Paulo)	FACULDADE DE MEDICINA DE SÃO JOSÉ DO RIO PRETO - FAMERP - SP	53999616.0.2082.5415
14	Hospital de Base do Distrito Federal (Brasília, Distrito Federal)	FUNDAÇÃO DE ENSINO E PESQUISA EM CIÊNCIAS DA SAÚDE/ FEPECS/ SES/ DF	53999616.0.2008.5553
15	Hospital de Pronto Socorro Nelson Marchezan (Canoas, Rio Grande do Sul)	HOSPITAL MOINHOS DE VENTO – HMV	53999616.0.2081.5330

16	Hospital de Clínicas de Porto Alegre (Porto Alegre, Rio Grande do Sul)	HOSPITAL DE CLÍNICAS DE PORTO ALEGRE - HCPA / UFRGS	53999616.0.2010.5327
17	Hospital de Ensino Doutor Washington Antônio de Barros (Petrolina, Pernambuco)	FUNDAÇÃO UNIVERSIDADE FEDERAL DO VALE DO SÃO FRANCISCO	53999616.0.2056.5196
18	Hospital de Pronto Socorro de Porto Alegre (Porto Alegre, Rio Grande do Sul)	SECRETARIA MUNICIPAL DE SAÚDE DE PORTO ALEGRE/ SMSPA	53999616.0.2050.5338
19	Hospital de Pronto Socorro Dr. João Lúcio Pereira Machado (Manaus, Amazonas)	FUNDAÇÃO HOSPITAL ADRIANO JORGE – FHAJ	53999616.0.2088.0007
20	Hospital de Pronto Socorro João Paulo II (Porto Velho, Rondônia)	HOSPITAL MOINHOS DE VENTO – HMV	53999616.0.2072.5330
21	Hospital de Urgência de Goiânia (Goiânia, Goiás)	HOSPITAL DE URGÊNCIA DE GOIÂNIA – HUGO	53999616.0.2058.0033
22	Hospital de Urgência e Emergência de Rio Branco (Rio Branco, Acre)	HOSPITAL DAS CLÍNICAS DO ACRE - HCA/FUNDHACRE	53999616.0.2069.5009
23	Hospital de Urgência de Sergipe (Aracaju, Sergipe)	HOSPITAL MOINHOS DE VENTO – HMV	53999616.0.2073.5330
24	Hospital Dr. Carlos Macieira (São Luís, Maranhão)	CENTRO UNIVERSITÁRIO DO MARANHÃO – UNICEUMA	53999616.0.2053.5084
25	Hospital e Maternidade Angelina Caron (Campina Grande do Sul, Paraná)	HOSPITAL E MATERNIDADE ANGELINA CARON/PR	53999616.0.2052.5226
26	Hospital Estadual de Urgência e Emergência de Vitória (Vitória, Espirito Santo)	CENTRO INTEGRADO DE ATENÇÃO A SAÚDE - CIAS/ UNIMED VITÓRIA	53999616.0.2057.5061
27	Hospital Estadual Getúlio Vargas (Rio de Janeiro, Rio de Janeiro)	HOSPITAL MOINHOS DE VENTO – HMV	53999616.0.2093.5330
28	Hospital Evangélico de Londrina (Londrina, Paraná)	ASSOCIAÇÃO EVANGÉLICA BENEFICENTE DE LONDRINA – AEBEL	53999616.0.2014.5696
29	Hospital Geral Cleriston Andrade (Feira de Santana, Bahia)	SECRETARIA DA SAÚDE DO ESTADO DA BAHIA - SESAB	53999616.0.2048.0052
30	Hospital Geral de Fortaleza (Fortaleza, Ceará)	HOSPITAL GERAL DE FORTALEZA/SUS	53999616.0.2076.5040
31	Hospital Geral de Nova Iguaçu (Nova Iguaçu, Rio de Janeiro)	HOSPITAL GERAL DE NOVA IGUAÇU (HGNI) – RJ	53999616.0.2046.5254
32	Hospital Geral de Taipas (São Paulo, São Paulo)	HOSPITAL MOINHOS DE	53999616.0.2086.5330

