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Impact of Targeted Hypothermia in Expanded Criteria Organ Donors on Recipient Kidney-Graft Function: Study Protocol for a Multicenter Randomized Controlled Trial (HYPOREME)

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1 **Impact of Targeted Hypothermia in Expanded Criteria Organ Donors on Recipient**
 2 **Kidney-Graft Function: Study Protocol for a Multicenter Randomized Controlled Trial**
 3 **(HYPOREME)**

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3 **1 List of abbreviations**
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7 3 DGF: delayed graft function

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9 4 DSMB: Data Safety Monitoring Board

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11 5 ECD: expanded criteria donor

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13 6 eCRF: electronic case report form

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15 7 ICU: intensive care unit

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17 8 ITT: intention-to-treat

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19 9 KR: kidney recipient

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21 10 KTx: kidney transplantation

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3 **1 ABSTRACT**
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8 **3 Introduction:** Expanded-criteria donors (ECDs) are used to reduce the shortage of kidneys
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10 for transplantation. However, kidneys from ECDs are associated with an increased risk of
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12 delayed graft function (DGF). DGF is a risk factor for allograft loss and mortality.
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15 HYPOREME will be the first trial comparing targeted hypothermia to normothermia in
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17 ECDs. We hypothesize that targeted hypothermia will decrease the incidence of DGF in
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19 recipients of kidneys from ECDs.
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21 **9 Methods and analysis:** HYPOREME is a multicenter randomized controlled trial comparing
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23 the effect on kidney function in recipients of targeted hypothermia (34 to 35°C) and
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25 normothermia (36.5 to 37.5°C) in the ECDs. The temperature intervention starts from
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27 randomization (after legal determination of death by neurologic criteria) and is maintained
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29 until aortic clamping in the operating room. We aim to enroll 289 ECDs in order to analyze
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31 the kidney function of 516 recipients in the 53 participating centers. The primary outcome is
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33 the occurrence of DGF in kidney recipients, defined as a requirement for renal replacement
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35 therapy within 7 days after transplantation (not counting a single session for hyperkalemia
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37 during the first 24 hours). Secondary outcomes include the proportion of patients with
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39 individual organs transplanted in each group; the number of organs transplanted from each
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41 ECD; and the vital status and kidney function of the recipients 7 days, 28 days, 3 months, and
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43 1 year after transplantation. An interim analysis is planned after the enrolment of 258 kidney
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45 recipients.
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51 **22 Ethics and dissemination:** The trial was approved by the ethics committee of the French
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53 Intensive Care Society (CE-SRLF-16-07) on April 26, 2016 and by the competent French
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55 authorities on April 20, 2016 (Comité de Protection des Personnes - TOURS-Région Centre-
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57 Ouest 1, registration #2016-S3). Findings will be published in peer-reviewed journals and
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1 presented during national and international scientific meetings.

2 **Trial Registration:** NCT03098706.

3 4 **Strengths and limitations of this study**

- 5 • HYPOREME will be the first large randomized controlled trial (RCT) to evaluate the
6 impact of targeted hypothermia on the function of kidneys from expanded-criteria
7 donors (ECDs) after transplantation.
- 8 • The trial is open, since the nature of the intervention on the ECDs makes the blinding
9 of the healthcare staff to group assignment impossible.
- 10 • The results of this RCT are expected to provide intensivists with additional guidance
11 about the optimal management of deceased organ donors.

12
13
14 **Keywords:** Organ donor, kidney transplantation, hypothermia, renal replacement therapy,
15 delayed graft function

1 BACKGROUND

2 Kidney transplantation (KTx) is the best therapeutic option for patients with end-stage
3 renal disease and improves both survival and quality of life (1). The use of expanded-criteria
4 donors (ECDs) in solid-organ transplantation was implemented in 2002 in the United States
5 to address the issue of organ donor shortage (2). In 2017 in France, half the KTxs were
6 performed with ECDs (3). Although the use of ECDs undoubtedly expands the pool of
7 deceased organ donors, it is associated with a significant risk of delayed graft function (DGF)
8 after transplantation (4,5). DGF is reported in up to 50% of kidney recipients (6) and is a
9 significant risk factor for allograft loss and mortality (7,8). Moreover, DGF is associated with
10 both acute rejection and worse long-term renal allograft function (9). Thus, developing new
11 strategies to reduce the risk of DGF is a major priority in KTx. Optimizing ECD management
12 from the confirmation of neurologic death to organ recovery in the operating room has been
13 shown to increase the organ yield per donor (10). Conceivably, better ECD management may
14 also improve renal allograft function after transplantation.

15 Hypothermia may help to preserve renal function in donors (11). Experimental data have
16 shown that mild hypothermia reduces cell metabolism, inflammation, and free-radical
17 production (12). A randomized controlled trial conducted in the United States in 2015 found
18 that targeted hypothermia (34 to 35°C) in deceased organ donors reduced the incidence of
19 DGF in kidney recipients compared to normothermia (36.5 to 37.5°C), from 39.2% to 28.2%
20 ($P=0.02$) (13). A subgroup analysis from this trial suggested that kidney recipients from
21 ECDs benefited the most from donor targeted hypothermia. However, this result needs to be
22 confirmed. Therefore, we designed a multicenter randomized controlled trial (HYPOREME)
23 to test the safety and efficacy of targeted hypothermia compared to normothermia as part of
24 the management of ECDs. We hypothesized that targeted hypothermia in ECDs would
25 decrease the incidence of DFG in kidney recipients.

1 METHODS/DESIGN

2 3 **Trial design and settings**

4 HYPOREME is a multicenter, randomized, controlled, open-label trial comparing
5 two parallel groups of patients.

6 7 **Participants, interventions, outcomes**

8 *Participating units*

9 A total of 53 French intensive care units (ICUs) and transplant centers are
10 participating in the study (30 university hospitals and 23 general hospitals). All participating
11 ICU staff members are trained and experienced in the procedures and protocols of organ
12 donation and in the management of deceased organ donors.

13 14 *Study population and recruitment modalities*

15 This study involves two distinct populations:

- 16 • Deceased ECDs for whom the diagnosis of death is made based on neurologic
17 criteria in compliance with French law. ECDs are defined as deceased donors who
18 are older than 60 years or who are aged 50-59 years and have at least two other risk
19 factors (history of hypertension, creatinine >132 µmol/L, and/or cerebrovascular
20 cause of death). The study intervention (targeted temperature management) applies to
21 this population.
- 22 • Kidney recipients who receive a kidney allograft from the above-described ECDs.
23 The effect of the study intervention is evaluated in this population based on allograft
24 function.

25 Deceased ECDs and kidney recipients must fulfil all of the criteria listed below to be

1 included in the study.

2 *Inclusion criteria for deceased ECDs*

- 3 - Traumatic, vascular, or other brain injuries responsible for death defined by
4 neurologic criteria,
5 - Legal determination of death based on neurologic criteria in compliance with French
6 law,
7 - Organ donation procedure engaged in compliance with French law,
8 - Deceased ECD older than 60 years or aged 50-59 years with at least two other risk
9 factors (history of hypertension, creatinine >132µmol/L, and/or cerebrovascular cause
10 of death),
11 - Next of kin informed of the study.

12 *Inclusion criteria for kidney transplant recipients:*

- 13 - Patient registered on the waiting list for KTx,
14 - Patient informed of the study,
15 - Age 18 years or older at the time of the pretransplantation evaluation,
16 - Patient covered by the statutory French health insurance.

17 Deceased organ donors or kidney recipients fulfilling one or more of the following
18 criteria are not included in the study.

19 *Exclusion criteria for deceased organ donors:*

- 20 - Donors with circulatory death or donors who died after treatment limitation,
21 - Patient registered in the French registry for refusing organ and tissue donations,
22 - Pregnancy,
23 - Age less than 18 years,
24 - Adult under guardianship,

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2
3 1 - Contraindication to organ donation identified according to the current
4
5 2 recommendations of the French Biomedicine Agency (*Agence de la Biomédecine*).

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8 3 *Exclusion criteria for kidney transplant recipients:*

- 9
10 4 - Refusal to participate in the study expressed by the patient,
11
12 5 - Pregnancy,
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14 6 - Age less than 18 years,
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17 7 - Adult under guardianship, or correctional facility inmate.
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22 9 ***Study intervention***

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24 10 The intervention is initiated after study inclusion and randomization. Deceased ECDs
25
26 11 are allocated at random to one of the two targeted temperature strategies (Figure 1). The
27
28 12 designated targeted temperature strategy is initiated as soon as possible after randomization
29
30 13 and continues until aortic clamping in the operating room. The objective is to reach the
31
32 14 targeted temperature range within 4 hours after randomization.

