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# BMJ Open

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

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Manuscripts

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

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1  
2  
3 66 **ABSTRACT**  
4

5 67 **Introduction:** There is an increasing demand for multi-organ donors for organ  
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7  
8 68 transplantation programmes. This study protocol describes the Donation Network to  
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10 69 Optimise Organ Recovery Study (DONORS), a planned cluster randomised controlled  
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12 70 trial that aims to evaluate the effectiveness of the implementation of an evidence-based  
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14 71 goal-directed checklist for potential brain-dead donor management in intensive care  
15  
16 72 units (ICUs) in reducing the loss of potential donors due to cardiac arrest.  
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18  
19 73 **Methods and analysis:** The study will include ICUs of at least 60 Brazilian sites with  
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21 74 an average of >10 annual notifications of valid potential organ donors. Hospitals will be  
22  
23 75 randomly assigned (with a 1:1 allocation ratio) to the intervention group, which will  
24  
25 76 involve the implementation of an evidence-based goal-directed checklist for potential  
26  
27 77 organ donor maintenance, or the control group, which will maintain the usual care  
28  
29 78 practices of the ICU. Team members from all participating ICUs will receive training on  
30  
31 79 how to conduct family interviews for organ donation. The primary outcome will be loss  
32  
33 80 of potential donors due to cardiac arrest. Secondary outcomes will include the number  
34  
35 81 of actual organ donors, the number of organs recovered per actual donor, and the total  
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37 82 number of cardiac arrests among all potential organ donors.  
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42 83 **Ethics and dissemination:** The Institutional Review Board of the Co-ordinating  
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44 84 institution and of each participating site must individually approve the study. We will  
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46 85 request a waiver of prospective informed consent from substitute decision makers.  
47  
48 86 Study results will be disseminated to the general medical community through  
49  
50 87 publications in peer-reviewed medical journals.  
51

52  
53 88 **Keywords:** brain death, cardiac arrest, organ donation, checklist, quality improvement  
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56 89 **Trial registration:** ClinicalTrials.gov, NCT03179020, registered 23 March 2017.  
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3 90 **Strengths and limitations of this study**  
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- 5 91 • This is the first randomised trial to evaluate whether a goal-directed checklist for  
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7  
8 92 the management of potential brain-dead donors may be useful in reducing  
9  
10 93 cardiac arrests and contributing to increase organ availability for transplants.  
11  
12 94 • The preparation of the goal-directed checklist was preceded by the review of a  
13  
14 95 clinical practice guideline following the Grades of Recommendation  
15  
16 96 Assessment, Development and Evaluation (GRADE) system.  
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19 97 • Brazil is a country with a wide spectrum of demographic and socioeconomic  
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21 98 scenarios; the diversity of institutions to be included in DONORS will allow us  
22  
23 99 to provide results in a broad range of demographic and socioeconomic scenarios.  
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26 100 • Main study limitations are the unblinded design and the high heterogeneity of  
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28 101 care and outcomes expected among centres in the study.  
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## 102 INTRODUCTION

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

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

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3 127 related bloodstream infection, and clinical checklists to ensure patient safety in the  
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5 128 ICU.[7-10]  
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7  
8 129 There is a lack of evidence for the use of checklists regarding the clinical  
9  
10 130 aspects of improving organ availability for transplantation of brain-dead donors. Some  
11  
12 131 observational studies have reported that the application of a goal-directed checklist to  
13  
14 132 guide the management of potential brain-dead organ donors may reduce the rate of  
15  
16 133 cardiac arrest and increase the number of organs recovered per donor. [11-18] However,  
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18 134 given the relatively small number of studies, their observational design and  
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20 135 inconsistency of findings, this literature cannot yet support the use of a goal-directed  
21  
22 136 checklist in the current management of brain-dead organ donors [19].  
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26 137 Our hypothesis is that supporting the management of potential organ donors  
27  
28 138 with the use of an evidence-based bedside checklist may reduce the loss of potential  
29  
30 139 organ donors due to cardiac arrest and increase the number of donors and organs  
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32 140 transplanted per donor. In this protocol, we describe the methods to be used in the  
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34 141 Donation Network to Optimise Organ Recovery Study (DONORS).  
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## 40 143 **OBJECTIVES**

### 41 42 144 **Primary objective**

43  
44 145 The primary objective is to evaluate the effectiveness of the implementation of  
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46 146 an evidence-based bedside checklist, containing goals and recommendations of care as  
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48 147 guidance for the management of potential organ donors, in reducing potential organ  
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50 148 donor losses due to cardiac arrest.  
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### 55 56 150 **Secondary objectives**

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3 151 Secondary objectives are to assess whether the evidence-based goal-directed checklist is  
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5 152 effective in (a) increasing the number of actual organ donors and (b) increasing the  
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7 153 number of organs recovered per actual donor.  
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## 11 155 **METHODS AND ANALYSIS**

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14 156 The protocol is registered at ClinicalTrials.gov (NCT03179020) and the  
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17 157 present manuscript provides additional details regarding study design and methodology.  
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19 158

### 20 21 22 159 **Study design**

23  
24 160 DONORS is a parallel cluster randomised controlled trial involving ICUs of  
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26 161 Brazilian hospitals. We will randomly assign hospitals to the intervention group,  
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28 162 comprising the checklist implementation, or the control group, consisting of usual care  
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30 163 in each ICU (Figure 1).  
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### 33 34 35 165 **Participants**

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37 166 Cluster eligibility, recruitment and exclusion criteria

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40 167 We will invite adult ICUs with an average of at least 10 annual notifications of  
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42 168 potential organ donors in the prior two years. Information regarding notifications is  
43  
44 169 provided by the Brazilian National Transplant System.  
45

46  
47 170 Coronary care units, intermediate care units and emergency departments are not  
48  
49 171 eligible. We will also exclude institutions that already systematically use checklists as  
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51 172 guidance for the management of potential organ donors supported by implementation  
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53 173 tools, such as guidelines and clinical decision algorithms for bedside use, in print or  
54  
55 174 digital form.  
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58 175 Patient eligibility and exclusion criteria  
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3 176 We will screen and include consecutive potential organ donors, as confirmed  
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5 177 by the first clinical examination consistent with having brain death, within the age range  
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7 178 of 14 to 90 years. Only ICU patients will be included; potential donors outside the ICU  
8  
9 179 will be included in the study if admitted to ICU within three hours of initial assessment.  
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12 180 Diagnosis of brain death will be made according to the Brazilian Federal Board  
13  
14 181 of Medicine guidance, consisting of: two clinical examinations performed by two  
15  
16 182 different physicians and one apnoea test followed by neuro-imaging (transcranial  
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18 183 Doppler, cerebral arteriography, electroencephalography, or brain scintigraphy).[20, 21]  
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20 184 We will exclude brain-dead patients who are not candidates for organ donation (Online  
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22 185 Supplementary File 1).  
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## 27 187 **Interventions**

### 28 188 Checklist for potential brain-dead donor management

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30 189 The intervention group checklist derives from a clinical practice guideline  
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32 190 (CPG) for potential organ donor management. The CPG recommendations were  
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34 191 developed from July 2016 to March 2017 as a joint initiative of the Brazilian Ministry  
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36 192 of Health, Brazilian Association of Intensive Care Medicine (AMIB), and Brazilian  
37  
38 193 Association of Organ Transplantation (ABTO).[22] The recommendations were  
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40 194 developed using the Grading of Recommendations, Assessment, Development and  
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42 195 Evaluation (GRADE) system.[23] The following criteria were considered in the  
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44 196 decision-making process: the risks and benefits of interventions; the quality of evidence  
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46 197 for risks and benefits; resource use and costs; and acceptability by healthcare  
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48 198 professionals.  
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51 199 We will provide on-site training in each ICU for healthcare professionals to  
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53 200 inform how to implement the checklist and how to apply the intended  
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3 201 recommendations. The goals and recommendations involve temperature control,  
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5 202 mechanical ventilation, haemodynamic control, endocrine and metabolic control, and  
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7 203 use of antibiotics and blood products, as required. The full checklist is available in  
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10 204 Online Supplementary File 2. Figure 2 describes the logic model for the intervention to  
11  
12 205 be tested in this study.

13  
14 206 The checklist application protocol will be activated at the time of potential  
15  
16 207 donor inclusion in the study and repeated every six hours until organ recovery or loss of  
17  
18 208 the potential donor. A member of the Intra-Hospital Transplant Co-ordination (IHTC)  
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20 209 or a designated ICU professional will apply the checklist. The same individual will be  
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22 210 responsible for prompting the medical team to modify medical management if any  
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24 211 inappropriate aspect of care is noted. Table 1 shows the strategies to promote effective  
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26 212 implementation of this intervention.  
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213 **Table 1.** Strategies to maximise adherence to study interventions and co-interventions.

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**Strategies**

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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

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3 216 ICUs in the control group will continue with their usual management of  
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5 217 potential organ donors. They will not be informed of the items assessed in the goal-  
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7 218 directed checklist or the strategies to enhance compliance.  
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10 219

## 11 220 **Co-interventions**

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14 221 All ICU teams and IHTC members of the participating institutions will receive  
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16 222 training in family interviews for organ donation. The training and interview process  
17  
18 223 have been based primarily on the Spanish model of Communication in Critical  
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20 224 Situations (Online Supplementary File 3).[23-27] Training consists of two components:  
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22 225 (1) face-to-face training of one ICU team representative and one IHTC member of each  
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24 226 institution; and (2) provision of an online, self-instructional course for all ICU team  
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26 227 members and IHTC members participating in the study (Table 1). These co-  
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28 228 interventions aim to standardise ICU strategies in relation to family interviews, reducing  
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30 229 variability between participating sites. This is important for the trial due to three main  
31  
32 230 reasons: (a) inadequate interviews may result in a lower rate of effective donation  
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34 231 (secondary outcomes of the study), independently of potential donor management; (b)  
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36 232 reducing variability between participating sites may have an impact on reducing the  
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38 233 intra-cluster correlation of the study, increasing its power; and (c) training strategies  
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40 234 might enhance the engagement of the participating sites, especially those in the control  
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42 235 group, thereby balancing a potential Hawthorne effect.  
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## 50 237 **Sample size**

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52 238 With 60 ICUs, we will need to include 19 potential organ donors per site  
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54 239 (1,140 potential donors) to detect an absolute reduction of donor losses due to cardiac  
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56 240 arrests of 10% (from 28% in the control group to 18% in the intervention group),[12]  
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3 241 considering an intra-class correlation coefficient (ICC) of 0.05, power of 80%, and a  
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5 242 two-sided alpha level of 5%. Therefore, considering a possible variation in cluster size  
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7 243 and its impact on statistical power, we intend to include a minimum of 60 ICUs with at  
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9 244 least 1,200 potential organ donors, not allowing more than 30 participants in each  
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11 245 cluster.  
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### 16 247 **Randomisation**

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19 248 We will randomly assign ICUs to the intervention group or control group with  
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21 249 a 1:1 allocation ratio using blocks of variable sizes (2 and 4) and stratified by the  
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23 250 estimated annual number of notifications of brain death in each site (sites with  $\leq 29$  and  
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25 251  $> 29$ ). ICUs from the same institution are not considered independent clusters to avoid  
26  
27 252 contamination. We will randomise the ICUs consecutively as per the date of  
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29 253 authorisation of the principal investigator to implement the study in the institution,  
30  
31 254 obtained after the Institutional Review Board (IRB) approval. To ensure allocation  
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33 255 concealment, a statistician from the study co-ordinating office will be responsible for  
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35 256 the randomisation process, with all researchers involved in the trial blinded to the  
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37 257 allocation sequence.  
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### 43 259 **Outcomes**

44  
45  
46 260 The primary outcome will be the number of potential organ donor losses due to  
47  
48 261 cardiac arrest, defined as any loss of potential donors for cardiac arrest that occurs after  
49  
50 262 patient enrolment, while the subject remains eligible for organ donation (no  
51  
52 263 contraindications, family approval or waiting family decision for donation). Losses of  
53  
54 264 potential donors due to other factors (e.g., family refusal or contraindication to organ  
55  
56 265 donation after patient inclusion) will not be considered for this outcome.  
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3 266 The secondary outcomes will be:  
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5 267 1) number of actual organ donors, defined as donors for whom the surgical  
6  
7 268 procedure for organ recovery has been initiated (irrespective of organ recovery);  
8  
9  
10 269 2) number of solid organs recovered per actual donor (ranging from zero to  
11  
12 270 seven organs per donor, as follows: liver; heart; pancreas; two lungs; and two kidneys).