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33	Hospital Geral Prof. Osvaldo Brandão Vilela (Maceió, Alagoas)	CENTRO UNIVERSITÁRIO TIRADENTES - UNIT/AL	53999616.0.2071.5641
34	Hospital Instituto Dr. José Frota (Fortaleza, Ceará)	INSTITUTO DR. JOSÉ FROTA - IJF/ PREFEITURA DE FORTALEZA	53999616.0.2075.5047
35	Hospital João XXIII Fundação Hospitalar do Estado de Minas Gerais (Belo Horizonte, Minas Gerais)	FUNDAÇÃO HOSPITALAR DO ESTADO DE MINAS GERAIS - FHEMIG	53999616.0.2099.5119
36	Hospital Municipal Irmã Dulce (Praia Grande, São Paulo)	FACULDADE DE MEDICINA DO ABC\FUNDAÇÃO DO ABC - FMABC	53999616.0.2083.0082
37	Hospital Norte Paranaense (Arapongas, Paraná)	HOSPITAL NORTE PARANAENSE - ASSOCIAÇÃO NORTE PARANAENSE	53999616.0.2067.8017
38	Hospital Nossa Senhora do Rocio de Campo Largo (Campo Largo, Paraná)	UFPR - HOSPITAL DE CLÍNICAS DA UNIVERSIDADE FEDERAL DO PARANÁ	53999616.0.2064.0096
39	Hospital Padre Germano Lauck (Foz do Iguaçu, Paraná)	UNIOESTE – CENTRO DE CIÊNCIAS BIOLÓGICAS E DA SAÚDE DA UNIVERSIDADE	53999616.0.2091.0107
40	Hospital Paulistano (São Paulo, São Paulo)	HOSPITAL PRÓ-CARDÍACO - ESHO EMPRESA DE SERVIÇOS HOSPITALARES	53999616.0.2084.5533
41	Hospital Regional do Cariri (Juazeiro do Norte, Ceará)	INSTITUTO DE SAÚDE E GESTÃO HOSPITALAR - ISGH	53999616.0.2077.5684
42	Hospital Regional do Vale do Paraíba (Taubaté, São Paulo)	UNITAU - UNIVERSIDADE DE TAUBATÉ	53999616.0.2097.5501
43	Hospital Regional Norte (Sobral, Ceará)	INSTITUTO DE SAÚDE E GESTÃO HOSPITALAR - ISGH	53999616.0.2045.5684
44	Hospital Regional Tarcísio de Vasconcelos Maia (Natal, Rio Grande do Norte)	HOSPITAL MOINHOS DE VENTO – HMV	53999616.0.2079.5330
45	Hospital Santa Rita de Maringá (Maringá, Paraná)	HOSPITAL MOINHOS DE VENTO – HMV	53999616.0.2066.5330
46	Hospital São Paulo (São Paulo, São Paulo)	UNIFESP - HOSPITAL SÃO PAULO - HOSPITAL UNIVERSITÁRIO	53999616.0.2003.5505
47	Hospital São Vicente de Paulo (Passo Fundo, Rio Grande do Sul)	UNIVERSIDADE DE PASSO FUNDO/ PRÓ-REITORIA DE PESQUISA E PÓS	53999616.0.2032.5342

48	Hospital São Vicente de Paulo Guarapuava (Guarapuava, Paraná)	UNIVERSIDADE ESTADUAL DO CENTRO OESTE - UNICENTRO	53999616.0.2068.0106
49	Hospital Universitário Ciências Médicas (Belo Horizonte, Minas Gerais)	COMITÊ DE ÉTICA EM PESQUISA CIÊNCIAS MÉDICAS - MG (CEPCM-MG)	53999616.0.2033.5134
50	Hospital Universitário de Cascavel do Oeste do Paraná (Cascavel, Paraná)	UNIOESTE - CENTRO DE CIÊNCIAS BIOLÓGICAS E DA SAÚDE DA UNIVERSIDADE	53999616.0.2043.0107
51	Hospital Universitário de Maringá (Maringá, Paraná)	UNIVERSIDADE ESTADUAL DE MARINGÁ	53999616.0.2026.0104
52	Hospital Universitário Regional do Norte do Paraná (Londrina, Paraná)	UNIVERSIDADE ESTADUAL DE LONDRINA – UEL	53999616.0.2002.5231
53	Hospital Universitário Regional dos Campos Gerais (Ponta Grossa, Paraná)	FACULDADES PONTA GROSSA/ PR	53999616.0.2060.5689
54	Hospital Universitário São Francisco de Paula (Pelotas, Rio Grande do Sul)	UNIVERSIDADE CATÓLICA DE PELOTAS - UCPEL	53999616.0.2016.5339
55	Hospital Universitário São Francisco da Providência de Deus de Bragança Paulista (Bragança Paulista, São Paulo)	UNIVERSIDADE SÃO FRANCISCO-SP	53999616.0.2030.5514
56	Irmandade da Santa Casa de Misericórdia de São Paulo (São Paulo, São Paulo)	SANTA CASA DE MISERICÓRDIA DE SÃO PAULO	53999616.0.2029.5479
57	Irmandade Santa Casa de Misericórdia de Sorocaba (Sorocaba, São Paulo)	FACULDADE DE CIÊNCIAS MÉDICAS E DA SAÚDE DA PONTIFÍCIA UNIVERSIDADE CATÓLIA DE SÃO PAULO	53999616.0.2096.5373
58	Santa Casa de Belo Horizonte (Belo Horizonte, Minas Gerais)	SANTA CASA DE MISERICÓRDIA DE BELO HORIZONTE - SCMBH	53999616.0.2028.5138
59	Santa Casa de Campo Grande (Campo Grande, Mato Grosso do Sul)	HOSPITAL MOINHOS DE VENTO - HMV	53999616.0.2059.5330
60	Santa Casa de Misericórdia de Maringá (Maringá, Paraná)	HOSPITAL MOINHOS DE VENTO - HMV	53999616.0.2062.5330
61	Irmandade da Santa Casa de Porto Alegre (Porto Alegre, Rio Grande do Sul)	IRMANDADE DA SANTA CASA DE MISERICÓRDIA DE PORTO ALEGRE - ISCMPA	53999616.0.2013.5335
62	Santa Casa de Misericórdia de Sobral (Sobral, Ceará)	UNIVERSIDADE ESTADUAL VALE DO ACARAÚ - UVA	53999616.0.2078.5053
63	Hospital Municipal Djalma Marques (São Luís, Maranhão)	HOSPITAL E MATERNIDADE SÃO DOMINGOS	53999616.0.2080.5085