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35 15 - In the targeted hypothermia group, ECDs have mild hypothermia (34°C to 35°C)
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37 16 induced then maintained until aortic clamping in the operating room.
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39 17 - In the targeted normothermia group, patients have normothermia (36.5°C-37.5°C)
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41 18 induced and maintained until aortic clamping in the operating room.
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50 20 ***Targeted temperature protocol***

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52 21 No trial has demonstrated one method to be better than another for targeted
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54 22 temperature management. Therefore, to induce and maintain the ECDs at 34°C-35°C or
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56 23 36.5°C-37.5°C, each participating center uses its usual method and protocol. The method
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58 24 may involve active internal cooling or warming using specific devices, active external
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60 25 cooling or warming using specific devices, or active external cooling or warming without

1 specific devices. A standard protocol of targeted temperature management was provided to
2 each participating center (supplementary appendix, Figure 1). Body temperature is recorded
3 hourly from randomization to aortic clamping using invasive (intravascular catheter with a
4 temperature-sensing vascular probe placed in the femoral artery, Pulse Contour Cardiac
5 Output, PiCCO[®], or equivalent) or semi-invasive (esophageal probe, intra-rectal probe,
6 urinary probe) methods according to the device available and local protocol at each center.

8 ***General principles of management in both study arms***

9 The general management of deceased organ donors in the ICU and operating room
10 follows the standard protocol recommended by the French Biomedicine Agency in all
11 participating centers (supplementary appendix, Table 1) (14).

13 ***Study outcomes***

14 ***Primary outcome measure***

15 The primary outcome is the proportion of kidney recipients with DGF. DGF is
16 defined as a need for renal replacement therapy during the first week after transplantation
17 (not counting a single session of renal replacement therapy to treat hyperkalemia during the
18 first 24 hours after transplantation). DGF is determined for each kidney recipient at the
19 transplant center where the KTx was performed. The decision to commence renal
20 replacement therapy is left at the discretion of the nephrologist in charge.

21 In the rare case of transplantation of both kidneys from a donor into a single recipient,
22 that recipient is counted only once: the primary outcome measure is based on the presence or
23 absence of DGF in the kidney recipient.

25 ***Secondary outcome measures***

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3 1 The secondary outcomes for the ECDs consist in comparing the following between the two
4
5 2 arms:

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8 3 - number of organs recovered and number transplanted,
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10 4 - body temperature recorded hourly from randomization to aortic clamping,
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12 5 - number of severe cardiac arrhythmia episodes,
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14 6 - total volume of intravenous fluids administered,
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17 7 - need for vasopressors and inotropes, including total dose and maximal dose,
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19 8 - lowest and highest blood pressures,
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21 9 - cardiac arrest leading to abortion of the organ-donation procedure,
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23
24 10 - metabolic disturbances and coagulation disorders,
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26 11 - kidney function of organ donors: last serum creatinine and creatinine clearance before
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28 12 transfer to the operating room.

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31 13 The secondary outcomes for the kidney recipients consist in comparing the following
32
33 14 between the two arms:

- 34
35 15 - hospital length of stay after transplantation,
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37 16 - kidney graft function (serum creatinine) at hospital discharge on days 7 and 28, and 3
38
39 months and 1 year after transplantation,
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42 18 - persistent need for renal replacement therapy 28 days, 3 months, and 1 year after
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44 19 transplantation,
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47 20 - reason for renal replacement therapy implementation (sepsis, acute rejection, oliguria,
48
49 21 hyperkalemia),
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51 22 - hospital mortality,
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54 23 - day-28 (after transplantation) mortality,
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56 24 - day-90 (after transplantation) mortality,
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58 25 - day-365 (after transplantation) mortality.
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6 2 **Organization of the trial**
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8 3 Figure 1 is the study flowchart.
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12 5 **Recruitment modalities**
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15 6 All patients with a confirmed diagnosis of death based on neurologic criteria in
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17 7 compliance with French law and who meet the definition of ECDs will be screened for
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19 8 eligibility by the ICU physicians and clinical research nurses, around the clock and 7 days a
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21 9 week. Patients will be included after checking inclusion and non-inclusion criteria. A log of
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23 10 patients considered for study participation will be kept and will include the reasons for non-
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25 11 inclusion.
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31 13 **Randomization**
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33 14 Randomization is centralized and performed using a secure, computer-generated,
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35 15 interactive, web-response system available at each study center. Randomization is stratified
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37 16 on study center with a 1:1 ratio.
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42 18 **Blinding**
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45 19 The trial is open, since the nature of the intervention on the ECDs makes the blinding
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47 20 of the healthcare staff to group assignment impossible. However, the absence of blinding
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49 21 cannot have an impact on assessment of the primary outcome. Indeed, the primary outcome
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51 22 (the occurrence of DGF) is analyzed in another population of patients, namely kidney
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53 23 recipients. The nephrologists in charge of the kidney recipients, who decide whether renal
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55 24 replacement therapy is needed during the first week after transplantation, are blinded to the
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57 25 intervention arm of the donor.
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Sample size

According to a recent randomized controlled trial conducted in the United States (13) and to our local experience at the transplant center in Nantes (France), the proportions of recipients with renal DGF after transplantation from ECDs were 56.5% and 48%, respectively. In the US trial, the proportion with DGF was 56.5% in the normothermia group and 31% in the hypothermia group (13).

To demonstrate a 14% decrease in the proportion of recipients with DGF (from 48% in the normothermia group to 34% in the hypothermia group), a total of 516 kidney recipients are required (258 in each group) to provide 90% power with a two-sided alpha risk of 5%. The analysis of 516 kidney recipients theoretically requires 258 randomized ECDs. However, assuming an estimated attrition rate of 12% (i.e., ECDs who are randomized but for whom organs are not recovered or are recovered but not transplanted) and given that in rare cases both kidneys from a donor are transplanted into a single recipient, our enrolment target is 289 randomized ECDs.

Interim analysis

The sample size estimation is based on the primary outcome, i.e., the occurrence of DGF. However, there is some uncertainty related to the limited amount of data available in the literature. Accordingly, an interim analysis is planned after the enrolment of 258 kidney recipients. The primary objective of this interim analysis is to reassess the sample size of the study using the method proposed by Friede and Kieser (15,16). The probability of DGF will be estimated from all treatment groups combined in order to preserve blindness. This method makes it possible to maintain the initial clinical hypothesis (14% decrease in the frequency of DGF) and to control the type I error.

1 The interim analysis will be conducted by an independent Data Safety Monitoring Board
2 (DSMB), whose members are not otherwise involved in the trial. This DSMB consists of one
3 methodologist and two intensivists. For the interim analysis, the DSMB will have access to
4 the following unblinded results:

- 5 • For the ECDs: number of patients enrolled, body temperature, mean arterial pressure,
6 total dose of vasopressors and inotropes, episodes of severe arrhythmia or cardiac
7 arrest, number of organs recovered from the donor, reason why organs were not
8 recovered (if applicable), use of machine perfusion for organ storage, and cold
9 ischemia time.
- 10 • For the recipients: occurrence of DGF, need for renal replacement therapy during the
11 first week posttransplantation, allograft lost by day 7, vital status on day 7, severe
12 posttransplantation complications, serum creatinine <250 µmol/L on day 7, and
13 allograft function and vital status on day 28 posttransplantation.

14 The results of the interim analysis will not be disclosed unless they lead the DSMB to request
15 premature trial discontinuation.

17 ***Statistical analysis***

18 All analyses will be performed using SAS software (V.9.4). Analyses will be
19 conducted on data from the intention-to-treat (ITT) population as well as from the per-
20 protocol population.

21 For the primary analysis, sensitivity analyses will be performed with populations
22 defined as follows: first, the ITT population defined as all recipients who received kidneys
23 from the ECDs and, second, all donors, regardless of whether organs were recovered and
24 transplanted. The latter case (failure to recover organs) will be considered a failure for the
25 main outcome measure (occurrence of DGF).

1 In the per-protocol analysis, all randomized patients will be kept in the analysis
2 except those with one or more major protocol violations, such as failure to meet all the
3 inclusion criteria and none of the non-inclusion criteria, an inability to perform the surgical
4 procedure, or withdrawal of consent to participate in the study.

5 A statistical analysis report will be written to describe all the findings, according to
6 CONSORT Statement recommendations, while considering the specific features of the trial,
7 most notably the nonpharmacological nature of the intervention. The baseline features of the
8 groups established by randomization will be compared using descriptive statistics.
9 Continuous variables will be described as mean±SD if normally distributed and as median
10 [interquartile range] otherwise. Categorical data will be described as exact numbers and
11 percentages.

12 For the primary analysis, binary categorical data will be analyzed using random-effect
13 logistic regression adjusted to take into account the hierarchical structure of the data (kidneys
14 from the same donor) and variability across centers.

15 The number of organs transplanted per donor will be compared between the two
16 groups using Poisson regression model. Hospital length of stay will be compared between the
17 two groups using a generalized model with random effects models. Patient and graft
18 survivals will be compared using Cox regression models. All models will be adjusted on
19 centres and consider ECDs as random effects.

21 ***Handling missing data***

22 We expect no missing data for the primary outcome. The frequency of missing data
23 should be low for the other outcomes as the ECDs included in the study are hospitalized for a
24 few hours or days at the most in the intensive care unit. Kidney transplant recipients are
25 admitted to the nephrology department. Few patients will be lost to follow-up, as

1 hospitalization after KTx lasts routinely about 10 days. Only survival on day 28 and 3
2 months and 1 year after hospital discharge of recipients may be missing. We will not use any
3 technique to replace missing data. Missing data will be reported for each treatment arm.