14 271 The tertiary outcomes will include:

16  
17 272 1) the proportion of potential donors with adequate respiratory parameters  
18  
19 273 (defined as  $\text{PaO}_2 / \text{FiO}_2$  ratio  $\geq 200$ );  
20  
21 274 2) the proportion of potential donors with adequate body temperature (defined  
22  
23 275 as body temperature between  $34^\circ\text{C}$  and  $35^\circ\text{C}$  if haemodynamically stable and  $> 35^\circ\text{C}$  if  
24  
25 276 mean arterial pressure [MAP]  $< 65$  mm Hg or use of noradrenaline or dopamine);  
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27  
28 277 3) the proportion of potential donors with adequate circulatory parameters  
29  
30 278 (inadequate parameters defined as MAP  $< 65$  mm Hg or dose of noradrenaline  $\geq 0.1$   
31  
32 279 mc/kg/min or dose of dopamine  $\geq 15$  mcg/kg/min);  
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34  
35 280 4) organ dysfunction score, assessed by the Sequential Organ Failure  
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37 281 Assessment (SOFA) Score.

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### 42 283 **Blinding**

44 284 Due to the nature of the intervention, it will not be possible to blind  
45  
46 285 investigators or healthcare providers in this study. However, we will not disclose details  
47  
48 286 of the content of the checklist to the control group.

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### 54 288 **Data collection**

56 289 An ICU healthcare professional or an IHTC member will collect the data,  
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58 290 which will be recorded at the patient's bedside using a printed case report form and  
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3 291 subsequently transferred into an electronic data capture system (REDCap, Vanderbilt  
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5 292 University, Tennessee, USA).[28] Investigators will receive training for these activities  
6  
7 293 during the study initiation meeting.  
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10 294

### 11 295 **Data monitoring**

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14 296 The study statistician will be responsible for reviewing weekly data on all  
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16  
17 297 inclusions, checking data consistency, and checking whether all forms have been  
18  
19 298 completed correctly. Clinical research monitors will review all data collected and may  
20  
21 299 require supplementation or correction of inconsistent data according to the Good  
22  
23 300 Clinical Practices (GCP) recommended by the International Council for Harmonisation  
24  
25 301 (ICH).[29] On-site monitoring visits will take place after the fifth patient inclusion in  
26  
27 302 the site and when 100% of the projected number of inclusions for the site has been  
28  
29 303 achieved. Additional monitoring visits will be performed as needed, based on the  
30  
31 304 detection of data inconsistencies, errors in completing the forms, or suspected fraud.  
32  
33 305 Periodic remote follow-up will be performed via telephone or electronic messages with  
34  
35 306 the participating sites according to patient recruitment. The data to be collected from  
36  
37 307 each subject are summarised in Table 2.  
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3 308 **Table 2.** Data to be entered in the clinical record form of all potential organ donors  
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5 309 included in the study.  
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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 1<sup>st</sup> clinical examination for the diagnosis of brain death.
  4. Respiratory variables: tidal volume, mL; respiratory rate, mpm; PEEP, cm H<sub>2</sub>O; plateau pressure, cm H<sub>2</sub>O; peak pressure, cm H<sub>2</sub>O (if volume is controlled); FiO<sub>2</sub>, %  
Blood gas variables: PaO<sub>2</sub>, mm Hg; SaO<sub>2</sub>, %; PaCO<sub>2</sub>, mm Hg; base excess, mmol/dL; PvO<sub>2</sub>, mm Hg; SvO<sub>2</sub>, %; PvCO<sub>2</sub>, 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<sup>3</sup>; 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
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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 2<sup>nd</sup> 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.

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310 CVP, central venous pressure;  $\Delta Pp$ , pulse pressure respiratory variation;  $\Delta SV$ , stroke  
311 volume respiratory variation;  $FiO_2$ , fraction of inspired oxygen; ICU, intensive care  
312 unit;  $PaO_2$ , arterial partial pressure of oxygen;  $PaCO_2$ , arterial partial pressure of carbon  
313 dioxide;  $PvO_2$ , venous partial pressure of oxygen;  $PvCO_2$ , venous partial pressure of  
314 carbon dioxide; PEEP, positive end-expiratory pressure; SAPS 3, Simplified Acute  
315 Physiology Score 3;  $SaO_2$ , arterial oxygen saturation;  $SvO_2$ , venous oxygen saturation;  
316 IVCCI, inferior vena cava collapsibility index.  
317

### 318 **Statistical analysis**

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

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3 328 For the primary outcome, we will calculate hazard ratios (HR) considering the  
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5 329 time to the outcome, since patients will be subjected to management at different time  
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7 330 intervals in the institutions. Patients will be considered at risk for the occurrence of the  
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9 331 outcome of interest while under consideration as potential donors. If the outcome of  
10  
11 332 interest does not occur, patients' follow-up will be considered to have ended at the time  
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13 333 their management has been discontinued (family refusal or contraindication to  
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15 334 donation). We will conduct predefined subgroup analyses, considering the following  
16  
17 335 variables: age > 60 years; cause of the injury leading to potential brain death (traumatic  
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19 336 or non-traumatic); and patient severity on ICU admission defined by the Simplified  
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21 337 Acute Physiology Score 3 (SAPS 3) with a cut-off determined by its median. We will  
22  
23 338 conduct sensitivity analyses of adherence to the intervention and of the time interval  
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25 339 between the first clinical examination consistent with having brain death and inclusion  
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27 340 in the study.

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33 341 For secondary and tertiary outcomes, we will use models for correlated data,  
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35 342 considering the ICU as a cluster and each outcome with its own probability distribution.  
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37 343 We will conduct a sensitivity analysis of the outcome 'number of solid organs recovered  
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39 344 per actual donor', considering the number of kidneys harvested. We will analyse  
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41 345 secondary outcomes by adjusting for multiple hypothesis testing. For all statistical  
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43 346 comparisons, we will adopt a statistical significance level of 0.05. An up-to-date version  
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45 347 of the R programme (R Development Core Team) will be used to conduct analyses.  
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#### 50 51 349 **Study planning and implementation schedule**

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53 350 We finalised the study design and protocol in March 2016. The National Study  
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55 351 Investigators Meetings were held in two parts: 9–10 March 2017 and 8–9 June 2017. At  
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57 352 the time of manuscript preparation, 63 ICUs representative of the Brazilian geopolitical  
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3 353 territory are currently recruiting study subjects (Figure 3). On-site training started on  
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5 354 June 1, 2017. We expect that the recruitment will be completed in July 2019. The list of  
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7 355 sites included is available at ClinicalTrials.gov (NCT03179020).  
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### 11 357 **Organisational aspects of the study**

12  
13  
14 358 The study is sponsored and co-ordinated by the Moinhos de Vento Hospital,  
15  
16 359 Brazil, in partnership with the Brazilian Ministry of Health through the Programme of  
17  
18 360 Institutional Development of the Brazilian Unified Health System (PROADI-SUS) and  
19  
20 361 in association with the General Co-ordination Office of the National Transplant System  
21  
22 362 (CGSNT) and the Brazilian Research in Intensive Care Network (BRICNet). The study  
23  
24 363 is supported by the AMIB Committee for Organ Donation for Transplant, ABTO, the  
25  
26 364 Spanish National Transplant Organisation (ONT), and the organ procurement  
27  
28 365 organisations (OPOs) of the states of Santa Catarina and Rio Grande do Sul. The study  
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30 366 Steering Committee consists of intensivists, transplant co-ordinators and  
31  
32 367 epidemiologists with expertise in conducting multi-centre studies. The committee is  
33  
34 368 involved in the conception and design of the study, supervision of progress and  
35  
36 369 procedures during the study, and writing of the study report and any resulting study  
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38 370 manuscript.  
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### 47 372 **Ethics and dissemination**

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49 373 The study was designed in accordance with resolution No. 466/2012 of the  
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51 374 Brazilian National Health Council/Ministry of Health, the Declaration of Helsinki, the  
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53 375 Document of the Americas, and the ICH/GCP E6(R2) 2016. The study was approved by  
54  
55 376 the IRB of the Co-ordinating Centre (No. 53999616.0.1001.5330) and by the IRB of  
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57 377 each participating hospital. Participating in the intervention or control groups does not  
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3 378 imply any risk for the subjects included, since the groups will not be deprived of the  
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5 379 application of the most up-to-date recommendations. Because obtaining written  
6  
7 380 informed consent from patients' family members entails operational and methodological  
8  
9 381 difficulties, and would have a potential negative impact on organ donation as well, we  
10  
11 382 will request a waiver of informed consent in accordance with the IRB of each site.  
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14 383 This trial, regardless of the results, will be published in a peer-reviewed  
15  
16 384 medical journal and presented in scientific conferences and scientific meetings  
17  
18 385 involving the representatives of each participating hospital, of each Brazilian state  
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20 386 transplant centre, and of the Brazilian Ministry of Health.  
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## 25 388 **DISCUSSION**

26  
27 389 Despite the existence of CPGs that currently provide recommendations for a  
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29 390 'standard of care' in the management of potential organ donors,[22,28] they are not  
30  
31 391 always implemented, resulting in the risk of loss of specific organs due to management  
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33 392 failures or even multiple organ loss due to cardiac arrest of the potential donor.[1-4, 22,  
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35 393 30] CPGs usually do not have an impact on bedside practice in the short term, as they  
36  
37 394 rarely take into account clinical applicability.[31] Therefore, a CPG-based goal-directed  
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39 395 checklist associated with a clinician prompting system may be an effective approach to  
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41 396 improve physician adherence to CPG recommendations. Physician-centred healthcare  
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43 397 can be associated with non-adherence to basic recommendations of care, especially in  
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45 398 highly complex processes, such as the management of potential organ donors.[30] In  
46  
47 399 this context, we expect that these organisational adjustments, supported by a checklist-  
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49 400 based management strategy, will have a positive impact on organ donation.  
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53 401 Patel et al.[18] published the results of 671 multi-organ donors managed using  
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55 402 a goal-directed checklist in the United States. The predetermined goals were met in 45%  
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3 403 of cases prior to organ recovery, and the use of the goal-directed checklist significantly  
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5 404 increased the number of organs transplanted per donor.[18] Recently, we published a  
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7 405 prospective observational study that involved 27 ICUs in a southern Brazilian state  
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9 406 demonstrating that the use of a goal-directed checklist to guide the management of  
10  
11 407 deceased donors reduces potential brain-dead donor losses due to cardiac arrest.[12]  
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13 408 Compliance with the checklist increased after the start of the study from 52.1% to  
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15 409 85.8% ( $p < 0.001$ ). The use of the checklist was associated with a lower likelihood of  
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17 410 occurrence of cardiac arrest (odds ratio [OR]: 0.30, 95% CI: 0.18-0.49,  $p < 0.001$ ) and  
18  
19 411 an increase in the number of organs recovered per donor.[12] Although these results are  
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21 412 encouraging and reproduce the observations of other authors, the observational nature of  
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23 413 the studies provides only weak evidence on the subject.[13-18]

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28 414 The study design and basis for the implementation of DONORS may provide  
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30 415 new insights that can help overcome the weaknesses of previous observational studies.  
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32 416 The cluster randomisation design will limit selection biases, and we will count on a  
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34 417 large number of ICUs, which are responsible for a significant amount of brain death  
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36 418 notifications throughout Brazil. The DONORS design will include the evaluation of the  
37  
38 419 effectiveness of a goal-directed checklist strategy in different socioeconomic scenarios  
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40 420 in Brazil, allowing us to provide real-world evidence to support the practical clinical  
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42 421 applicability of the study findings. Finally, the characteristics of the institutional quality  
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44 422 improvement programme of this protocol will allow the potential benefits generated by  
45  
46 423 the proposed study model to be incorporated into ICUs and ultimately transferred to  
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48 424 other clinical areas for the care of critically ill patients.