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym – yes: Title page (page1)
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry – yes: Title page (page1), Abstract (page 4), Methods (page 8), and additional file named World_Health_Organization_Trial_Registration_Data_Set_rev
	2b	All items from the World Health Organization Trial Registration Data Set – yes: additional file named World_Health_Organization_Trial_Registration_Data_Set_rev
Protocol version	3	Date and version identifier – not applicable
Funding	4	Sources and types of financial, material, and other support – yes: Funding statement (page 30)
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors – yes: Title page (pages 1 to 3) and Authors' contributions (page 30)
	5b	Name and contact information for the trial sponsor – yes: Funding statement (page 30)
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities – yes: Organisational aspects of the study (page 19)
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) – yes: Organisational aspects of the study (page 19)
Introduction		

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention – yes: Introduction (page 6 to 7)
	6b	Explanation for choice of comparators – yes: Introduction (page 6 to 7)
Objectives	7	Specific objectives or hypotheses – yes: Introduction (page 7) and Objectives (page 7 and 8)
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) – yes: Methods and Analysis (pages 7 and 13)
Methods: Participants, interventions, and outcomes		
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained – yes: Methods and Analysis (page 8), and Study planning and implementation schedule (page 19)
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) – yes: Methods and Analysis (pages 8, 9 to 11)
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered) – yes: Methods and Analysis (pages 9 to12)
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) – not applicable
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) – yes: Methods and Analysis (pages 9 to12,17,18)
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial – yes: Methods and Analysis (page 11)
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended – yes: Methods and Analysis (pages 13,14,17,18)

Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) – yes: Study planning and implementation schedule (page 19) and Methods and Analysis (pages 9 to12)
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations – yes: Methods and Analysis (page 13)
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size – yes: Methods and Analysis (page 11)
Methods: Assignment of interventions (for controlled trials)		
Allocation:		
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions – yes: Methods and Analysis (page 13)
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned – yes: Methods and Analysis (page 13)
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions – yes: Methods and Analysis (page 13)
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how – yes: Methods and Analysis (page 13)
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial – not applicable
Methods: Data collection, management, and analysis		
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol – yes: Methods and analysis (pages 15, 16) – complementary information will be available at the statistical analysis plan paper

	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols – yes: Methods and analysis (pages 15, 16) – complementary information will be available at the statistical analysis plan paper
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol – yes: Methods and analysis (pages 15, 16) – complementary information will be available at the statistical analysis plan paper
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol – yes: Methods and analysis (pages 17, 18) – complementary information will be available at the statistical analysis plan paper
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) – yes: Methods and analysis (pages 17) – complementary information will be available at the statistical analysis plan paper
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) – yes: Methods and analysis (page 17) – complementary information will be available at the statistical analysis plan paper
Methods: Monitoring		
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed Complementary information will be available at the statistical analysis plan paper
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial Complementary information will be available at the statistical analysis plan paper
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct Complementary information will be available at the statistical analysis plan paper

Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor Methods and analysis (page 15) – complementary information will be available at the statistical analysis plan paper
Ethics and dissemination		
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval – yes: Ethics and dissemination (pages 19, 20) and additional file "Sites and IRB approval"
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) – yes: Ethics and dissemination (pages 19, 20)
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) – yes: Ethics and dissemination (pages 19, 20)
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable – not applicable
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial – yes: Methods and analysis (page 15)
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site – yes, Competing interests' statement (page 30) and individual conflict of interest forms
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators – yes: Data sharing (page 30)
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation – not applicable
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions – yes: Ethics and dissemination (pages 19, 20)
	31b	Authorship eligibility guidelines and any intended use of professional writers – not applicable
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code – yes: Data sharing (page 30)

Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates – not applicable
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable – not applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.