4 5 ***Data collection and follow-up***

6 The donor will be followed from randomization to aortic clamping in the operating
7 room. The following data will be recorded until aortic clamping in the operating room: date
8 and time of death based on neurologic criteria, demographic and clinical data, treatments
9 administered, laboratory tests, body temperature, adverse events (mainly cardiac arrhythmias,
10 cardiac arrest, coagulopathy, and refractory shock), number of organs recovered in the
11 operating room, use of machine perfusion for organ storage, and number of organs ultimately
12 transplanted.

13 The kidney recipient will be followed from transplantation to 1 year after
14 transplantation. The following data will be recorded: demographic and clinical data,
15 treatments given, laboratory tests, cold ischemia time, and vital status and graft function on
16 days 7, 28, and 90 and after 1 year. Posttransplantation complications will be recorded during
17 the first 28 days following transplantation (mainly acute allograft rejection, cardiovascular
18 events, infections, and surgical complications). Table 1 is the flowchart of patient follow-up.

19 20 ***Data entry and monitoring***

21 An Internet-based data collection tool will be used to store the data of all the ECDs
22 and recipients. This electronic case-report form (eCRF) is a secure, interactive, web-response
23 system available at each study center. The eCRF is provided and managed by the biometrical
24 unit of the Nantes University Hospital (EA 4275 SPHERE “Methods for patient-centered

1 outcomes and health research”). Access to the eCRF will require only an Internet connection
2 and a browser.

3 Monitoring of the collected data and screening forms in each participating center will
4 be carried out by the Research Division Promotion Department of the Nantes University
5 Hospital. Research assistants will regularly perform on-site checks of adherence to the
6 protocol and accuracy of the recorded data.

8 ***Confidentiality and source data archiving***

9 The medical data about each patient will be communicated only to the institution (i.e.,
10 the sponsor) with which the chief investigator is affiliated or to a person appointed by the
11 chief investigator and the sponsor under conditions that ensure the confidentiality of the
12 patient data. During or at completion of the study, the data collected from the study
13 participants and communicated by the individuals involved in the study will be rendered
14 anonymous. The study investigators will archive all study data for at least 15 years after the
15 end of the study.

17 ***Protocol amendments***

18 Any modifications to the protocol will require a formal amendment to the protocol.
19 Such amendment will be reviewed by the Research Division Promotion Department of the
20 Nantes University Hospital and agreed by the competent French authorities (Comité de
21 Protection des Personnes - TOURS-Région Centre-Ouest 1) prior to implementation. Any
22 modifications to the protocol will be communicated without delay to relevant parties
23 (investigators and trial participants).

25 ***Dissemination policy***

1 The publication policy will comply with international recommendations (N Engl J
2 Med, 1997; 336:309-315) and the CONSORT statement (<http://www.consort-statement.org>).
3 Findings will be published in peer-reviewed journals and presented during national and
4 international scientific meetings. Communications and scientific reports relevant to this study
5 will be under the responsibility of the study coordinator (EC), who will obtain the approval
6 of the other investigators.

7 Substantive contributions of investigators, clinicians, researchers, and statisticians to
8 the design, conduct, interpretation, and reporting of the trial will be granted of authorship on
9 the final trial report.

10 Full protocol and participant-level dataset will be made available for scientific
11 purpose on reasonable request, after the agreement of the ethics and steering committee.

12 13 ***Patient and public involvement***

14 Neither the patients nor the public are involved in the conduct of the study.

15 16 **DISCUSSION**

17 HYPOREME will be the first large randomized controlled trial to evaluate the impact
18 of targeted hypothermia on the function of kidneys received from ECDs. The results are
19 expected to provide intensivists with additional guidance about the optimal management of
20 deceased organ donors.

21 22 **TRIAL STATUS**

23 The first trial inclusion was on November 9, 2017. The protocol version is identified
24 RC16_0041_Protocol HYPOREME V10.1 on December 12, 2020. The scheduled interim
25 analysis was done on December 5, 2019, after the inclusion of 258 kidney recipients. The

1 interim analysis led the DSMB to recommend continuation of the study without modification
2 of the protocol and confirmed the initial goal of enrolling 516 kidney recipients. In addition,
3 the DSMB suggested a second interim analysis after the inclusion of 350 kidney recipients.
4 The second interim analysis was done on February 11, 2021, and led the DSMB to
5 recommend continuation of the study without modification of the protocol. On February 11,
6 2021, 349 kidney recipients had been included. The trial is expected to be completed in June
7 2021.

9 **DECLARATIONS**

10 ***Ethics approval***

11 The HYPOREME trial was approved by the ethics committee of the French Intensive
12 Care Society (CE-SRLF-16-07) on April 26, 2016 and by the competent French authorities
13 on April 20, 2016 (Comité de Protection des Personnes - TOURS-Région Centre-Ouest 1,
14 registration #2016-S3) and was registered on ClinicalTrials (NCT03098706) in April 2017.

16 ***Consent to participate***

17 In compliance with French law, at the time of declaration of death based on neurologic
18 criteria, the French registry of persons refusing organ and tissue donation is examined to
19 confirm that the deceased patient is not registered. In addition, families or next of kin are
20 interviewed to check that the patient had not expressed unwillingness to donate organs and/or
21 tissues. During the same meeting, information about the study is given orally and an
22 information letter is handed to the family. That this information was delivered is documented
23 in the donor's medical chart by the local investigator. Legal statutes do not require informed
24 consent from families or next of kin for study inclusion, given that no harm can come to a
25 deceased patient.

1 Prior to study initiation, all the participating transplant centers were contacted. Each
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1 Prior to study initiation, all the participating transplant centers were contacted. Each
2 transplant center approved the study protocol. The allocation of organs to specific recipients
3 occurs based on the national regulations set forth by the French Agency of Biomedicine. The
4 transplant center that receives the organs from an included ECD is informed of the study
5 inclusion but blinded to the treatment arm. Kidney recipients are informed of the study orally
6 and via a written information sheet and are then asked to provide their written informed
7 consent to participation in the trial. That this information was delivered is documented in the
8 medical chart of the kidney recipient by the investigator.

9 Model consent form and other related documentation given to participants and
10 authorized surrogates are provided in the supplementary appendix.

12 ***Access to data***

13 Only the statisticians of the trial and the members of the DSMB have access to the
14 intra-study dataset in order to ensure that the results are not disclosed prior the end of the
15 trial. After study completion, site investigators will have access to the full dataset if a formal
16 request is approved by the steering committee.

18 ***Availability of data and materials***

19 Not applicable

21 ***Competing Interests***

22 EC received fees for lectures and conference talks and had travel and accommodation
23 expenses related to attending scientific meetings covered by Gilead, Baxter and Sanofi-
24 Genzyme.

1 ***Trial sponsor and Funding***

2 The sponsor of the trial is the Centre Hospitalier Universitaire de Nantes (Direction de
3 la recherché et de l'Innovation – 5, allée de l'île Gloriette, 44093 Nantes cedex 01, France,
4 Phone : +33 253 482 835).

5 The HYPOREME trial received a grant from the French Ministry of Health in 2016
6 (Programme Hospitalier de Recherche Clinique Inter-Régional 2016; API16/N/033) and a
7 grant from the French Intensive Care Society in 2018.

8 Sponsor and funders had no role and no ultimate authority over the study design;
9 collection, management, analysis, and interpretation of data; writing of the report; and the
10 decision to submit the report for publication

12 ***Authors' contributions***

13 NB and EC prepared the first draft of the manuscript.

14 JR, MP, NB, and EC wrote the manuscript.

15 JR, NB, MP, MH, and EC participated in designing the HYPOREME study.

16 MP and VS wrote the statistical analysis plan and performed the sample size
17 estimation.

18 NB and JR obtained funding for the study.

19 NB, EC, MP, MH, KA, BR, AD, LD, MP, SH, PT, JMB, LMM, FL, RR, TB, TK,
20 AT, OL, JFV, ML, RL, CV, AG, PB, CQ, PYE, OH, AR, YL, JCV, MB, OM, MHV, FH,
21 DS, AC, DG, LA, MH, NK, VM, JB, MLQD, EM, TB, PG, AEH, PM, AG, CH, BF, CM,
22 CGC, NB, JPR, AD, SD, SCO, LF, SG, LA, LR, DB, AH, PFW, FM, ED, DD, EA, CO, VS
23 and JR contributed to acquire the study data.

24 All authors revised the manuscript for important intellectual content and read and
25 approved the final version of the manuscript.