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51 425 The implementation of a goal-directed checklist for the management of  
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53 426 potential donors is a complex intervention, with multiple components. It is important to  
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55 427 state that, as in most quality improvement studies, how the intervention is implemented  
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3 428 is crucial to the interpretation of the results. In this respect, through this protocol, we  
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5 429 aimed to describe in detail all the interventions and co-interventions proposed in the  
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7 430 study in order to allow reproducibility of our procedures in other settings. In addition,  
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9 431 the logic model presented in the study (Figure 2) is intended to explore the relationships  
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11 432 between the activities proposed in the intervention and the mediators of the effect, such  
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13 433 as improved clinical management of potential donors and enhanced communication  
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15 434 with the ICU team about the expected outcomes. Also important is that, although the  
16  
17 435 study focuses on assessing short-term outcomes in potential donors (e.g., cardiac arrest  
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19 436 and number of organs recovered), potential beneficial outcomes are expected for  
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21 437 transplant recipients, such as improved graft function, survival and quality of life.  
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26 438 Our study has some limitations. First, high variability in care and outcomes  
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28 439 among institutions is expected. Although the chosen ICC may be considered  
29  
30 440 conservative, there are no estimates in the literature for the proposed intervention, which  
31  
32 441 may result in lack of power if the actual ICC is larger than the estimate. In spite of the  
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34 442 procedures to avoid the transfer of information about the checklist to ICUs in the  
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36 443 control group, although with low probability this possibility should be considered,  
37  
38 444 thereby exposing the details of the content of the goal-directed checklist for the control  
39  
40 445 group. Furthermore, although stratified randomisation is planned for this study, we must  
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42 446 take into consideration the differences in the number of brain death notifications among  
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44 447 ICUs, which will recruit patients at different rates, which in turn may generate learning  
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46 448 curves that may have an impact on the final cluster randomisation trial results. In order  
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48 449 to minimise this problem, we are allowing a maximum of 30 patients to be recruited per  
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50 450 each study site; however, some ICUs may recruit a small number of patients. In  
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52 451 addition, the trial is testing the effectiveness of the proposed intervention by means of  
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54 452 an implementation strategy that may be considered feasible to replicate in other settings.  
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3 453 Inadequate adherence to the checklist may have an impact on the results observed in the  
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5 454 intervention group, showing no effect that may be either due to lack of efficacy of the  
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7 455 intervention or due to its suboptimal implementation. Another important aspect to  
8  
9 456 highlight is that, although we expect to see an improvement in the quality of organs  
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11 457 with the use of the checklist, therefore improving outcomes for organ-transplant  
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13 458 recipients, we are limiting the data collection and study procedures to potential donors,  
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15 459 not allowing direct assumptions about its possible effects.  
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## 461 **CONCLUSIONS**

462 We expect that the results from DONORS will provide information regarding  
463 the practical use of checklist-guided management interventions for potential multi-organ  
464 donors that may contribute to reducing potential donor losses due to cardiac arrest or  
465 other relevant outcomes. At this time, with the increasing demand for organs for  
466 transplantation, standardised, evidence-based guidelines that may be adopted globally  
467 by ICUs and by transplant co-ordinators are needed to improve the availability and  
468 quality of organs available for donation. The evidence generated by this trial will have  
469 great potential to contribute positively to the donation of organs.  
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3 569 **Authors' contributions**  
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5 570 All authors contributed to the study design and revised this manuscript: GAW, CCR,  
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13 574 RGR, CT, LCPA, FAB, LSH, and MF also helped with the study design, and GAW  
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15 575 drafted the first version of the article. JA, CAF, and RRN, helped with centre  
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17 576 recruitment and with the co-intervention aspects. GAW, JA, CMG and DBS co-  
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53 591 The datasets used and/or analysed during the current study will be available from the  
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3 605 **FIGURE LEGENDS**  
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5 606 **Figure 1.** Study flow diagram.  
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7 607 ICUs, intensive care units; IRB, Institutional Review Board; ITT, intention-to-treat;  
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12 609 **Figure 2.** Logic model for the checklist intervention.  
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14 610 **Figure 3.** Geographical distribution of the participating intensive care units in Brazil.  
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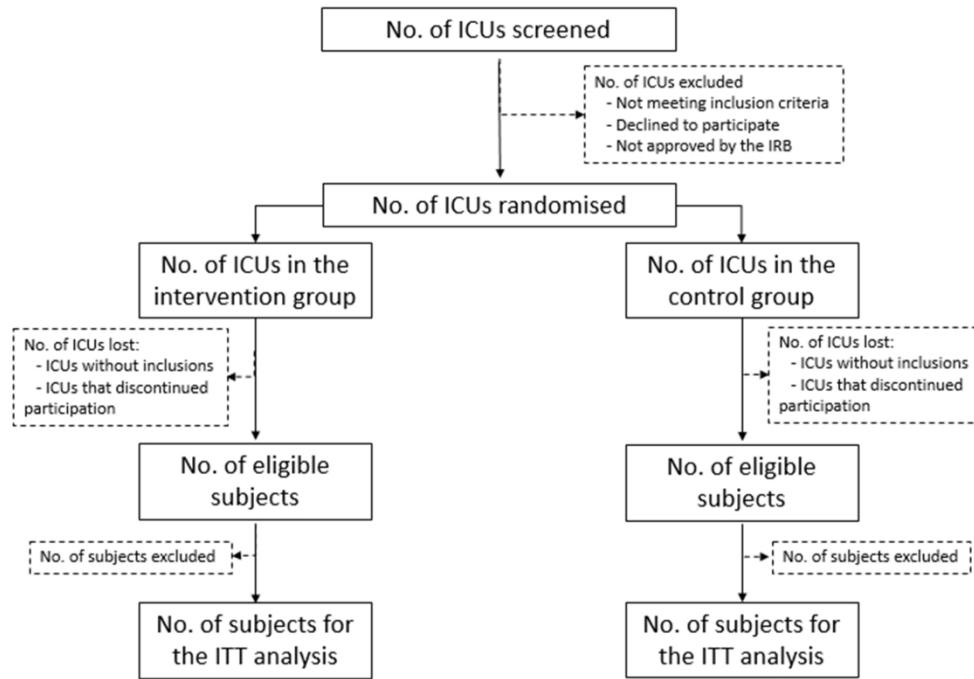
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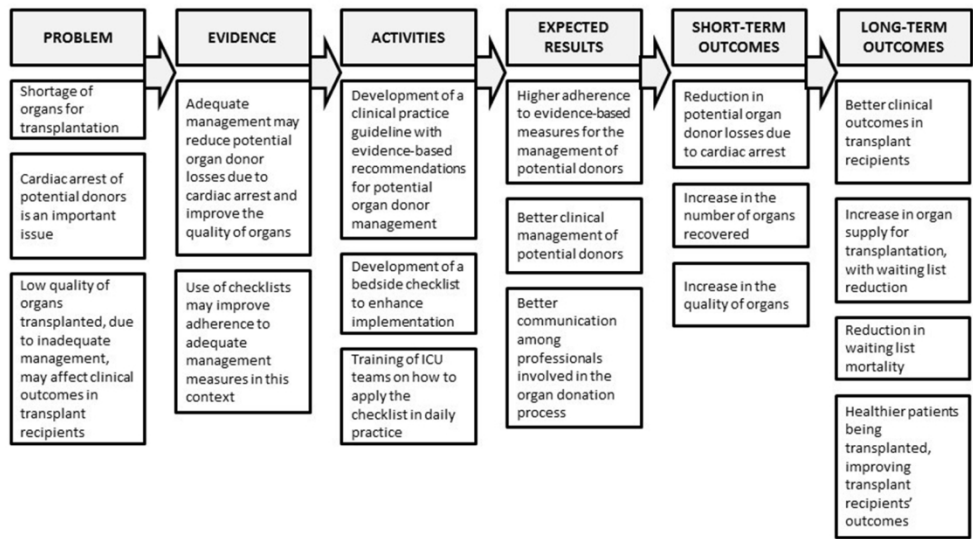




Study flow diagram.  
ICUs, intensive care units; IRB, Institutional Review Board; ITT, intention-to-treat; No., number

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Logic model for the checklist intervention.

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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.

<b>Age</b>	<b>Infection</b>	<b>History of cancer</b>
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).

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4 **Online Supplementary File 2.** English translation of the final version of the bedside checklist.  
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7 **Name:** \_\_\_\_\_  
8

9 **Date and time of 1<sup>st</sup> clinical examination consistent with brain death:** \_\_\_\_/\_\_\_\_/\_\_\_\_ :\_\_\_\_  
10

11 **Current date and time:** \_\_\_\_/\_\_\_\_/\_\_\_\_ :\_\_\_\_  
12  
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14	15	16	17	18	19	20	21	22
GOALS TO BE ACHIEVED	STATUS			IMMEDIATE ACTIONS WHEN STATUS = "NO"	ACTION TAKEN?			
23 SaO <sub>2</sub> ≥ 90%?	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> NA	Adjust FiO <sub>2</sub> and/or PEEP to SaO <sub>2</sub> ≥ 90%	<input type="checkbox"/> Yes	<input type="checkbox"/> No		
24 Tidal volume of 6 to 8 mL/kg of predicted weight?	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> NA	Adjust Vt to 6 to 8 mL/kg	<input type="checkbox"/> Yes	<input type="checkbox"/> No		
25 PEEP ≥ 8 cm H <sub>2</sub> O?	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> NA	Adjust PEEP to ≥ 8 cm H <sub>2</sub> O	<input type="checkbox"/> Yes	<input type="checkbox"/> No		
26 MAP ≥ 65 mm Hg and good tissue perfusion after 27 crystalloid bolus?	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> NA	Continue fluid infusion while there is volume responsiveness (e.g.: ΔPp ≥ 13% / ΔMAP ≥ 8% / ΔSV ≥ 10% / CVP < 8 mm Hg)	<input type="checkbox"/> Yes	<input type="checkbox"/> No		
28 MAP ≥ 65 mm Hg and good tissue perfusion after 29 volume adjustment?	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> NA	Maintain / initiate noradrenaline (dopamine if bradycardia)	<input type="checkbox"/> Yes	<input type="checkbox"/> No		

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4	Vasopressin and hydrocortisone were associated				Associate vasopressin (1 IU bolus + 0.5-2.4 IU / h) and	<input type="checkbox"/> Yes	<input type="checkbox"/> No
5							
6	after maintaining / initiating noradrenaline /	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> NA	Associate hydrocortisone 100 mg 8/8 h	<input type="checkbox"/> Yes	<input type="checkbox"/> No
7							
8	desopamine?						
9							
10							
11					Assess need for volume replacement		
12	Diuresis < 4 mL/kg/h?	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> NA	Maintain / initiate vasopressin or desmopressin (IV)	<input type="checkbox"/> Yes	<input type="checkbox"/> No
13							
14							
15							
16	Na <sup>+</sup> < 155 mEq/L?	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> NA	Correct and order laboratory control in 6 h	<input type="checkbox"/> Yes	<input type="checkbox"/> No
17							
18	K <sup>+</sup> between 3.5 and 5.5 mEq/L?	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> NA	Correct and order laboratory control in 6 h	<input type="checkbox"/> Yes	<input type="checkbox"/> No
19							
20							
21	Mg <sup>++</sup> > 1.6 mEq/L?	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> NA	Correct and order laboratory control in 6 h	<input type="checkbox"/> Yes	<input type="checkbox"/> No
22							
23					Insulin IV to maintain glycaemia between 140 and 180	<input type="checkbox"/> Yes	<input type="checkbox"/> No
24	Capillary glycaemia < 180 mg/dL?	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> NA	mg/dL		
25							
26							
27							
28	Haemoglobin ≥ 7 g/dL?	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> NA	Transfuse red blood cells to Hb ≥ 7g/dL	<input type="checkbox"/> Yes	<input type="checkbox"/> No
29							
30	Absence of infection?	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> NA	Initiate / maintain antibiotic therapy	<input type="checkbox"/> Yes	<input type="checkbox"/> No
31							
32	Proper body temperature?				Get 34 to 35°C if without vasopressor	<input type="checkbox"/> NA	<input type="checkbox"/> Yes
33							<input type="checkbox"/> No
34	No vasopressor: Goal: 34-35°C (after clinical	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> NA	Get > 35°C if with vasopressor	<input type="checkbox"/> NA	<input type="checkbox"/> Yes
35							<input type="checkbox"/> No
36	tests)						
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4 With vasopressor: > 35°C  
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9 **Nurse:** \_\_\_\_\_ **Intensivist:** \_\_\_\_\_

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11 CVP, central venous pressure;  $\Delta Pp$ , pulse pressure respiratory variation;  $\Delta SV$ , stroke volume respiratory variation;  $FiO_2$ , fraction of inspired  
12 oxygen; Hb, haemoglobin;  $K^+$ , potassium; MAP, mean arterial pressure;  $Mg^{++}$ , magnesium;  $Na^+$ , sodium; PEEP, positive end-expiratory  
13 pressure;  $SaO_2$ , arterial oxygen saturation;  $V_t$ , tidal volume.  
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**Online Supplementary File 3.** Family interview support guide.