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6 **Acknowledgments**
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For peer review only

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1 **FIGURE LEGENDS**

2 **Figure 1:** Study flowchart

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1 TABLES

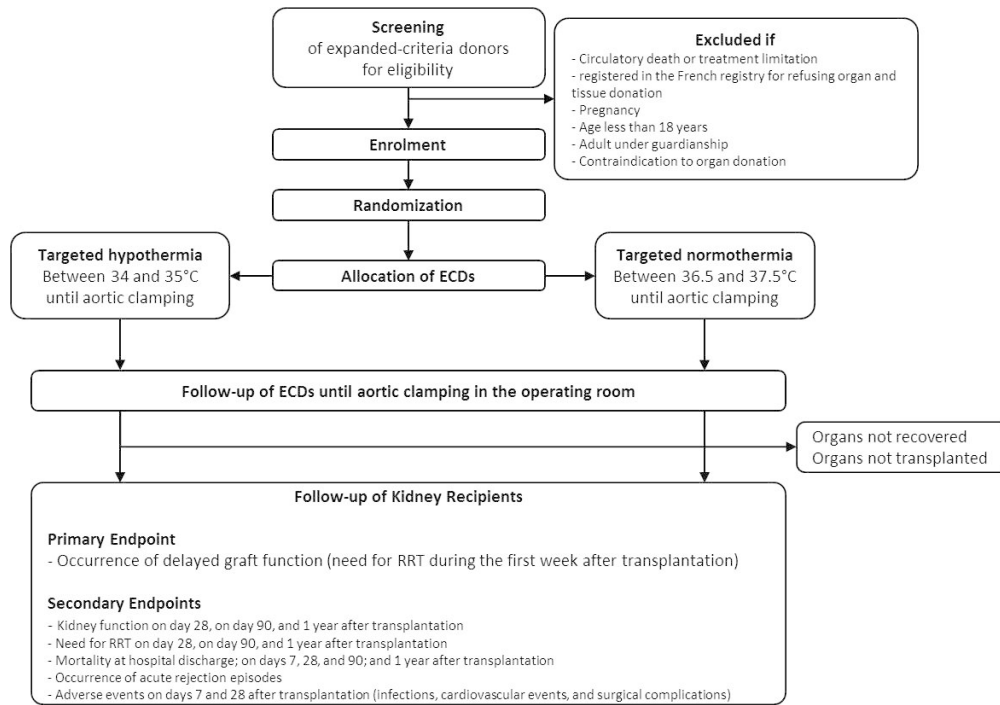
2
3 **Table 1: Flow-chart of patient follow-up**

	Inclusion	D0*	Operating room	Dx	D7**	D28**	D90*	One year End of follow-up**	
	ECD			Kidney recipient					
Eligibility: check inclusion and exclusion criteria (for both ECD and KR)	X			DAY OF TRANSPLANTATION					
ECD: information of family/next of kin	X								
KR: information of the patient	X								
Randomization (ECD)		X							
Demographic characteristics		X							
Vital signs		X	X						
Laboratory tests		X	X			X	X	X	X
Body temperature		X	X						
Treatments		X	X			X			
Renal replacement therapy						X	X	X	X
Infectious complications						X	X		
Surgical complications						X	X		
Cardiovascular complications						X	X		
Acute rejection episodes						X	X		
Vital status					X	X	X	X	

5
6 * from time of inclusion to 11:59 pm

7 ** Day-7, day-28, day-90 and 1 year posttransplantation (Dx).

8 ECD, expanded criteria donor; KR, kidney recipient



Study flowchart

198x139mm (150 x 150 DPI)

Supplementary Appendix

Figure 1: Targeted temperature management protocol provided to each center

→ Targeted hypothermia (34-35°C) by internal cooling or warming device

The use of an intravenous bolus of cold (4°C) isotonic saline is not recommended.

→ Targeted hypothermia (34-35°C) by external cooling or warming with no specific device

- According to the local protocol or as an example:
 - Cooling can be obtained using one or more of the following methods:
 - Place 2 cold wet sheets (4°C) on the patient. Take care to keep the sheets wet to optimize cooling by convection.
 - Place ice packs wrapped in a towel on the following sites:
 - 1 on each side of the neck
 - 1 below each armpit
 - 2 on the abdomen
 - 1 on each groin
 - Place a fan with blades at the end of the bed directed towards the patient.

→ Targeted hypothermia (34-35°C) by internal or external cooling or warming with a specific device

- According to the local protocol or as an example:
 - Place the device on the patient and set the target temperature at 33°C.

Table 1: ICU management of deceased organ-donors*

Donor Management Goals	Parameters
General management	
Heart rate (bpm)	60-120
Mean arterial pressure (mmHg)	65-70
Hemoglobin (g/dL)	7-10
SpO ₂ (%)	≥95
PaO ₂ (mmHg)	>80
Urinary output (mL·kg ⁻¹ ·h ⁻¹)	0.5-3
Lactate (mmol/L)	<2
Metabolic disorders	
Serum sodium (mmol/L)	130-150
Serum glucose (mmol/L)	4-8
pH	7.35-7.45
Serum potassium, calcium, phosphate, magnesium	Maintain within normal range
Hemodynamic parameters**	
ScVO ₂ (%)	≥70
Cardiac index (L·min ⁻¹ ·m ⁻²)	2.5-3
Central venous pressure (mmHg)	8-10
Pulmonary artery wedge pressure (mmHg)	6-10
Systemic vascular resistance (dynes·seconds·cm ⁻⁵)	800-1200

* From the following reference: Boulard G Ann Fr Anesth Reanim. 2005 Jul;24(7):836-43. doi: 10.1016/j.annfar.2005.05.020.

** If invasive monitoring is implemented (not mandatory)

SPIRIT Checklist for *Trials*

Complete this checklist by entering the page and line numbers where each of the items listed below can be found in your manuscript.

Your manuscript may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please state "n/a" and provide a short explanation. **Leaving an item blank or stating "n/a" without an explanation will lead to your manuscript being returned before review.**

Upload your completed checklist as an additional file when you submit to *Trials*. You must reference this additional file in the main text of your protocol submission. The completed SPIRIT figure must be included within the main body of the protocol text and can be downloaded here: <http://www.spirit-statement.org/schedule-of-enrolment-interventions-and-assessments/>

In your methods section, please state that you used the SPIRIT reporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. *BMJ*. 2013;346:e7586

Reporting Item		Page and Line Number	Reason if not applicable
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Page 1, Lines 1-3
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	Page 23, Lines 11-14
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	Page 23, Lines 11-14
Protocol version	#3	Date and version identifier	Page 22, Lines 23-24
Funding	#4	Sources and types of financial, material, and other	Page 25, Lines 5-7

136/bmjopen-2021-052845 on 28 March 2022. Downloaded from <http://bmjopen.bmj.com/> on April 19, 2024 by guest. Protected by copyright.

		support		
1 2 3 4 5	Roles and responsibilities: contributorship	#5a Names, affiliations, and roles of protocol contributors	Page 25, Lines 12-23	
6 7 8 9 10	Roles and responsibilities: sponsor contact information	#5b Name and contact information for the trial sponsor	Pages 1-6; Page 24, Lines 6-7	
11 12 13 14 15 16 17 18 19	Roles and responsibilities: sponsor and funder	#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	Page 25, Lines 5-10	
20 21 22 23 24 25 26 27 28 29	Roles and responsibilities: committees	#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)	Page 20, Lines 21-24; Page 21, Lines 1-6	
30	Introduction			
31 32 33 34 35 36 37 38 39	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	Page 10, Lines 2-22	
40 41 42 43 44	Background and rationale: choice of	#6b Explanation for choice of comparators	Page 10, Lines 17-20	

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1	comparators			
2	Objectives	#7	Specific objectives or hypotheses	Page 10, Lines 22-25
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, non-inferiority, exploratory)	Page 10, Lines 22-25; Page 11, Lines 3-5; Page 17, Lines 8-10
5				
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11				
12	Methods: Participants, interventions, and outcomes			
13				
14	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	Page 11, Lines 3-12
15				
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21	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)	Page 11, Lines 14-25 ; Page 12, Lines 1-25; Page 13, Lines 1-7
22				
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28	Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	Page 13, Lines 9-18
29				
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33	Interventions: modifications	#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. No harm can come to a deceased patient. Accordingly no intervention modifications are planned
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40	Interventions: adherence	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory	Not applicable. The intervention is applied to deceased patients
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		tests)		
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	Page 14, Lines 8-11	
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	Page 14, Lines 13-25 ; Page 15, Lines 1-25	
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)	Page 30, Table 1	
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	Page 17, Lines 2-15	
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	Page 16, Lines 5-11	
Methods: Assignment of interventions (for controlled trials)				
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of	Page 16, Lines 13-16	