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**PREPARING FOR THE FAMILY INTERVIEW**

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**FOUNDATIONS: Establishing an aid relationship with family members**

**Triad: Respect, Empathy, and Authenticity**

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**READ THE ACTIONS BELOW CAREFULLY BEFORE EACH STEP OF  
THE FAMILY INTERVIEW**

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- |  |   |
|--|---|
| <b>1. Arranging the location of the interview</b>              | <input type="checkbox"/> Well-ventilated place or room<br><input type="checkbox"/> Restricted access (avoid interferences)<br><input type="checkbox"/> Enough space and chairs for all participants<br><input type="checkbox"/> No barriers between interviewer and interviewee (e.g., table, chairs, etc.)<br><input type="checkbox"/> Facial tissues and water are available<br><input type="checkbox"/> Phones are turned off          |
| <b>2. Defining the interview participants</b>                  | <input type="checkbox"/> ICU physician<br><input type="checkbox"/> Transplant co-ordinator and/or ICU nurse are present<br><input type="checkbox"/> 1st*/2nd** degree relatives or legally authorised representative***<br><p>*1st degree relatives: father, mother, children, full siblings; **2nd degree relatives: grandparents, grandchildren; ***Legally authorised representative: Surrogate/ judicial (documented)<sup>1</sup></p> |
| <b>3. Reviewing the components of non-verbal communication</b> | <input type="checkbox"/> Have all family members sitting down<br><input type="checkbox"/> Leave land-line phones off the hook and turn off mobile phones<br><input type="checkbox"/> 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 – 1<sup>st</sup> clinical examination**

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- |   |  |
|---|--|
| <b>Key points of the first<br/>conference</b> | <ul style="list-style-type: none"> <li><input type="checkbox"/> <b>The ICU physician is responsible for<br/>communicating about the possibility of death</b></li> <li><input type="checkbox"/> <b>Communicate the <u>possibility</u> of brain death to the<br/>family</b></li> </ul> |
|---|--|
-

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- **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

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## STEP 2 - SECOND FAMILY CONFERENCE

### COMMUNICATING THE BRAIN DEATH – after 2 clinical tests and neuro-imaging evidence

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#### 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”

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## STEP 3 - THIRD FAMILY CONFERENCE

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**INTERVIEW FOR MULTI-ORGAN DONATION - after the family's  
understanding of the death**

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**Key points of the third  
conference**

**Person leading the interview:**

- 1<sup>st</sup> option: IHTC/OPO member
- 2<sup>nd</sup> 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

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**STEP 4 - PLANNING THE APPROACH ACCORDING TO THE FAMILY'S  
DECISION**

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**FAMILY CONSENT FOR  
DONATION**

**FAMILY REFUSAL FOR  
DONATION**

**- Obtain the Family Consent Form,  
fully and correctly completed**

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- 1  
2  
3 - Complete the death certificate
- 4  
5  
6 - **Evaluate the possibility of a rescue**  
7 **interview** for donation after family  
8 conflicts have been resolved
- 9  
10 - **Consider withdrawing therapeutic**  
11 **support** “The physician is legally and  
12 ethically entitled to withdraw therapeutic  
13 support, including mechanical ventilation,  
14 and release the body to the family.”<sup>2</sup>  
15  
16  
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21 - Complete the death certificate  
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- 

## DEATH CERTIFICATE or FORENSIC MEDICAL EXAMINATION

### ICU physician’s responsibility

- 
- | □ NON-VIOLENT DEATH  | □ VIOLENT DEATH  |
|--|--|
| <p>28</p> <p>29 - Complete the “<b>Death Certificate</b>”</p> <p>30 including the <b>date and time of death</b> and</p> <p>31 the data of the <b>last examination</b></p> <p>32 <b>performed</b> (2<sup>nd</sup> clinical examination) <b>or</b></p> <p>33 neuro-imaging evidence.</p> <p>34</p> <p>35</p> <p>36</p> <p>37</p> <p>38</p> <p>39</p> <p>40</p> <p>41</p> <p>42</p> <p>43</p> <p>44</p> <p>45</p> <p>46</p> <p>47</p> <p>48</p> <p>49</p> <p>50</p> | <p>30 - Complete the “<b>Forensic Medical</b></p> <p>31 <b>Examination Referral Form</b>” including</p> <p>32 the <b>date and time of death</b> and the data of</p> <p>33 the <b>last examination performed</b> (2<sup>nd</sup></p> <p>34 clinical examination) <b>or</b> neuro-imaging</p> <p>35 evidence.</p> <p>36</p> <p>37 - Request the Forensic Medical Institute</p> <p>38 for <b>AUTHORISATION TO REMOVE</b></p> <p>39 <b>ORGANS OR TISSUES</b></p> <p>40</p> <p>41</p> <p>42</p> <p>43</p> <p>44</p> <p>45</p> <p>46</p> <p>47</p> <p>48</p> <p>49</p> <p>50</p> |
- 

<sup>1</sup> Brazilian Federal Law No. 10211 of March 23, 2001;

<sup>2</sup> Brazilian Federal Board of Medicine – Resolution No. 1826 of December 6, 2007.



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
<b>Administrative information</b>		
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)
<b>Introduction</b>		
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)

1			
2	Objectives	7	Specific objectives or hypotheses (yes, Introduction and Objectives)
3			
4	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)
5			
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10	<b>Methods: Participants, interventions, and outcomes</b>		
11			
12	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)
13			
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16			
17	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)
18			
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23	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered ) (yes, Methods and analysis)
24			
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28		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)
29			
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32		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) (yes, Methods and analysis)
33			
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37		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial (yes, Methods and analysis)
38			
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40	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)
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48	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)
49			
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54	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)
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2 Recruitment 15 Strategies for achieving adequate participant enrolment to reach  
3 target sample size (yes, Methods and analysis)  
4

5 **Methods: Assignment of interventions (for controlled trials)**  
6

7 Allocation:

8  
9 Sequence generation 16a Method of generating the allocation sequence (eg, computer-  
10 generated random numbers), and list of any factors for stratification.  
11 To reduce predictability of a random sequence, details of any planned  
12 restriction (eg, blocking) should be provided in a separate document  
13 that is unavailable to those who enrol participants or assign  
14 interventions (yes, Methods and analysis)  
15  
16

17 Allocation concealment 16b Mechanism of implementing the allocation sequence (eg, central  
18 telephone; sequentially numbered, opaque, sealed envelopes),  
19 describing any steps to conceal the sequence until interventions are  
20 assigned (yes, Methods and analysis)  
21  
22

23 Implementation 16c Who will generate the allocation sequence, who will enrol participants,  
24 and who will assign participants to interventions (yes, Methods and  
25 analysis)  
26

27 Blinding (masking) 17a Who will be blinded after assignment to interventions (eg, trial  
28 participants, care providers, outcome assessors, data analysts), and  
29 how (yes, Methods and analysis)  
30  
31

32 17b If blinded, circumstances under which unblinding is permissible, and  
33 procedure for revealing a participant's allocated intervention during  
34 the trial (unblinded study)  
35

36 **Methods: Data collection, management, and analysis**  
37

38 Data collection methods 18a Plans for assessment and collection of outcome, baseline, and other  
39 trial data, including any related processes to promote data quality (eg,  
40 duplicate measurements, training of assessors) and a description of  
41 study instruments (eg, questionnaires, laboratory tests) along with  
42 their reliability and validity, if known. Reference to where data  
43 collection forms can be found, if not in the protocol (yes, Methods and  
44 analysis – complementary information will be available at the  
45 statistical analysis plan paper)  
46  
47  
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49 18b Plans to promote participant retention and complete follow-up,  
50 including list of any outcome data to be collected for participants who  
51 discontinue or deviate from intervention protocols (yes, Methods and  
52 analysis – complementary information will be available at the  
53 statistical analysis plan paper)  
54  
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2	Data	19	Plans for data entry, coding, security, and storage, including any
3	management		related processes to promote data quality (eg, double data entry;
4			range checks for data values). Reference to where details of data
5			management procedures can be found, if not in the protocol (yes,
6			Methods and analysis – complementary information will be available
7			at the statistical analysis plan paper)
8			
9			
10	Statistical	20a	Statistical methods for analysing primary and secondary outcomes.
11	methods		Reference to where other details of the statistical analysis plan can be
12			found, if not in the protocol (yes, Methods and analysis –
13			complementary information will be available at the statistical analysis
14			plan paper)
15			
16			
17		20b	Methods for any additional analyses (eg, subgroup and adjusted
18			analyses) (yes, Methods and analysis – complementary information
19			will be available at the statistical analysis plan paper)
20			
21		20c	Definition of analysis population relating to protocol non-adherence
22			(eg, as randomised analysis), and any statistical methods to handle
23			missing data (eg, multiple imputation) (yes, Methods and analysis –
24			complementary information will be available at the statistical analysis
25			plan paper)
26			
27			
28	<b>Methods: Monitoring</b>		
29			
30	Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role
31			and reporting structure; statement of whether it is independent from
32			the sponsor and competing interests; and reference to where further
33			details about its charter can be found, if not in the protocol.
34			Alternatively, an explanation of why a DMC is not needed (yes,
35			Methods and analysis)
36			
37			
38		21b	Description of any interim analyses and stopping guidelines, including
39			who will have access to these interim results and make the final
40			decision to terminate the trial (yes, Methods and analysis –
41			complementary information will be available at the statistical analysis
42			plan paper)
43			
44			
45	Harms	22	Plans for collecting, assessing, reporting, and managing solicited and
46			spontaneously reported adverse events and other unintended effects
47			of trial interventions or trial conduct (yes, Methods and analysis –
48			complementary information will be available at the statistical analysis
49			plan paper)
50			
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52	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and
53			whether the process will be independent from investigators and the
54			sponsor (yes, Methods and analysis – complementary information will
55			be available at the statistical analysis plan paper)
56			
57			
58	<b>Ethics and dissemination</b>		
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1			
2	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval (yes, Ethics and dissemination)
3			
4			
5	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)
6			
7			
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9			
10	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)
11			
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14			
15		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable (not applicable)
16			
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19	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)
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24	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site (conflict of interest forms)
25			
26			
27	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)
28			
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31	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)
32			
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36	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)
37			
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43		31b	Authorship eligibility guidelines and any intended use of professional writers (not applicable)
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46		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code (yes, Data sharing)
47			
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50	<b>Appendices</b>		
51			
52	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates (not applicable)
53			
54			
55	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)
56			
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1 \*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013  
2 Explanation & Elaboration for important clarification on the items. Amendments to the  
3 protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT  
4 Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](#)"  
5 license.  
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# 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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Secondary Subject Heading:	Intensive care
Keywords:	brain death, cardiac arrest, organ donation, checklist, quality improvement

SCHOLARONE™  
Manuscripts

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

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3 67 **ABSTRACT**  
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5 68 **Introduction:** There is an increasing demand for multi-organ donors for organ  
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8 69 transplantation programmes. This study protocol describes the Donation Network to  
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10 70 Optimise Organ Recovery Study (DONORS), a planned cluster randomised controlled  
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12 71 trial that aims to evaluate the effectiveness of the implementation of an evidence-based,  
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14 72 goal-directed checklist for brain-dead potential organ donor management in intensive  
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16 73 care units (ICUs) in reducing the loss of potential donors due to cardiac arrest.  
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19 74 **Methods and analysis:** The study will include ICUs of at least 60 Brazilian sites with  
20  
21 75 an average of >10 annual notifications of valid potential organ donors. Hospitals will be  
22  
23 76 randomly assigned (with a 1:1 allocation ratio) to the intervention group, which will  
24  
25 77 involve the implementation of an evidence-based, goal-directed checklist for potential  
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27 78 organ donor maintenance, or the control group, which will maintain the usual care  
28  
29 79 practices of the ICU. Team members from all participating ICUs will receive training on  
30  
31 80 how to conduct family interviews for organ donation. The primary outcome will be loss  
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33 81 of potential donors due to cardiac arrest. Secondary outcomes will include the number  
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35 82 of actual organ donors and the number of organs recovered per actual donor.  
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39 83 **Ethics and dissemination:** The Institutional Review Board (IRB) of the Co-ordinating  
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41 84 centre and of each participating site individually approved the study. We requested a  
42  
43 85 waiver of informed consent for the IRB of each site. Study results will be disseminated  
44  
45 86 to the general medical community through publications in peer-reviewed medical  
46  
47 87 journals.  
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50 88 **Keywords:** brain death, cardiac arrest, organ donation, checklist, quality improvement  
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53 89 **Trial registration:** ClinicalTrials.gov, NCT03179020, registered June 7, 2017.  
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3 90 **Strengths and limitations of this study**  
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- 5 91 • This is the first randomised trial to evaluate whether a goal-directed checklist for  
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8 92 the management of brain-dead potential organ donors may be useful in reducing  
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10 93 cardiac arrests and contributing to increase organ availability for transplants.  
11  
12 94 • The preparation of the goal-directed checklist was preceded by the review of a  
13  
14 95 clinical practice guideline following the Grades of Recommendation  
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16 96 Assessment, Development and Evaluation (GRADE) system.  
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18  
19 97 • Brazil is a country with a wide spectrum of demographic and socioeconomic  
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21 98 scenarios; the diversity of institutions to be included in DONORS will allow us  
22  
23 99 to provide results in a broad range of demographic and socioeconomic scenarios.  
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26 100 • Main study limitations are the unblinded design and the high heterogeneity of  
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28 101 care and outcomes expected among centres in the study.  
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## 102 INTRODUCTION