1		any factors for stratification. To reduce		
2		predictability of a random sequence, details of any		
3		planned restriction (eg, blocking) should be		
4		provided in a separate document that is		
5		unavailable to those who enrol participants or		
6		assign interventions		
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10	Allocation concealment	#16b Mechanism of implementing the allocation	Page 16, Lines 13-16	
11	mechanism	sequence (eg, central telephone; sequentially		
12		numbered, opaque, sealed envelopes), describing		
13		any steps to conceal the sequence until		
14		interventions are assigned		
15				
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17				
18	Allocation:	#16c Who will generate the allocation sequence, who	Page 16, Lines 5-16	
19	implementation	will enrol participants, and who will assign		
20		participants to interventions		
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22				
23	Blinding (masking)	#17a Who will be blinded after assignment to	Page 16, Lines 18-25	
24		interventions (eg, trial participants, care providers,		
25		outcome assessors, data analysts), and how		
26				
27				
28	Blinding (masking):	#17b If blinded, circumstances under which unblinding		Not applicable. The intervention makes
29	emergency unblinding	is permissible, and procedure for revealing a		blinding of the healthcare staff impossible.
30		participant's allocated intervention during the trial		
31				
32				
33	Methods: Data collection, management, and analysis			
34				
35	Data collection plan	#18a Plans for assessment and collection of outcome,	Page 20, Lines 5-18	
36		baseline, and other trial data, including any		
37		related processes to promote data quality (eg,		
38		duplicate measurements, training of assessors)		
39		and a description of study instruments (eg,		
40		questionnaires, laboratory tests) along with their		
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		reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol		
Data collection plan: retention	#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	Page 20, Lines 5-18	
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	Page 20, Lines 20-24; Page 21, Lines 1-15	
Statistics: outcomes	#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	Page 18, Lines 18-25	
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	Page 19, Lines 5-18	
Statistics: analysis population and missing data	#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)	Page 19, Lines 1-25	
Methods: Monitoring				
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting	Page 21, Lines 3-6	

1		structure; statement of whether it is independent		
2		from the sponsor and competing interests; and		
3		reference to where further details about its		
4		charter can be found, if not in the protocol.		
5		Alternatively, an explanation of why a DMC is not		
6		needed		
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10	Data monitoring: interim	#21b	Description of any interim analyses and stopping	Page 18, Lines 1-4
11	analysis		guidelines, including who will have access to these	
12			interim results and make the final decision to	
13			terminate the trial	
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16	Harms	#22	Plans for collecting, assessing, reporting, and	Not applicable. No harms can come to a
17			managing solicited and spontaneously reported	deceased patient.
18			adverse events and other unintended effects of	
19			trial interventions or trial conduct	
20				
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22				
23	Auditing	#23	Frequency and procedures for auditing trial	Page 18, Lines 1-4
24			conduct, if any, and whether the process will be	
25			independent from investigators and the sponsor	
26				
27				
28	Ethics and dissemination			
29				
30	Research ethics approval	#24	Plans for seeking research ethics committee /	Page 23, Lines 11-14
31			institutional review board (REC / IRB) approval	
32				
33				
34	Protocol amendments	#25	Plans for communicating important protocol	Page 21, Lines 17-23
35			modifications (eg, changes to eligibility criteria,	
36			outcomes, analyses) to relevant parties (eg,	
37			investigators, REC / IRBs, trial participants, trial	
38			registries, journals, regulators)	
39				
40				
41				
42	Consent or assent	#26a	Who will obtain informed consent or assent from	Page 23, Lines 16-25 ;
43				
44				

		potential trial participants or authorised surrogates, and how (see Item 32)	Page 24, Lines 1-10	
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable		Not applicable. No ancillary studies are planned at this stage
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	Page 21, Lines 9-15	
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	Page 24, Lines 21-24	
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	Page 24, Lines 12-16	
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. No ancillary studies are planned at this stage
Dissemination policy: trial results	#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	Page 22, Lines 1-6	
Dissemination policy:	#31b	Authorship eligibility guidelines and any intended	Page 22, Lines 7-9	

1	authorship		use of professional writers		
2	Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Page 22, Lines 10-11	
3					
4					
5	Appendices				
6	Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	Page 24, Lines 9-10	
7					
8	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. No storage of biological specimens are planned for this study
9					
10					

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. This checklist can be completed online using <https://www.goodreports.org/> a tool made by the EQUATOR Network in collaboration with Penelope.ai

BMJ Open

Impact of Targeted Hypothermia in Expanded Criteria Organ Donors on Recipient Kidney-Graft Function: Study Protocol for a Multicenter Randomized Controlled Trial (HYPOREME)

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2021-052845.R1
Article Type:	Protocol
Date Submitted by the Author:	01-Sep-2021
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8	Larmet, Raphaëlle; Centre Hospitalier Universitaire de Rennes, Service de Réanimation Chirurgicale
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10	Vigneau, Cecile; Centre Hospitalier Universitaire de Rennes, Service de Néphrologie
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14	Bouju, Pierre; Centre Hospitalier de Bretagne Sud, Lorient, Service de Réanimation
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16	quentin, charlotte; Centre Hospitalier de Saint-Malo, Service de Réanimation polyvalente
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49	Le Quintrec-Donnette, Moglie; Centre Hospitalier Universitaire de Montpellier, Service de Néphrologie et Transplantation
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	<p>de Paris, Créteil, Service de Néphrologie et Transplantation Heng, Anne Elisabeth; Centre Hospitalier Universitaire de Clermont-Ferrand, Service de Néphrologie et Immunologie Clinique Merville, Pierre; Centre Hospitalier Universitaire de Bordeaux service de Nephrologie Transplantation Dialyse Aphereses Garin, Aude; Centre Hospitalier de Dreux, Service de Réanimation Polyvalente Hiesse, christian; Hôpital Foch, Suresnes, Service de Néphrologie Fermier, Brice; Centre Hospitalier de Blois, Service de Réanimation mousson, christiane; Centre Hospitalier Universitaire de Dijon, Service de Néphrologie Guyot-Colosio, Charlotte; Centre Hospitalier Universitaire de Reims, Service de Néphrologie Bouvier, Nicolas; Centre Hospitalier Universitaire de Caen, Service de Néphrologie Rerolle, Jean-Philippe; Centre Hospitalier Universitaire de Limoges, Service de Néphrologie Durrbach, Antoine; Hôpital Kremlin-Bicêtre, Assistance Publique Hôpitaux de Paris, Service de Néphrologie drouin, sarah; APHP Sorbonne-Université, Hôpital Pitié-Salpêtrière, Service Médico-Chirurgical de Transplantation Rénale Caillard, sophie; Centre Hospitalier Universitaire de Strasbourg, Service de Néphrologie et Transplantation Frimat, Luc; CHRU Nancy, Université de Lorraine, Nephrology Department Girerd, Sophie; Hôpital Brabois, Centre Hospitalier Régional Universitaire de Nancy, Service de Néphrologie et transplantation albano, Laetitia; Centre Hospitalier Universitaire de Nice, Service de Néphrologie et Transplantation rostaing, Lionel; CHU Grenoble Alpes, Service de Néphrologie, Hémodialyse, Aphèreses et Transplantation Rénale bertrand, dominique; Centre Hospitalier Universitaire de Rouen, Service de Néphrologie Hertig, Alexandre; Hôpital Tenon, Université de Paris, Assistance Publique –Hôpitaux de Paris, Service de Néphrologie Westeel, Pierre-Francois; Centre Hospitalier Universitaire d’Amiens, Service de Néphrologie Montini, Florent; Centre Hospitalier Henri Duffaut, Avignon, Service de Réanimation Delpierre, Eric; Grand Hôpital de l’Est Francilien, Marne La Vallée, Service de Réanimation dorez, dider; Centre Hospitalier Annecy Genevois, Service de Réanimation Polyvalente alamartine, eric; Centre Hospitalier Universitaire de Saint-Etienne, Service de Néphrologie Dialyse et Transplantation Rénale Ouisse, Carole; University Hospital Centre Nantes, Intensive Care unit, Unité d'Investigation clinique Sebillé, Veronique; University Hospital Centre Nantes, Direction de la Recherche, Plateforme de Méthodologie et Biostatistique; Université de Nantes, INSERM SPHERE U1246 Methods for Patient-centered Outcomes and Health Research Reignier, Jean; CHU Nantes, Médecine intensive réanimation</p>
Primary Subject Heading:	Intensive care
Secondary Subject Heading:	Renal medicine
Keywords:	Renal transplantation < NEPHROLOGY, Dialysis < NEPHROLOGY, INTENSIVE & CRITICAL CARE

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Manuscripts

1 **Impact of Targeted Hypothermia in Expanded Criteria Organ Donors on Recipient**
2 **Kidney-Graft Function: Study Protocol for a Multicenter Randomized Controlled Trial**
3 **(HYPOREME)**

4
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3 **1 List of abbreviations**
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8 3 DGF: delayed graft function
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10 4 DSMB: Data Safety Monitoring Board
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12 5 ECD: expanded criteria donor
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14 6 eCRF: electronic case report form
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16 7 ICU: intensive care unit
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18 8 ITT: intention-to-treat
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20 9 KR: kidney recipient
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22 10 KTx: kidney transplantation
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24 11 RCT: randomized controlled trial
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3 **1 ABSTRACT**
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8 **3 Introduction:** Expanded-criteria donors (ECDs) are used to reduce the shortage of kidneys
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10 for transplantation. However, kidneys from ECDs are associated with an increased risk of
11
12 delayed graft function (DGF). DGF is a risk factor for allograft loss and mortality.
13

14
15 **6 HYPOREME** will be a large multicenter randomized controlled trial (RCT) comparing
16
17 targeted hypothermia to normothermia in ECDs. We hypothesize that targeted hypothermia
18
19 will decrease the incidence of DGF in recipients of kidneys from ECDs.
20

21
22 **9 Methods and analysis:** HYPOREME is a multicenter RCT comparing the effect on kidney
23
24 function in recipients of targeted hypothermia (34 to 35°C) and normothermia (36.5 to
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26 37.5°C) in the ECDs. The temperature intervention starts from randomization (after legal
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28 determination of death by neurologic criteria) and is maintained until aortic clamping in the
29
30 operating room. We aim to enroll 289 ECDs in order to analyze the kidney function of 516
31
32 recipients in the 53 participating centers. The primary outcome is the occurrence of DGF in
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34 kidney recipients, defined as a requirement for renal replacement therapy within 7 days after
35
36 transplantation (not counting a single session for hyperkalemia during the first 24 hours).
37
38 Secondary outcomes include the proportion of patients with individual organs transplanted in
39
40 each group; the number of organs transplanted from each ECD; and the vital status and
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42 kidney function of the recipients 7 days, 28 days, 3 months, and 1 year after transplantation.
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44 An interim analysis is planned after the enrolment of 258 kidney recipients.
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50 **21 Ethics and dissemination:** The trial was approved by the ethics committee of the French
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52 Intensive Care Society (CE-SRLF-16-07) on April 26, 2016 and by the competent French
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54 authorities on April 20, 2016 (Comité de Protection des Personnes - TOURS-Région Centre-
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56 Ouest 1, registration #2016-S3). Findings will be published in peer-reviewed journals and
57
58 presented during national and international scientific meetings.
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3 1 **Trial Registration:** NCT03098706.
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8 3 **Strengths and limitations of this study**
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- 10 4 • HYPOREME will be a large multicenter randomized controlled trial (RCT) to
11 evaluate the impact of targeted hypothermia on the function of kidneys from
12 5 expanded-criteria donors (ECDs) after transplantation.
13 6
14 7 • All participating centers were selected based on their high level of experience and
15 8 expertise in organ transplantation.
16 9 • Assessors for both primary and secondary outcomes on kidney recipients are blinded
17 10 to the intervention arm of the donor.
18 11 • Research assistants from the Research Division Promotion Department of the Nantes
19 12 University Hospital will regularly perform on-site checks of adherence to the protocol
20 13 and accuracy of the recorded data.
21 14 • A minimal duration of targeted temperature management is not requested by the study
22 15 protocol
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18 **Keywords:** Organ donor, kidney transplantation, hypothermia, renal replacement therapy,
19 delayed graft function
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1 BACKGROUND

2 Kidney transplantation (KTx) is the best therapeutic option for patients with end-stage
3 renal disease and improves both survival and quality of life (1). The use of expanded-criteria
4 donors (ECDs) in solid-organ transplantation was implemented in 2002 in the United States
5 to address the issue of organ donor shortage (2). In 2017 in France, half the KTxs were
6 performed with ECDs (3). Although the use of ECDs undoubtedly expands the pool of
7 deceased organ donors, it is associated with a significant risk of delayed graft function (DGF)
8 after transplantation (4,5). DGF is reported in up to 50% of kidney recipients (6) and is a
9 significant risk factor for allograft loss and mortality (7,8). Moreover, DGF is associated with
10 both acute rejection and worse long-term renal allograft function (9). Thus, developing new
11 strategies to reduce the risk of DGF is a major priority in KTx. Optimizing ECD management
12 from the confirmation of neurologic death to organ recovery in the operating room has been
13 shown to increase the organ yield per donor (10). Conceivably, better ECD management may
14 also improve renal allograft function after transplantation.

15 Hypothermia may help to preserve renal function in donors (11). Experimental data have
16 shown that mild hypothermia reduces cell metabolism, inflammation, and free-radical
17 production (12). A randomized controlled trial conducted in the United States in 2015 found
18 that targeted hypothermia (34 to 35°C) in deceased organ donors reduced the incidence of
19 DGF in kidney recipients compared to normothermia (36.5 to 37.5°C), from 39.2% to 28.2%
20 ($P=0.02$) (13). An a-priori defined stratum of patients from this trial suggested that kidney
21 recipients from ECDs benefited the most from donor targeted hypothermia. Therefore, we
22 designed a multicenter randomized controlled trial (HYPOREME) to test the safety and
23 efficacy of targeted hypothermia compared to normothermia as part of the management of
24 ECDs. We hypothesized that targeted hypothermia in ECDs would decrease the incidence of
25 DFG in kidney recipients.

1 **METHODS/DESIGN**

2 3 **Trial design and settings**

4 HYPOREME is a multicenter, randomized, controlled, trial comparing two parallel
5 groups of patients.

6 7 **Participants, interventions, outcomes**

8 ***Participating units***

9 A total of 53 French intensive care units (ICUs) and transplant centers are
10 participating in the study (30 university hospitals and 23 general hospitals). All participating
11 centers were carefully selected based on their high level of experience and expertise in the
12 management of organs donors, the process of organ transplantation, and clinical research. In
13 each participating center, a referring team for organ transplantation is identified to ensure
14 knowledge, training and compliance to the protocols edited by the French Biomedicine
15 Agency (national recommendation).

16 17 ***Study population and recruitment modalities***

18 This study involves two distinct populations:

- 19 • Deceased ECDs for whom the diagnosis of death is made based on neurologic
20 criteria in compliance with French law. ECDs are defined as deceased donors who
21 are older than 60 years or who are aged 50-59 years and have at least two other risk
22 factors (history of hypertension, creatinine >132 µmol/L, and/or cerebrovascular
23 cause of death). The study intervention (targeted temperature management) applies to
24 this population.
- 25 • Kidney recipients who receive a kidney allograft from the above-described ECDs.

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3 1 The effect of the study intervention is evaluated in this population based on allograft
4
5 2 function.

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8 3 Deceased ECDs and kidney recipients must fulfil all of the criteria listed below to be
9
10 4 included in the study.

11
12 5 *Inclusion criteria for deceased ECDs*

- 13
14 6 - Traumatic, vascular, or other brain injuries responsible for death defined by
15
16 7 neurologic criteria,
17
18 8 - Legal determination of death based on neurologic criteria in compliance with French
19
20 9 law,
21
22 10 - Organ donation procedure engaged in compliance with French law,
23
24 11 - Deceased ECD older than 60 years or aged 50-59 years with at least two other risk
25
26 12 factors (history of hypertension, creatinine >132µmol/L, and/or cerebrovascular cause
27
28 13 of death),
29
30 14 - Next of kin informed of the study.

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32
33 15 *Inclusion criteria for kidney transplant recipients:*

- 34
35 16 - Patient registered on the waiting list for KTx,
36
37 17 - Patient informed of the study,
38
39 18 - Age 18 years or older at the time of the pretransplantation evaluation,
40
41 19 - Patient covered by the statutory French health insurance.

42
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44 20 Deceased organ donors or kidney recipients fulfilling one or more of the following
45
46 21 criteria are not included in the study.

47
48 22 *Exclusion criteria for deceased organ donors:*

- 49
50 23 - Donors with circulatory death or donors who died after treatment limitation,
51
52 24 - Patient registered in the French registry for refusing organ and tissue donations,
53
54 25 - Pregnancy,

- 1 - Age less than 18 years,
- 2 - Adult under guardianship,
- 3 - Contraindication to organ donation identified according to the current
- 4 recommendations of the French Biomedicine Agency (*Agence de la Biomédecine*).

5 *Exclusion criteria for kidney transplant recipients:*

- 6 - Refusal to participate in the study expressed by the patient,
- 7 - Pregnancy,
- 8 - Age less than 18 years,
- 9 - Adult under guardianship, or correctional facility inmate.

10

11 ***Study intervention***

12 The intervention is initiated after study inclusion and randomization. Deceased ECDs
13 are allocated at random to one of the two targeted temperature strategies (Figure 1). The
14 designated targeted temperature strategy is initiated as soon as possible after randomization
15 and continues until aortic clamping in the operating room. The objective is to reach the
16 targeted temperature range within 4 hours after randomization.

- 17 - In the targeted hypothermia group, ECDs have mild hypothermia (34°C to 35°C)
18 induced then maintained until aortic clamping in the operating room.
- 19 - In the targeted normothermia group, patients have normothermia (36.5°C-37.5°C)
20 induced and maintained until aortic clamping in the operating room.

21 Once the targeted temperature is reached, there is no request for a minimal duration of time
22 spent at the targeted temperature before the aortic clamping in the operating room.

23

24 ***Targeted temperature protocol***

1 No trial has demonstrated one method to be better than another for targeted
2 temperature management. Therefore, to induce and maintain the ECDs at 34°C-35°C or
3 36.5°C-37.5°C, each participating center uses its usual method and protocol. The method
4 may involve active internal cooling or warming using specific devices, active external
5 cooling or warming using specific devices, or active external cooling or warming without
6 specific devices. A standard protocol of targeted temperature management was provided to
7 each participating center (supplementary appendix, Figure 1). Body temperature is recorded
8 hourly from randomization to aortic clamping using invasive (intravascular catheter with a
9 temperature-sensing vascular probe placed in the femoral artery, Pulse Contour Cardiac
10 Output, PiCCO[®], or equivalent) or semi-invasive (esophageal probe, intra-rectal probe,
11 urinary probe) methods according to the device available and local protocol at each center.