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

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

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3 127 related bloodstream infection, and clinical checklists to ensure patient safety in the  
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5 128 ICU.[8-11]  
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7 129 There is a lack of evidence for the use of checklists regarding the clinical  
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10 130 aspects of improving organ availability for transplantation of brain-dead donors. Some  
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12 131 observational studies have reported that the application of a goal-directed checklist to  
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14 132 guide the management of brain-dead potential organ donors may reduce the rate of  
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16 133 cardiac arrest and increase the number of organs recovered per donor. [12-19] However,  
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18 134 given the relatively small number of studies, their observational design and  
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20 135 inconsistency of findings, often related with barriers to carrying out studies in this  
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22 136 scenario [5], this literature cannot yet support the use of a goal-directed checklist in the  
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24 137 current management of brain-dead potential organ donors [20].  
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28 138 Our hypothesis is that supporting the management of potential organ donors  
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30 139 with the use of an evidence-based bedside checklist may reduce the loss of potential  
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32 140 organ donors due to cardiac arrest and increase the number of donors and organs  
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34 141 transplanted per donor. In this protocol, we describe the methods to be used in the  
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36 142 Donation Network to Optimise Organ Recovery Study (DONORS).  
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## 41 144 **OBJECTIVES**

### 42 145 **Primary objective**

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45 146 The primary objective is to evaluate the effectiveness of the implementation of  
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47 147 an evidence-based bedside checklist, containing goals and recommendations of care as  
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49 148 guidance for the management of brain-dead potential organ donors, in reducing  
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51 149 potential organ donor losses due to cardiac arrest.  
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### 55 151 **Secondary objectives**

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3 152 Secondary objectives are to assess whether the evidence-based, goal-directed checklist  
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5 153 is effective in (a) increasing the number of actual organ donors and (b) increasing the  
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7 154 number of organs recovered per actual donor.  
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## 11 156 **METHODS AND ANALYSIS**

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14 157 The protocol is registered at ClinicalTrials.gov (NCT03179020) and the  
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17 158 present manuscript provides additional details regarding study design and methodology.  
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19 159 The items from the World Health Organization trial registration data set are described in  
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21 160 the Online Supplementary File 1.  
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### 25 162 **Study design**

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28 163 DONORS is a parallel cluster randomised controlled trial involving ICUs of  
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30 164 Brazilian hospitals. We will randomly assign hospitals to the intervention group,  
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32 165 comprising the checklist implementation, or the control group, consisting of usual care  
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34 166 in each ICU (Figure 1).  
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### 38 168 **Participants**

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40 169 Cluster eligibility, recruitment and exclusion criteria

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43 170 We will invite adult ICUs with an average of at least 10 annual notifications of  
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45 171 potential organ donors in the prior two years. Information regarding notifications is  
46  
47 172 provided by the Brazilian National Transplant System.  
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50  
51 173 Coronary care units, intermediate care units and emergency departments are not  
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53 174 eligible. We will also exclude institutions that already systematically use checklists as  
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55 175 guidance for the management of potential organ donors supported by implementation  
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3 176 tools, such as guidelines and clinical decision algorithms for bedside use, in print or  
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5 177 digital form.  
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8 178 Patient eligibility and exclusion criteria  
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10 179 We will screen and include consecutive brain-dead potential organ donors, as  
11  
12 180 confirmed by the first clinical examination consistent with having brain death, within  
13  
14 181 the age range of 14 to 90 years. Only ICU patients will be included; potential donors  
15  
16 182 outside the ICU will be included in the study if admitted to ICU within three hours of  
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18 183 initial assessment.  
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21 184 Diagnosis of brain death will be made according to the Brazilian Federal Board  
22  
23 185 of Medicine guidance, consisting of: two clinical examinations performed by two  
24  
25 186 different physicians, in an interval of at least 1 hour between the examinations, and one  
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27 187 apnoea test followed by neuro-imaging (transcranial Doppler, cerebral arteriography,  
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29 188 electroencephalography, or brain scintigraphy).[21, 22] We will exclude brain-dead  
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31 189 patients who are not candidates for organ donation (Online Supplementary File 2).  
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37 191 **Interventions**  
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40 192 Checklist for brain-dead potential organ donors management  
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42 193 After a preliminary prospective study [13] that found a positive impact of a  
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44 194 clinical goal-directed protocol on reducing irreversible cardiac arrests in brain-dead  
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46 195 potential organ donors, an updated checklist was generated after drawing up a clinical  
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48 196 practice guideline (CPG) for brain-dead potential organ donor management. The CPG  
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50 197 recommendations were developed from July 2016 to March 2017, as a joint initiative of  
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52 198 the Brazilian Ministry of Health, Brazilian Association of Intensive Care Medicine  
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54 199 (AMIB), and Brazilian Association of Organ Transplantation (ABTO).[23] The  
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56 200 recommendations were developed using the Grading of Recommendations, Assessment,  
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3 201 Development and Evaluation (GRADE) system.[24] The following criteria were  
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5 202 considered in the decision-making process: the risks and benefits of interventions; the  
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7 203 quality of evidence for risks and benefits; resource use and costs; and acceptability by  
8  
9 204 healthcare professionals.

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12 205 The checklist was designed to address CPG goals and recommendations that  
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14 206 involve temperature control, mechanical ventilation, haemodynamic control, endocrine  
15  
16 207 and metabolic control, and use of antibiotics and blood products, as required, and  
17  
18 208 hormone administration (hydrocortisone, vasopressin and/or desmopressin, insulin).  
19  
20 209 Thyroid hormone was not recommended due to lack of evidence to confirm the benefit  
21  
22 210 of its use. [25,26] We tested the checklist in four ICUs with high volume in brain death  
23  
24 211 notifications that participated in the preliminary study [13] and make minimal  
25  
26 212 adjustments suggested by the professionals that tested the tool. The full checklist is  
27  
28 213 available in Online Supplementary File 3. Figure 2 describes the logic model for the  
29  
30 214 intervention to be tested in this study. We will provide on-site training in each ICU for  
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32 215 healthcare professionals to inform how to implement the checklist and how to apply the  
33  
34 216 intended recommendations.

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37 217 The checklist will be bedside applied immediately after the time of potential  
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39 218 donor inclusion in the study and repeated every six hours until organ recovery or loss of  
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41 219 the potential donor. A member of the Intra-Hospital Transplant Co-ordination (IHTC)  
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43 220 or a designated ICU professional will apply the paper-based checklist at the bedside.  
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45 221 The same individual will be responsible for personally prompting the medical team to  
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47 222 modify medical management if any inappropriate aspect of care is noted.  
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223

224 Usual care

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

228

### 229 **Co-interventions**

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

246

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

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**Strategies**

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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.
-



## 249 **Sample size**

250 With 60 ICUs, we will need to include 19 brain-dead potential organ donors  
251 per site (1,140 potential donors) to detect an absolute reduction of donor losses due to  
252 cardiac arrests of 10% (from 28% in the control group to 18% in the intervention  
253 group)[13], considering an intra-class correlation coefficient (ICC) of 0.05, power of  
254 80%, and a two-sided alpha level of 5%. Therefore, considering a possible variation in  
255 cluster size and its impact on statistical power, we intend to include a minimum of 60  
256 ICUs with at least 1,200 potential organ donors, not allowing more than 30 participants  
257 in each cluster.

## 259 **Randomisation**

260 We will randomly assign ICUs to the intervention group or control group with  
261 a 1:1 allocation ratio using blocks of variable sizes (2 and 4) and stratified by the  
262 estimated annual number of notifications of brain death in each site (sites with  $\leq 29$  and  
263  $> 29$ ). ICUs from the same institution are not considered independent clusters to avoid  
264 contamination. We will randomise the ICUs consecutively as per the date of  
265 authorisation of the principal investigator to implement the study in the institution,  
266 obtained after the Institutional Review Board (IRB) approval. To ensure allocation  
267 concealment, a statistician from the study co-ordinating office will be responsible for  
268 the randomisation process, with all researchers involved in the trial blinded to the  
269 allocation sequence.

## 271 **Outcomes**

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

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3 274 from irreversible or unreversed cardiac arrest that occurs after patient enrolment, while  
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5 275 the subject remains eligible for organ donation (no contraindications, family approval or  
6  
7 276 waiting family decision for donation). Losses of potential donors due to other factors  
8  
9  
10 277 (e.g., family refusal or contraindication to organ donation after patient inclusion) will  
11  
12 278 not be considered for this outcome.

13  
14 279 The secondary outcomes will be:

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16  
17 280 1) number of actual organ donors, indexed to brain-dead potential donors,  
18  
19 281 defined as donors for whom the surgical procedure for organ recovery has been initiated  
20  
21 282 (irrespective of organ recovery)[3];

22  
23  
24 283 2) number of solid organs recovered per actual donor (ranging from zero to  
25  
26 284 seven organs per donor, as follows: liver; heart; pancreas; two lungs; and two kidneys).

27  
28 285 The tertiary outcomes will include:

29  
30  
31 286 1) the proportion of potential donors with adequate respiratory parameters  
32  
33 287 (defined as  $\text{PaO}_2 / \text{FiO}_2$  ratio  $\geq 200$ );

34  
35 288 2) the proportion of potential donors with adequate body temperature (defined  
36  
37 289 as body temperature between 34°C and 35°C if haemodynamically stable and  $> 35^\circ\text{C}$  if  
38  
39 290 mean arterial pressure [MAP]  $< 65$  mm Hg or use of noradrenaline or dopamine);

40  
41  
42 291 3) the proportion of potential donors with adequate circulatory parameters  
43  
44 292 (inadequate parameters defined as MAP  $< 65$  mm Hg or dose of noradrenaline  $\geq 0.1$   
45  
46 293 mc/kg/min or dose of dopamine  $\geq 15$  mcg/kg/min);

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48  
49 294 4) organ dysfunction score, assessed by the Sequential Organ Failure  
50  
51 295 Assessment (SOFA) Score.

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56 297 **Blinding**

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3 298 Due to the nature of the intervention, it will not be possible to blind  
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5 299 investigators or healthcare providers in this study. However, we will not disclose details  
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7  
8 300 of the content of the checklist to the control group.  
9

10 301

### 11 302 **Data collection**

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13  
14 303 An ICU healthcare professional or an IHTC member will collect the data,  
15  
16 304 which will be recorded at the patient's bedside using a printed case report form and  
17  
18 305 subsequently transferred into an electronic data capture system (REDCap, Vanderbilt  
19  
20 306 University, Tennessee, USA).[32] Investigators will receive training for these activities  
21  
22 307 during the study initiation meeting.  
23

24 308

### 25 309 **Data monitoring**

26  
27  
28 310 The study statistician will be responsible for reviewing weekly data on all  
29  
30 311 inclusions, checking data consistency, and checking whether all forms have been  
31  
32 312 completed correctly. Clinical research monitors will review all data collected and may  
33  
34 313 require supplementation or correction of inconsistent data according to the Good  
35  
36 314 Clinical Practices (GCP) recommended by the International Council for Harmonisation  
37  
38 315 (ICH).[33] On-site monitoring visits will take place after the fifth patient inclusion in  
39  
40 316 the site and when 100% of the projected number of inclusions for the site has been  
41  
42 317 achieved. Additional monitoring visits will be performed as needed, based on the  
43  
44 318 detection of data inconsistencies, errors in completing the forms, or suspected fraud.  
45  
46 319 Periodic remote follow-up will be performed via telephone or electronic messages with  
47  
48 320 the participating sites according to patient recruitment. The data to be collected from  
49  
50 321 each subject are summarised in Table 2.  
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3 322 **Table 2.** Data to be entered in the clinical record form of all potential organ donors  
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5 323 included in the study.  
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- 
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 1<sup>st</sup> clinical examination for the diagnosis of brain death.
  4. Respiratory variables: tidal volume, mL; respiratory rate, mpm; PEEP, cm H<sub>2</sub>O; plateau pressure, cm H<sub>2</sub>O; peak pressure, cm H<sub>2</sub>O (if volume is controlled); FiO<sub>2</sub>, %  
Blood gas variables: PaO<sub>2</sub>, mm Hg; SaO<sub>2</sub>, %; PaCO<sub>2</sub>, mm Hg; base excess, mmol/dL; PvO<sub>2</sub>, mm Hg; SvO<sub>2</sub>, %; PvCO<sub>2</sub>, 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<sup>3</sup>; 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
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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 2<sup>nd</sup> 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.