12 13 ***General principles of management in both study arms***

14 The general management of deceased organ donors in the ICU and operating room
15 follows the standard protocol recommended by the French Biomedicine Agency in all
16 participating centers (supplementary appendix, Table 1) (14).

17 18 ***Study outcomes***

19 ***Primary outcome measure***

20 The primary outcome is the proportion of kidney recipients with DGF. DGF is
21 defined as a need for renal replacement therapy during the first week after transplantation
22 (not counting a single session of renal replacement therapy to treat hyperkalemia during the
23 first 24 hours after transplantation). DGF is determined for each kidney recipient at the
24 transplant center where the KTx was performed. The decision to commence renal
25 replacement therapy is left at the discretion of the nephrologist in charge.

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3 1 In the rare case of transplantation of both kidneys from a donor into a single recipient,
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5 2 that recipient is counted only once: the primary outcome measure is based on the presence or
6
7 3 absence of DGF in the kidney recipient.
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12 5 *Secondary outcome measures*
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14 6 The secondary outcomes for the ECDs consist of the following comparisons between the two
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16 7 arms:

- 17
18
19 8 - number of organs recovered and number transplanted,
20
21 9 - body temperature recorded hourly from randomization to aortic clamping,
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23
24 10 - number of severe cardiac arrhythmia episodes,
25
26 11 - total volume of intravenous fluids administered,
27
28 12 - need for vasopressors and inotropes, including total dose and maximal dose,
29
30
31 13 - lowest and highest blood pressures,
32
33 14 - cardiac arrest leading to abortion of the organ-donation procedure,
34
35 15 - metabolic disturbances and coagulation disorders,
36
37 16 - kidney function of organ donors: last serum creatinine and creatinine clearance before
38
39 17 transfer to the operating room.

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42 18 The secondary outcomes for the kidney recipients consist in comparing the following
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44 19 between the two arms:

- 45
46 20 - hospital length of stay after transplantation,
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48 21 - kidney graft function (serum creatinine) at hospital discharge on days 7 and 28, and 3
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50 22 months and 1 year after transplantation,
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52 23 - persistent need for renal replacement therapy 28 days, 3 months, and 1 year after
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54 24 transplantation,
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56 25 - reason for renal replacement therapy implementation (sepsis, acute rejection, oliguria,
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3 1 hyperkalemia),
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5 2 - hospital mortality,
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8 3 - day-28 (after transplantation) mortality,
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10 4 - day-90 (after transplantation) mortality,
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12 5 - day-365 (after transplantation) mortality.
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7 **Organization of the trial**

8 Figure 1 is the study flowchart.
9

10 ***Recruitment modalities***

11 All patients with a confirmed diagnosis of death based on neurologic criteria in
12 compliance with French law and who meet the definition of ECDs will be screened for
13 eligibility by the ICU physicians and clinical research nurses, around the clock and 7 days a
14 week. Patients will be included after checking inclusion and non-inclusion criteria. A log of
15 patients considered for study participation will be kept and will include the reasons for non-
16 inclusion.
17

18 ***Randomization***

19 Randomization is centralized and performed using a secure, computer-generated,
20 interactive, web-response system available at each study center. Randomization is stratified
21 on study center with a 1:1 ratio.
22

23 ***Blinding***

24 The nature of the intervention on the ECDs makes the blinding of the ICU staff to
25 group assignment impossible. However, the assessors for both primary and secondary
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1 outcomes on kidney recipients are blinded to the intervention arm of the donor. Indeed, the
2 nephrologists in charge of the kidney recipients, who decide whether renal replacement
3 therapy is needed during the first week after transplantation, and the kidney recipients are
4 blinded to the intervention arm of the donor.

6 ***Sample size***

7 According to a recent randomized controlled trial conducted in the United States (13) the
8 proportion of recipients with DGF after kidney transplantation from ECDs was 56.5%. In our
9 local experience at the transplant center in Nantes (France), the proportion of recipients with
10 DGF after kidney transplantation from ECDs was 48%. In the US trial, the proportion with
11 DGF was 56.5% in the normothermia group and 31% in the hypothermia group (13).

12 Based on our local experience, we hypothesized that the rate of DGF after kidney
13 transplantation from ECDs would be 48%. We kept the hypothesis of the US trial of a 30%
14 relative difference in the rate of DGF between the study groups (13). To demonstrate a 14%
15 decrease in the proportion of recipients with DGF (from 48% in the normothermia group to
16 34% in the hypothermia group), a total of 516 kidney recipients are required (258 in each
17 group) to provide 90% power with a two-sided alpha risk of 5%. The analysis of 516 kidney
18 recipients theoretically requires 258 randomized ECDs. However, assuming an estimated
19 attrition rate of 12% (i.e., ECDs who are randomized but for whom organs are not recovered
20 or are recovered but not transplanted) and given that in rare cases both kidneys from a donor
21 are transplanted into a single recipient, our enrolment target is 289 randomized ECDs.

23 ***Interim analysis***

24 The sample size estimation is based on the primary outcome, i.e., the occurrence of
25 DGF. However, there is some uncertainty related to the limited amount of data available in

1 the literature. Accordingly, an interim analysis is planned after the enrolment of 258 kidney
2 recipients. The primary objective of this interim analysis is to reassess the sample size of the
3 study using the method proposed by Friede and Kieser (15,16). The probability of DGF will
4 be estimated from all treatment groups combined in order to preserve blindness. This method
5 makes it possible to maintain the initial clinical hypothesis (14% decrease in the frequency of
6 DGF) and to control the type I error.

7 The interim analysis will be conducted by an independent Data Safety Monitoring Board
8 (DSMB), whose members are not otherwise involved in the trial. This DSMB consists of one
9 methodologist and two intensivists. For the interim analysis, the DSMB will have access to
10 the following unblinded results:

- 11 • For the ECDs: number of patients enrolled, body temperature, mean arterial pressure,
12 total dose of vasopressors and inotropes, episodes of severe arrhythmia or cardiac
13 arrest, number of organs recovered from the donor, reason why organs were not
14 recovered (if applicable), use of machine perfusion for organ storage, and cold
15 ischemia time.
- 16 • For the recipients: occurrence of DGF, need for renal replacement therapy during the
17 first week posttransplantation, allograft lost by day 7, vital status on day 7, severe
18 posttransplantation complications, serum creatinine $<250 \mu\text{mol/L}$ on day 7, and
19 allograft function and vital status on day 28 posttransplantation.

20 The results of the interim analysis will not be disclosed unless they lead the DSMB to request
21 premature trial discontinuation.

23 ***Statistical analysis***

1 All analyses will be performed using SAS software (V.9.4). Analyses will be
2 conducted on data from the intention-to-treat (ITT) population as well as from the per-
3 protocol population.

4 For the primary analysis, sensitivity analyses will be performed with populations
5 defined as follows: first, the ITT population defined as all recipients who received kidneys
6 from the ECDs and, second, all donors, regardless of whether organs were recovered and
7 transplanted. The latter case (failure to recover organs) will be considered a failure for the
8 main outcome measure (occurrence of DGF).

9 In the per-protocol analysis, all randomized patients will be kept in the analysis
10 except those with one or more major protocol violations, such as failure to meet all the
11 inclusion criteria and none of the non-inclusion criteria, an inability to perform the surgical
12 procedure, or withdrawal of consent to participate in the study.

13 A statistical analysis report will be written to describe all the findings, according to
14 CONSORT Statement recommendations, while considering the specific features of the trial,
15 most notably the nonpharmacological nature of the intervention. The baseline features of the
16 groups established by randomization will be compared using descriptive statistics.
17 Continuous variables will be described as mean±SD if normally distributed and as median
18 [interquartile range] otherwise. Categorical data will be described as exact numbers and
19 percentages.

20 For the primary analysis, binary categorical data will be analyzed using random-effect
21 logistic regression adjusted to take into account the hierarchical structure of the data (kidneys
22 from the same donor) and variability across centers.

23 The number of organs transplanted per donor will be compared between the two
24 groups using Poisson regression model. Hospital length of stay will be compared between the
25 two groups using a generalized model with random effects models. Patient and graft

1 survivals will be compared using Cox regression models. All models will be adjusted on
2 centres and consider ECDs as random effects.

3 4 ***Handling missing data***

5 We expect no missing data for the primary outcome. Graft loss during the first week
6 after transplantation will be classified as DGF. Similarly, death within the first week after
7 transplantation will be classified as DGF. Surgical complications which do not require
8 resuming dialysis during the first week post transplantation will be classified as no DGF
9 while those which require resuming dialysis will be classified as DGF. If unexpectedly data
10 are missing for the primary outcome, sensitivity analyses will be performed using the worst-
11 case scenario (missing data considered the worst case for the hypothermia group) as well as
12 the best-case scenario (missing data considered the best case for the hypothermia group) and
13 the maximum bias scenario (missing data considered the best or worst case in the
14 normothermia and hypothermia groups respectively).