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324 CVP, central venous pressure;  $\Delta Pp$ , pulse pressure respiratory variation;  $\Delta SV$ , stroke  
325 volume respiratory variation;  $FiO_2$ , fraction of inspired oxygen; ICU, intensive care  
326 unit;  $PaO_2$ , arterial partial pressure of oxygen;  $PaCO_2$ , arterial partial pressure of carbon  
327 dioxide;  $PvO_2$ , venous partial pressure of oxygen;  $PvCO_2$ , venous partial pressure of  
328 carbon dioxide; PEEP, positive end-expiratory pressure; SAPS 3, Simplified Acute  
329 Physiology Score 3;  $SaO_2$ , arterial oxygen saturation;  $SvO_2$ , venous oxygen saturation;  
330 IVCCI, inferior vena cava collapsibility index.  
331

### 332 **Statistical analysis**

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

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3 342 For the primary outcome, we will calculate hazard ratios (HR) considering the  
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5 343 time to the outcome, since patients will be subjected to management at different time  
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7 344 intervals in the institutions. Patients will be considered at risk for the occurrence of the  
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9 345 outcome of interest while under consideration as potential donors. If the outcome of  
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11 346 interest does not occur, patients' follow-up will be considered to have ended at the time  
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13 347 their management has been discontinued (family refusal or contraindication to  
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15 348 donation). We will conduct predefined subgroup analyses, considering the following  
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17 349 variables: age > 60 years; cause of the injury leading to potential brain death (traumatic  
18  
19 350 or non-traumatic); and patient severity on ICU admission defined by the Simplified  
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21 351 Acute Physiology Score 3 (SAPS 3) with a cut-off determined by its median. We will  
22  
23 352 conduct sensitivity analyses of adherence to the intervention (compliance with checklist  
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25 353 proposed measures) and of the time interval between the first clinical examination  
26  
27 354 consistent with having brain death and inclusion in the study.  
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33 355 For secondary and tertiary outcomes, we will use models for correlated data,  
34  
35 356 considering the ICU as a cluster and each outcome with its own probability distribution.  
36  
37 357 We will conduct a sensitivity analysis of the outcome 'number of solid organs recovered  
38  
39 358 per actual donor', considering the number of kidneys harvested. We will analyse  
40  
41 359 secondary outcomes by adjusting for multiple hypothesis testing. For all statistical  
42  
43 360 comparisons, we will adopt a statistical significance level of 0.05. An up-to-date version  
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45 361 of the R programme (R Development Core Team) will be used to conduct analyses.  
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### 50 51 363 **Study planning and implementation schedule**

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53 364 We finalised the study design and protocol in March 2016. The National Study  
54  
55 365 Investigators Meetings were held in two parts: 9–10 March 2017 and 8–9 June 2017. At  
56  
57 366 the time of manuscript preparation, 63 ICUs representative of the Brazilian geopolitical  
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3 367 territory are currently recruiting study subjects (Figure 3). On-site training started on  
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5 368 June 1, 2017. We expect that the recruitment will be completed in December 2019. The  
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7 369 list of sites included is available at ClinicalTrials.gov (NCT03179020).  
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### 11 371 **Organisational aspects of the study**

12  
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14 372 The study is sponsored and co-ordinated by the Moinhos de Vento Hospital,  
15  
16 373 Brazil, in partnership with the Brazilian Ministry of Health through the Programme of  
17  
18 374 Institutional Development of the Brazilian Unified Health System (PROADI-SUS) and  
19  
20 375 in association with the General Co-ordination Office of the National Transplant System  
21  
22 376 (CGSNT) and the Brazilian Research in Intensive Care Network (BRICNet). The study  
23  
24 377 is supported by the AMIB Committee for Organ Donation for Transplant, ABTO, the  
25  
26 378 Spanish National Transplant Organisation (ONT), and the organ procurement  
27  
28 379 organisations (OPOs) of the states of Santa Catarina and Rio Grande do Sul. The study  
29  
30 380 Steering Committee consists of intensivists, transplant co-ordinators and  
31  
32 381 epidemiologists with expertise in conducting multi-centre studies. The committee is  
33  
34 382 involved in the conception and design of the study, supervision of progress and  
35  
36 383 procedures during the study, and writing of the study report and any resulting study  
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38 384 manuscript.  
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### 47 386 **Ethics and dissemination**

48  
49 387 The study was designed in accordance with resolution No. 466/2012 of the  
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51 388 Brazilian National Health Council/Ministry of Health, the Declaration of Helsinki, the  
52  
53 389 Document of the Americas, and the ICH/GCP E6(R2) 2016 [33]. The study was  
54  
55 390 approved by the IRB of the Co-ordinating Centre (No. 53999616.0.1001.5330) and by  
56  
57 391 the IRB of each participating site (Online Supplementary File 5). Participating in the  
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3 392 intervention or control groups does not imply any risk for the subjects included, since  
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5 393 the groups will not be deprived of the application of the most up-to-date  
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7 394 recommendations. Because obtaining written informed consent from patients' family  
8  
9 395 members entails operational and methodological difficulties, and would have a potential  
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11 396 negative impact on organ donation as well, we requested a waiver of informed consent  
12  
13 397 for the IRB of each participating site.  
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16  
17 398 This trial, regardless of the results, will be published in a peer-reviewed  
18  
19 399 medical journal and presented in scientific conferences and scientific meetings  
20  
21 400 involving the representatives of each participating hospital, of each Brazilian state  
22  
23 401 transplant centre, and of the Brazilian Ministry of Health.  
24  
25

26 402

### 27 28 403 **Patient and Public Involvement**

29  
30 404 Considering the characteristics of the study population, the patients were not directly  
31  
32 405 involved in the research question, study design, study participants recruitment and study  
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34 406 conduction.  
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### 38 39 408 **DISCUSSION**

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42 409 Despite the existence of CPGs that currently provide recommendations for a  
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44 410 'standard of care' in the management of potential organ donors,[23,29] they are not  
45  
46 411 always implemented, resulting in the risk of loss of specific organs due to management  
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48 412 failures or even multiple organ loss due to cardiac arrest of the potential donor.[1-4, 23,  
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50 413 34] CPGs usually do not have an impact on bedside practice in the short term, as they  
51  
52 414 rarely take into account clinical applicability.[35] Therefore, a CPG-based goal-directed  
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54 415 checklist associated with a clinician prompting system may be an effective approach to  
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56 416 improve physician adherence to CPG recommendations. Physician-centred healthcare  
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3 417 can be associated with non-adherence to basic recommendations of care, especially in  
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5 418 highly complex processes, such as the management of potential organ donors.[34] In  
6  
7 419 this context, we expect that these organisational adjustments, supported by a checklist-  
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9 420 based management strategy, will have a positive impact on organ donation.  
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12 421 Patel et al.[19] published the results of 671 multi-organ donors managed using  
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14 422 a goal-directed checklist in the United States. The predetermined goals were met in 45%  
15  
16 423 of cases prior to organ recovery, and the use of the goal-directed checklist significantly  
17  
18 424 increased the number of organs transplanted per donor.[19] Recently, we published a  
19  
20 425 prospective observational study that involved 27 ICUs in a southern Brazilian state  
21  
22 426 demonstrating that the use of a goal-directed checklist to guide the management of  
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24 427 deceased donors reduces brain-dead potential organ donor losses due to cardiac  
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26 428 arrest.[13] Compliance with the checklist increased after the start of the study from  
27  
28 429 52.1% to 85.8% ( $p < 0.001$ ). The use of the checklist was associated with a lower  
29  
30 430 likelihood of occurrence of cardiac arrest (odds ratio [OR]: 0.30, 95% CI: 0.18-0.49,  
31  
32 431  $p < 0.001$ ) and an increase in the number of organs recovered per donor.[13] Although  
33  
34 432 these results are encouraging and reproduce the observations of other authors, the  
35  
36 433 observational nature of the studies provides only weak evidence on the subject.[14-19]  
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40 434 The study design and basis for the implementation of DONORS may provide  
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42 435 new insights that can help overcome the weaknesses of previous observational studies,  
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44 436 often related with barriers to conduct studies in deceased organ donors.[5] The cluster  
45  
46 437 randomisation design will limit selection biases, and we will count on a large number of  
47  
48 438 ICUs, which are responsible for a significant amount of brain death notifications  
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50 439 throughout Brazil. The DONORS design will include the evaluation of the effectiveness  
51  
52 440 of a goal-directed checklist strategy in different socioeconomic scenarios in Brazil,  
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54 441 allowing us to provide real-world evidence to support the practical clinical applicability  
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3 442 of the study findings. In addition, the trial is testing the effectiveness of the proposed  
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5 443 intervention by means of an implementation strategy that may be considered feasible to  
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7 444 replicate in different settings. Finally, the characteristics of the institutional quality  
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9 445 improvement programme of this protocol will allow the potential benefits generated by  
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11 446 the proposed study model to be incorporated into ICUs and ultimately transferred to  
12  
13 447 other clinical areas for the care of critically ill patients.  
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16  
17 448 The implementation of a goal-directed checklist for the management of  
18  
19 449 potential donors is a complex intervention, with multiple components. It is important to  
20  
21 450 state that, as in most quality improvement studies, how the intervention is implemented  
22  
23 451 is crucial to the interpretation of the results. In this respect, through this protocol, we  
24  
25 452 aimed to describe in detail all the interventions and co-interventions proposed in the  
26  
27 453 study in order to allow reproducibility of our procedures in other settings. In addition,  
28  
29 454 the logic model presented in the study (Figure 2) is intended to explore the relationships  
30  
31 455 between the activities proposed in the intervention and the mediators of the effect, such  
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33 456 as improved clinical management of potential donors and enhanced communication  
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35 457 with the ICU team about the expected outcomes. Also important is that, although the  
36  
37 458 study focuses on assessing short-term outcomes in potential donors (e.g., cardiac arrest  
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39 459 and number of organs recovered), potential beneficial outcomes are expected for  
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41 460 transplant recipients, such as improved graft function, survival and quality of life.  
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47 461 Our study has some limitations. First, high variability in care and outcomes  
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49 462 among institutions is expected. Although the chosen ICC may be considered  
50  
51 463 conservative, there are no estimates in the literature for the proposed intervention, which  
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53 464 may result in lack of power if the actual ICC is larger than the estimate. In spite of the  
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55 465 procedures to avoid the transfer of information about the checklist to ICUs in the  
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57 466 control group, although with low probability this possibility should be considered,  
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3 467 thereby exposing the details of the content of the goal-directed checklist for the control  
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5 468 group. Furthermore, although stratified randomisation is planned for this study, we must  
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7 469 take into consideration the differences in the number of brain death notifications among  
8  
9 470 ICUs, which will recruit patients at different rates, which in turn may generate learning  
10  
11 471 curves that may have an impact on the final cluster randomisation trial results. In order  
12  
13 472 to minimise this problem, we are allowing a maximum of 30 patients to be recruited per  
14  
15 473 each study site; however, some ICUs may recruit a small number of patients. Inadequate  
16  
17 474 adherence to the checklist may have an impact on the results observed in the  
18  
19 475 intervention group, showing no effect that may be either due to lack of efficacy of the  
20  
21 476 intervention or due to its suboptimal implementation. Another important aspect to  
22  
23 477 highlight is that, although we expect to see an improvement in the quality of organs  
24  
25 478 with the use of the checklist, therefore improving outcomes for organ-transplant  
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27 479 recipients, we are limiting the data collection and study procedures to potential donors,  
28  
29 480 not allowing direct assumptions about its possible effects. Finally, a possible variability  
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31 481 in the care of patients with catastrophic brain injury (CBI), before its evolution to brain  
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33 482 death, may occur among the study sites. On the other hand, the results may contribute as  
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35 483 an indirect evidence for the management of patients who have a CBI.  
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## 44 485 **CONCLUSIONS**

46 486 We expect that the results from DONORS will provide information regarding  
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48 487 the practical use of checklist-guided management interventions for potential multi-organ  
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50 488 donors that may contribute to reducing potential donor losses due to cardiac arrest or  
51  
52 489 other relevant outcomes. At this time, with the increasing demand for organs for  
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54 490 transplantation, standardised, evidence-based guidelines that may be adopted globally  
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56 491 by ICUs and by transplant co-ordinators are needed to improve the availability and  
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492 quality of organs available for donation. The evidence generated by this trial will have  
493 great potential to contribute positively to the donation of organs.

For peer review only

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3 606 **Authors' contributions**  
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53 628 The datasets used and/or analysed during the current study will be available from the  
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3 642 **FIGURE LEGENDS**  
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5 643 **Figure 1.** Study flow diagram.  
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8 644 IRB, Institutional Review Board; No., number  
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10 645 **Figure 2.** Logic model for the checklist intervention.  
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12 646 **Figure 3.** Geographical distribution of the participating intensive care units in Brazil.  
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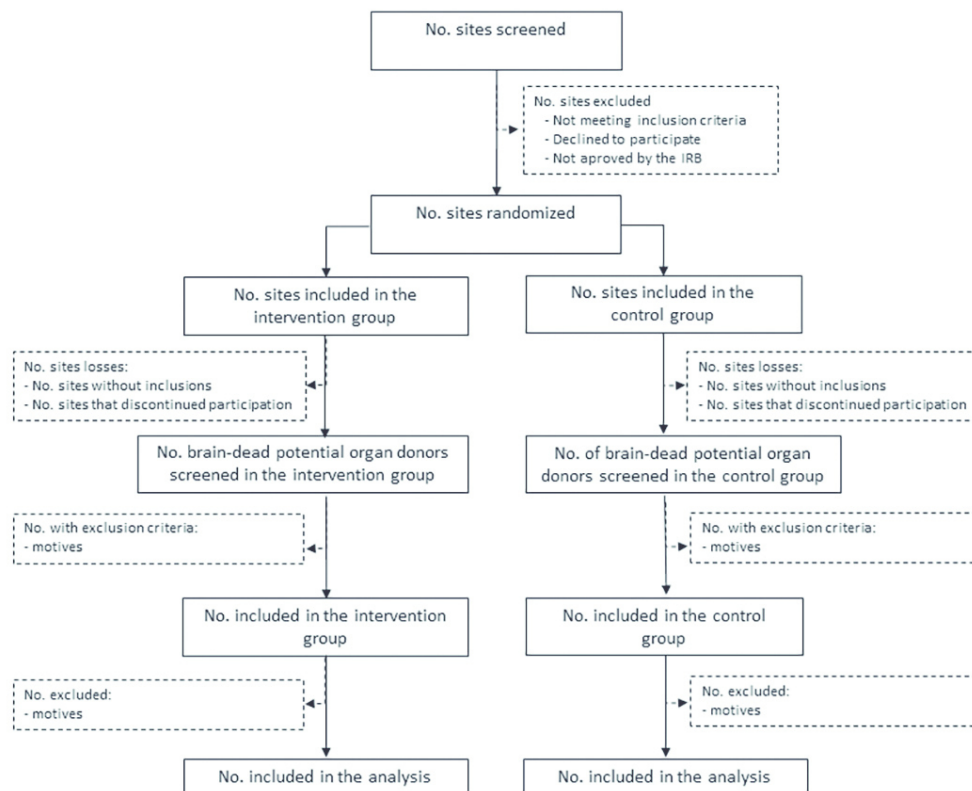
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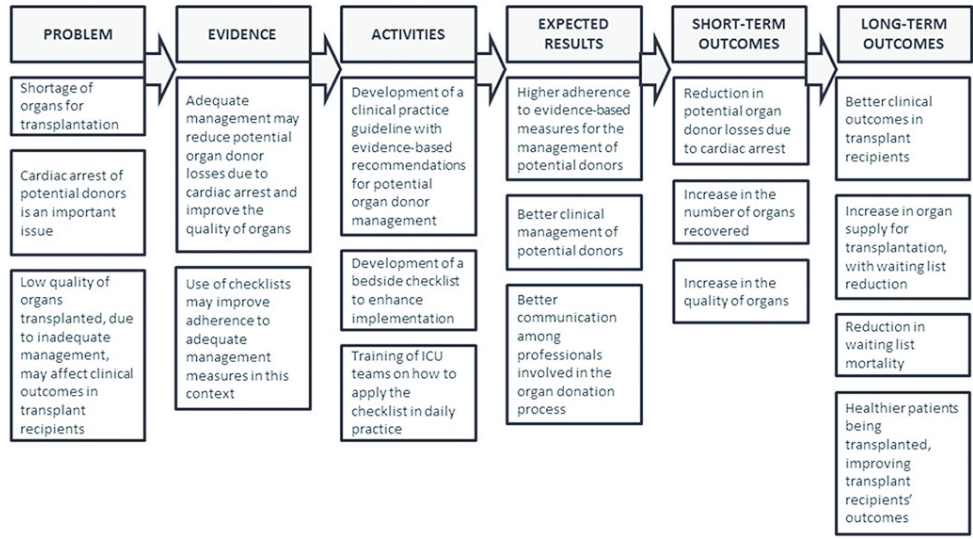
For peer review only



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

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Logic model for the checklist intervention.

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Geographical distribution of the participating intensive care units in Brazil.  
(map base copyright obtained from [www.gettyimages.pt](http://www.gettyimages.pt))

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**Online Supplementary File 1.** Items from the World Health Organisation Trial

## Registration Data Set.

<b>DATA CATEGORY</b>	<b>INFORMATION</b>
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
Contact for scientific 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

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	<ol style="list-style-type: none"> <li>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.</li> <li>2) Control comparator: management of the potential donor according to usual care.</li> </ol>
Key inclusion and exclusion criteria	<ol style="list-style-type: none"> <li>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.</li> </ol>

	<p>2) For potential donors</p> <p>Inclusion criteria: age of 14 years or older, suspected brain death after the first clinical test.</p> <p>Exclusion criteria: age &gt; 90 years, HIV, metastatic cancer, uncontrolled sepsis, acute hepatitis, malaria, acute viral infections, cryptococcal meningoencephalitis and prion diseases, active tuberculosis treated for &lt;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.</p>
Study type	<p>Interventional</p> <p>Allocation: randomized</p> <p>Intervention model: parallel</p> <p>Masking: open label</p> <p>Primary purpose: prevention</p>
Date of first enrolment	20 <sup>th</sup> 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.

<b>Age</b>	<b>Infection</b>	<b>History of cancer</b>
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 1<sup>st</sup> clinical examination consistent with brain death: \_\_\_\_/\_\_\_\_/\_\_\_\_ \_\_\_\_:\_\_\_\_

Current date and time: \_\_\_\_/\_\_\_\_/\_\_\_\_ \_\_\_\_:\_\_\_\_

GOALS TO BE ACHIEVED	STATUS			IMMEDIATE ACTIONS WHEN STATUS = "NO"	ACTION TAKEN?	
SaO <sub>2</sub> ≥ 90%?	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> NA	Adjust FiO <sub>2</sub> and/or PEEP to SaO <sub>2</sub> ≥ 90%	<input type="checkbox"/> Yes	<input type="checkbox"/> No
Vt of 6 to 8 mL/kg of predicted weight?	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> NA	Adjust Vt to 6 to 8 mL/kg	<input type="checkbox"/> Yes	<input type="checkbox"/> No
PEEP ≥ 8 cm H <sub>2</sub> O?	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> NA	Adjust PEEP to ≥ 8 cm H <sub>2</sub> O	<input type="checkbox"/> Yes	<input type="checkbox"/> No
MAP ≥ 65 mmHg and good tissue perfusion after crystalloid bolus?	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> NA	Continue fluid infusion while there is volume responsiveness (ex.: ΔPp ≥ 13% / ΔMAP ≥ 8% / ΔSV ≥ 10% / CVP < 8 mmHg)	<input type="checkbox"/> Yes	<input type="checkbox"/> No
MAP ≥ 65 mmHg and good tissue perfusion after volume adjustment?	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> NA	Maintain / initiate noradrenaline (dopamine if bradycardia)	<input type="checkbox"/> Yes	<input type="checkbox"/> No

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4	Vasopressin and hydrocortisone were associated							
5					Add vasopressin (1 IU bolus + 0.5-2.4 IU / h) and	<input type="checkbox"/> Yes	<input type="checkbox"/> No	
6	after maintaining / initiating noradrenaline /	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> NA				
7					Add hydrocortisone 100 mg 8/8 h	<input type="checkbox"/> Yes	<input type="checkbox"/> No	
8	dopamine?							
9								
10								
11					Assess need for volume replacement			
12	Diuresis < 4 mL/kg/h?	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> NA		<input type="checkbox"/> Yes	<input type="checkbox"/> No	
13					Maintain / initiate vasopressin or desmopressin (IV)			
14								
15	Na <sup>+</sup> < 155 mEq/L?	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> NA	Correct and order laboratory control in 6 h	<input type="checkbox"/> Yes	<input type="checkbox"/> No	
16								
17								
18	K <sup>+</sup> between 3.5 and 5.5 mEq/L?	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> NA	Correct and order laboratory control in 6 h	<input type="checkbox"/> Yes	<input type="checkbox"/> No	
19								
20								
21	Mg <sup>++</sup> > 1.6 mEq/L?	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> NA	Correct and order laboratory control in 6 h	<input type="checkbox"/> Yes	<input type="checkbox"/> No	
22								
23					Insulin IV to maintain glycaemia between 140 and 180			
24	Capillary glycaemia < 180 mg/dL?	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> NA	mg/dL	<input type="checkbox"/> Yes	<input type="checkbox"/> No	
25								
26								
27	Haemoglobin ≥ 7 g/dL?	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> NA	Transfuse red blood cells to Hb ≥ 7g/dL	<input type="checkbox"/> Yes	<input type="checkbox"/> No	
28								
29	Absence of infection?	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> NA	Initiate / maintain antibiotic therapy	<input type="checkbox"/> Yes	<input type="checkbox"/> No	
30								
31								
32	Proper body temperature?							
33					Get 34 to 35°C if without vasopressor	<input type="checkbox"/> NA	<input type="checkbox"/> Yes	<input type="checkbox"/> No
34	No vasopressor: Goal: 34-35°C (after clinical	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> NA				
35	assessments)				Get > 35°C if with vasopressor	<input type="checkbox"/> NA	<input type="checkbox"/> Yes	<input type="checkbox"/> No
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4 With vasopressor: > 35°C  
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9 **Nurse:** \_\_\_\_\_ **Intensivist:** \_\_\_\_\_

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11 CVP, central venous pressure;  $\Delta Pp$ , pulse pressure respiratory variation;  $\Delta SV$ , stroke volume respiratory variation;  $FiO_2$ , fraction of inspired  
12 oxygen; Hb, haemoglobin;  $K^+$ , potassium; MAP, mean arterial pressure;  $Mg^{++}$ , magnesium;  $Na^+$ , sodium; PEEP, positive end-expiratory  
13 pressure;  $SaO_2$ , arterial oxygen saturation;  $V_t$ , tidal volume.  
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**Online Supplementary File 4.** Family interview support guide.

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**PREPARING FOR THE FAMILY INTERVIEW**

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**GROUNDS: Establishing an aid relationship with family members**

**Triad: Respect, Empathy, and Authenticity**

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**READ THE ACTIONS BELOW CAREFULLY BEFORE EACH STEP OF  
THE FAMILY INTERVIEW**

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- |  |   |
|--|---|
| <b>1. Arranging the location of the interview</b>              | <input type="checkbox"/> Well-ventilated place or room<br><input type="checkbox"/> Restricted access (avoid interferences)<br><input type="checkbox"/> Enough space and chairs for all participants<br><input type="checkbox"/> No barriers between interviewer and interviewee (e.g., table, chairs, etc.)<br><input type="checkbox"/> Facial tissues and water are available<br><input type="checkbox"/> Phones are turned off          |
| <b>2. Defining the interview participants</b>                  | <input type="checkbox"/> ICU physician<br><input type="checkbox"/> Transplant co-ordinator and/or ICU nurse are present<br><input type="checkbox"/> 1st*/2nd** degree relatives or legally authorised representative***<br>*1st degree relatives: father, mother, children, full siblings;<br>**2nd degree relatives: grandparents, grandchildren;<br>***Legally authorised representative: Surrogate/ judicial (documented) <sup>1</sup> |
| <b>3. Reviewing the components of non-verbal communication</b> | <input type="checkbox"/> Have all family members sitting down<br><input type="checkbox"/> Leave land-line phones off the hook and turn off mobile phones<br><input type="checkbox"/> 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”

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**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”

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**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 possibility of brain death to the family**
-

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- **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

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## STEP 2 - SECOND FAMILY CONFERENCE

### COMMUNICATING THE BRAIN DEATH – after 2 clinical tests and neuro-imaging evidence

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**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”

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## STEP 3 - THIRD FAMILY CONFERENCE

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**INTERVIEW FOR MULTI-ORGAN DONATION - after the family's  
understanding of the death**

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**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

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**STEP 4 - PLANNING THE APPROACH ACCORDING TO THE FAMILY'S  
DECISION**

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**FAMILY CONSENT FOR  
DONATION**

**FAMILY REFUSAL FOR  
DONATION**

**- Obtain the Family Consent Form,  
fully and correctly completed**

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3 - Complete the death certificate
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6 - **Evaluate the possibility of a rescue**  
7 **interview** for donation after family  
8 conflicts have been resolved
- 9  
10 - **Consider withdrawing therapeutic**  
11 **support** “The physician is legally and  
12 ethically entitled to withdraw therapeutic  
13 support, including mechanical ventilation,  
14 and release the body to the family.”<sup>2</sup>  
15  
16  
17  
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19  
20  
21 - Complete the death certificate  
22
- 

## DEATH CERTIFICATE or FORENSIC MEDICAL EXAMINATION

### ICU physician’s responsibility

- 
- | □ NON-VIOLENT DEATH   | □ VIOLENT DEATH   |
|---|---|
| <p>28</p> <p>29 - Complete the “<b>Death Certificate</b>”</p> <p>30 including the <b>date and time of death</b> and</p> <p>31 the data of the <b>last examination</b></p> <p>32 <b>performed</b> (2nd clinical examination) <b>or</b></p> <p>33 neuro-imaging evidence.</p> <p>34</p> <p>35</p> <p>36</p> <p>37</p> <p>38</p> <p>39</p> <p>40</p> <p>41</p> <p>42</p> <p>43</p> <p>44</p> <p>45</p> <p>46</p> <p>47</p> <p>48</p> <p>49</p> <p>50</p> | <p>30 Complete the “<b>Forensic Medical</b></p> <p>31 <b>Examination Referral Form</b>” including</p> <p>32 the <b>date and time of death</b> and the data of</p> <p>33 the <b>last examination performed</b> (2nd</p> <p>34 clinical examination) <b>or</b> neuro-imaging</p> <p>35 evidence.</p> <p>36</p> <p>37 - Request the Forensic Medical Institute</p> <p>38 for <b>AUTHORISATION TO REMOVE</b></p> <p>39 <b>ORGANS OR TISSUES</b></p> <p>40</p> <p>41</p> <p>42</p> <p>43</p> <p>44</p> <p>45</p> <p>46</p> <p>47</p> <p>48</p> <p>49</p> <p>50</p> |
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<sup>1</sup> Brazilian Federal Law No. 10211 of March 23, 2001;

<sup>2</sup> 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
7 8 9	Co-ordinating centre: Hospital Moinhos de Vento –(Porto Alegre, Rio Grande do Sul)	HOSPITAL MOINHOS DE VENTO – H MV	53999616.0.1001.5330
11 12 13	1 Hospital Alberto Urquiza Wanderley (João Pessoa, Paraíba)	HOSPITAL MOINHOS DE VENTO – H MV	53999616.0.2031.5330
15 16	2 Hospital Beneficência Portuguesa de São Paulo (São Paulo, São Paulo)	HOSPITAL BENEFICÊNCIA PORTUGUESA DE SÃO PAULO	53999616.0.2037.5483
18 19 20 21	3 Hospital Bom Jesus de Ponta Grossa (Ponta Grossa, Paraná)	CENTRO DE ENSINO SUPERIOR DOS CAMPOS GERAIS - CESCAGE/PR	53999616.0.2061.5215
22 23	4 Hospital Bom Jesus de Toledo (Toledo, Paraná)	HOSPITAL MOINHOS DE VENTO – H MV	53999616.0.2063.5330
25	5 Hospital Bruno Born (Lajeado, Rio Grande do Sul)	CENTRO UNIVERSITÁRIO UNIVATES	53999616.0.2027.5310
27 28	6 Casa de Saúde de Santos (Santos, São Paulo)	HOSPITAL GUILHERME ALVARO	53999616.0.2020.5448
30 31 32	7 Hospital Cristo Redentor (Porto Alegre, Rio Grande do Sul)	HOSPITAL NOSSA SENHORA DA CONCEIÇÃO - GRUPO HOSPITALAR CONCEIÇÃO	53999616.0.2035.5530
34	8 Hospital da Restauração (Recife, Pernambuco)	HOSPITAL DA RESTAURAÇÃO	53999616.0.2055.5198
35 36 37	9 Hospital das Clínicas de Botucatu (Botucatu, São Paulo)	UNESP -FACULDADE DE MEDICINA DE BOTUCATU	53999616.0.2017.5411
38 39 40 41	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
42 43 44	11 Hospital das Clínicas de Minas Gerais (Belo Horizonte, Minas Gerais)	UNIVERSIDADE FEDERAL DE MINAS GERAIS	53999616.0.2041.5149
45 46 47	12 Hospital das Clínicas de Rio Branco (Rio Branco, Acre)	HOSPITAL DAS CLÍNICAS DO ACRE - HCA/FUNDHACRE	53999616.0.2070.5009
48 49 50 51	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
53 54 55 56	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
57 58 59	15 Hospital de Pronto Socorro Nelson Marchezan (Canoas, Rio Grande do Sul)	HOSPITAL MOINHOS DE VENTO – H MV	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, Espírito 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

		VENTO – HMV	
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 CATÓLICA 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 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents\*

Section/item	Item No	Description
<b>Administrative information</b>		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym – <b>yes: Title page (page 1)</b>
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry – <b>yes: Title page (page 1), Abstract (page 4), Methods (page 8), and additional file named World_Health_Organization_Trial_Registration_Data_Set_rev</b>
	2b	All items from the World Health Organization Trial Registration Data Set – <b>yes: additional file named World_Health_Organization_Trial_Registration_Data_Set_rev</b>
Protocol version	3	Date and version identifier – <b>not applicable</b>
Funding	4	Sources and types of financial, material, and other support – <b>yes: Funding statement (page 30)</b>
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors – <b>yes: Title page (pages 1 to 3) and Authors' contributions (page 30)</b>
	5b	Name and contact information for the trial sponsor – <b>yes: Funding statement (page 30)</b>
	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 – <b>yes: Organisational aspects of the study (page 19)</b>
	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) – <b>yes: Organisational aspects of the study (page 19)</b>

**Introduction**

1			
2	Background and	6a	Description of research question and justification for undertaking the
3	rationale		trial, including summary of relevant studies (published and
4			unpublished) examining benefits and harms for each intervention –
5			yes: Introduction (page 6 to 7)
6			
7		6b	Explanation for choice of comparators – yes: Introduction (page 6 to
8			7)
9			
10	Objectives	7	Specific objectives or hypotheses – yes: Introduction (page 7) and
11			Objectives (page 7 and 8)
12			
13			
14	Trial design	8	Description of trial design including type of trial (eg, parallel group,
15			crossover, factorial, single group), allocation ratio, and framework (eg,
16			superiority, equivalence, noninferiority, exploratory) – yes: Methods
17			and Analysis (pages 7 and 13)
18			
19			
20	<b>Methods: Participants, interventions, and outcomes</b>		
21			
22	Study setting	9	Description of study settings (eg, community clinic, academic hospital)
23			and list of countries where data will be collected. Reference to where
24			list of study sites can be obtained – yes: Methods and Analysis (page
25			8), and Study planning and implementation schedule (page 19)
26			
27			
28	Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility
29			criteria for study centres and individuals who will perform the
30			interventions (eg, surgeons, psychotherapists) – yes: Methods and
31			Analysis (pages 8, 9 to 11)
32			
33			
34	Interventions	11a	Interventions for each group with sufficient detail to allow replication,
35			including how and when they will be administered) – yes: Methods
36			and Analysis (pages 9 to 12)
37			
38		11b	Criteria for discontinuing or modifying allocated interventions for a
39			given trial participant (eg, drug dose change in response to harms,
40			participant request, or improving/worsening disease) – not applicable
41			
42		11c	Strategies to improve adherence to intervention protocols, and any
43			procedures for monitoring adherence (eg, drug tablet return,
44			laboratory tests) – yes: Methods and Analysis (pages 9 to 12, 17, 18)
45			
46			
47		11d	Relevant concomitant care and interventions that are permitted or
48			prohibited during the trial – yes: Methods and Analysis (page 11)
49			
50	Outcomes	12	Primary, secondary, and other outcomes, including the specific
51			measurement variable (eg, systolic blood pressure), analysis metric
52			(eg, change from baseline, final value, time to event), method of
53			aggregation (eg, median, proportion), and time point for each
54			outcome. Explanation of the clinical relevance of chosen efficacy and
55			harm outcomes is strongly recommended – yes: Methods and
56			Analysis (pages 13, 14, 17, 18)
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2	Participant	13	Time schedule of enrolment, interventions (including any run-ins and
3	timeline		washouts), assessments, and visits for participants. A schematic
4			diagram is highly recommended (see Figure) – <b>yes: Study planning</b>
5			<b>and implementation schedule (page 19) and Methods and Analysis</b>
6			<b>(pages 9 to12)</b>
7			
8	Sample size	14	Estimated number of participants needed to achieve study objectives
9			and how it was determined, including clinical and statistical
10			assumptions supporting any sample size calculations – <b>yes: Methods</b>
11			<b>and Analysis (page 13)</b>
12			
13			
14	Recruitment	15	Strategies for achieving adequate participant enrolment to reach
15			target sample size – <b>yes: Methods and Analysis (page 11)</b>
16			

### Methods: Assignment of interventions (for controlled trials)

#### Allocation:

21			
22	Sequence	16a	Method of generating the allocation sequence (eg, computer-
23	generation		generated random numbers), and list of any factors for stratification.
24			To reduce predictability of a random sequence, details of any planned
25			restriction (eg, blocking) should be provided in a separate document
26			that is unavailable to those who enrol participants or assign
27			interventions – <b>yes: Methods and Analysis (page 13)</b>
28			
29			
30	Allocation	16b	Mechanism of implementing the allocation sequence (eg, central
31	concealment		telephone; sequentially numbered, opaque, sealed envelopes),
32	mechanism		describing any steps to conceal the sequence until interventions are
33			assigned – <b>yes: Methods and Analysis (page 13)</b>
34			
35	Implementation	16c	Who will generate the allocation sequence, who will enrol participants,
36			and who will assign participants to interventions – <b>yes: Methods and</b>
37			<b>Analysis (page 13)</b>
38			
39			
40	Blinding	17a	Who will be blinded after assignment to interventions (eg, trial
41	(masking)		participants, care providers, outcome assessors, data analysts), and
42			how – <b>yes: Methods and Analysis (page 13)</b>
43			
44			
45		17b	If blinded, circumstances under which unblinding is permissible, and
46			procedure for revealing a participant's allocated intervention during
47			the trial – <b>not applicable</b>
48			

### Methods: Data collection, management, and analysis

51	Data collection	18a	Plans for assessment and collection of outcome, baseline, and other
52	methods		trial data, including any related processes to promote data quality (eg,
53			duplicate measurements, training of assessors) and a description of
54			study instruments (eg, questionnaires, laboratory tests) along with
55			their reliability and validity, if known. Reference to where data
56			collection forms can be found, if not in the protocol – <b>yes: Methods</b>
57			<b>and analysis (pages 15, 16) – complementary information will be</b>
58			<b>available at the statistical analysis plan paper</b>
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- 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**

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2	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor <b>Methods and analysis (page 15) – complementary information will be available at the statistical analysis plan paper</b>
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8	<b>Ethics and dissemination</b>		
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10	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval – <b>yes: Ethics and dissemination (pages 19, 20) and additional file “Sites and IRB approval”</b>
11			
12			
13			
14	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) – <b>yes: Ethics and dissemination (pages 19, 20)</b>
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20	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) – <b>yes: Ethics and dissemination (pages 19, 20)</b>
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24		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable – <b>not applicable</b>
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29	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 – <b>yes: Methods and analysis (page 15)</b>
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34	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site – <b>yes, Competing interests’ statement (page 30) and individual conflict of interest forms</b>
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39	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 – <b>yes: Data sharing (page 30)</b>
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43	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 – <b>not applicable</b>
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48	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 – <b>yes: Ethics and dissemination (pages 19, 20)</b>
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55		31b	Authorship eligibility guidelines and any intended use of professional writers – <b>not applicable</b>
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58		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code – <b>yes: Data sharing (page 30)</b>
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## Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates – <b>not applicable</b>
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 – <b>not applicable</b>

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\*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.

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