15 The frequency of missing data should be low for the other outcomes as the ECDs
16 included in the study are hospitalized for a few hours or days at the most in the intensive care
17 unit. Kidney transplant recipients are admitted to the nephrology department. Few patients
18 will be lost to follow-up, as hospitalization after KTx lasts routinely about 10 days. Only
19 survival on day 28 and 3 months and 1 year after hospital discharge of recipients may be
20 missing. We will not use any technique to replace missing data. Missing data will be reported
21 for each treatment arm.

22 23 ***Data collection and follow-up***

24 The donor will be followed from randomization to aortic clamping in the operating
25 room. The following data will be recorded until aortic clamping in the operating room: date

1 and time of death based on neurologic criteria, demographic and clinical data, treatments
2 administered, laboratory tests, body temperature (recorded hourly), adverse events (mainly
3 cardiac arrhythmias, cardiac arrest, coagulopathy, and refractory shock), number of organs
4 recovered in the operating room, use of machine perfusion for organ storage, and number of
5 organs ultimately transplanted. In France, the use of machine perfusion for organ storage is a
6 national recommendation from the French Biomedicine Agency since 2011 for all organs
7 recovered from ECDs. The use of such device is part of the standard of care and it is
8 expected that almost all kidneys will be placed on machine perfusion.

9 The kidney recipient will be followed from transplantation to 1 year after
10 transplantation. The following data will be recorded: demographic and clinical data,
11 treatments given, laboratory tests, cold ischemia time, and vital status and graft function on
12 days 7, 28, and 90 and after 1 year. Posttransplantation complications will be recorded during
13 the first 28 days following transplantation (mainly acute allograft rejection, cardiovascular
14 events, infections, and surgical complications). Table 1 is the flowchart of patient follow-up.

16 ***Data entry and monitoring***

17 An Internet-based data collection tool will be used to store the data of all the ECDs
18 and recipients. This electronic case-report form (eCRF) is a secure, interactive, web-response
19 system available at each study center. The eCRF is provided and managed by the biometrical
20 unit of the Nantes University Hospital (EA 4275 SPHERE “Methods for patient-centered
21 outcomes and health research”). Access to the eCRF will require only an Internet connection
22 and a browser.

23 Monitoring of the collected data and screening forms in each participating center will
24 be carried out by the Research Division Promotion Department of the Nantes University
25 Hospital. Research assistants will regularly perform on-site checks of adherence to the

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3 1 protocol and accuracy of the recorded data. Newsletters about the study will be regularly sent
4
5 2 by email to all participants to provide support, information, and to recall key instructions.
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4 ***Confidentiality and source data archiving***

5 The medical data about each patient will be communicated only to the institution (i.e.,
6 the sponsor) with which the chief investigator is affiliated or to a person appointed by the
7 chief investigator and the sponsor under conditions that ensure the confidentiality of the
8 patient data. During or at completion of the study, the data collected from the study
9 participants and communicated by the individuals involved in the study will be rendered
10 anonymous. The study investigators will archive all study data for at least 15 years after the
11 end of the study.
12

13 ***Protocol amendments***

14 Any modifications to the protocol will require a formal amendment to the protocol.
15 Such amendment will be reviewed by the Research Division Promotion Department of the
16 Nantes University Hospital and agreed by the competent French authorities (Comité de
17 Protection des Personnes - TOURS-Région Centre-Ouest 1) prior to implementation. Any
18 modifications to the protocol will be communicated without delay to relevant parties
19 (investigators and trial participants).
20

21 ***Patient and public involvement***

22 Neither the patients nor the public are involved in the study design.
23

24 **DISCUSSION**

1 HYPOREME will be a large randomized controlled trial to evaluate the impact of
2 targeted hypothermia on the function of kidneys received from ECDs. The results are
3 expected to provide intensivists with additional guidance about the optimal management of
4 deceased organ donors.

6 TRIAL STATUS

7 The first trial inclusion was on November 9, 2017. The protocol version is identified
8 RC16_0041_Protocol HYPOREME V10.1 on December 12, 2020. The scheduled interim
9 analysis was done on December 5, 2019, after the inclusion of 258 kidney recipients. The
10 interim analysis led the DSMB to recommend continuation of the study without modification
11 of the protocol and confirmed the initial goal of enrolling 516 kidney recipients. In addition,
12 the DSMB suggested a second interim analysis after the inclusion of 350 kidney recipients.
13 The second interim analysis was done on February 11, 2021, and led the DSMB to
14 recommend continuation of the study without modification of the protocol. On February 11,
15 2021, 349 kidney recipients had been included. The trial is expected to be completed in June
16 2021.

18 ETHICS AND DISSEMINATION

19 *Ethics approval*

20 The HYPOREME trial was approved by the ethics committee of the French Intensive
21 Care Society (CE-SRLF-16-07) on April 26, 2016 and by the competent French authorities
22 on April 20, 2016 (Comité de Protection des Personnes - TOURS-Région Centre-Ouest 1,
23 registration #2016-S3) and was registered on ClinicalTrials (NCT03098706) in April 2017.

25 *Consent to participate*

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3 1 In compliance with French law, at the time of declaration of death based on neurologic
4
5 2 criteria, the French registry of persons refusing organ and tissue donation is examined to
6
7 3 confirm that the deceased patient is not registered. In addition, families or next of kin are
8
9 4 interviewed to check that the patient had not expressed unwillingness to donate organs and/or
10
11 5 tissues. During the same meeting, information about the study is given orally and an
12
13 6 information letter is handed to the family. The information delivered is documented in the
14
15 7 donor's medical chart by the local investigator. Legal statutes do not require informed
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17 8 consent from families or next of kin for study inclusion, given that no harm can come to a
18
19 9 deceased patient.
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24 10 Prior to study initiation, all the participating transplant centers were contacted. Each
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26 11 transplant center approved the study protocol. The allocation of organs to specific recipients
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28 12 occurs based on the national regulations set forth by the French Agency of Biomedicine. The
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30 13 transplant center that receives the organs from an included ECD is informed of the study
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32 14 inclusion but blinded to the treatment arm. Kidney recipients are informed of the study orally
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34 15 and via a written information sheet and are then asked to provide their written informed
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36 16 consent to participation in the trial. That this information was delivered is documented in the
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38 17 medical chart of the kidney recipient by the investigator.
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42 18 Model consent form and other related documentation given to participants and
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44 19 authorized surrogates are provided in the supplementary appendix.
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49 21 ***Access to data***

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51 22 Only the statisticians of the trial and the members of the DSMB have access to the
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53 23 intra-study dataset in order to ensure that the results are not disclosed prior to the end of the
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55 24 trial. After study completion, site investigators will have access to the full dataset if a formal
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57 25 request is approved by the steering committee.
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2 ***Dissemination policy***

3 The publication policy will comply with international recommendations (N Engl J
4 Med, 1997; 336:309-315) and the CONSORT statement (<http://www.consort-statement.org>).
5 Findings will be published in peer-reviewed journals and presented during national and
6 international scientific meetings. Communications and scientific reports relevant to this study
7 will be under the responsibility of the study coordinator (EC), who will obtain the approval
8 of the other investigators.

9 Substantive contributions of investigators, clinicians, researchers, and statisticians to
10 the design, conduct, interpretation, and reporting of the trial will be granted of authorship on
11 the final trial report.

12 Full protocol and participant-level dataset will be made available for scientific
13 purpose on reasonable request, after the agreement of the ethics and steering committee.

15 ***Availability of data and materials***

16 Not applicable

18 ***Competing Interests***

19 EC received fees for lectures and conference talks and had travel and accommodation
20 expenses related to attending scientific meetings covered by Gilead, Baxter and Sanofi-
21 Genzyme.

23 ***Trial sponsor and Funding***

1 The sponsor of the trial is the Centre Hospitalier Universitaire de Nantes (Direction de
2 la recherché et de l’Innovation – 5, allée de l’île Gloriette, 44093 Nantes cedex 01, France,
3 Phone : +33 253 482 835).

4 The HYPOREME trial received a grant from the French Ministry of Health in 2016
5 (Programme Hospitalier de Recherche Clinique Inter-Régional 2016; API16/N/033) and a
6 grant from the French Intensive Care Society in 2018.

7 Sponsor and funders had no role and no ultimate authority over the study design;
8 collection, management, analysis, and interpretation of data; writing of the report; and the
9 decision to submit the report for publication

10

11 *Authors’ contributions*

12 NB and EC prepared the first draft of the manuscript.

13 JR, MP, NB, and EC wrote the manuscript.

14 JR, NB, MP, MH, and EC participated in designing the HYPOREME study.

15 MP and VS wrote the statistical analysis plan and performed the sample size
16 estimation.

17 NB and JR obtained funding for the study.

18 NB, EC, MP, MH, KA, BR, AD, LD, MP, SH, PT, JMB, LMM, FL, RR, TB, TK,
19 AT, OL, JFV, ML, RL, CV, AG, PB, CQ, PYE, OH, AR, YL, JCV, MB, OM, MHV, FH,
20 DS, AC, DG, LA, MH, NK, VM, JB, MLQD, EM, TB, PG, AEH, PM, AG, CH, BF, CM,
21 CGC, NB, JPR, AD, SD, SCO, LF, SG, LA, LR, DB, AH, PFW, FM, ED, DD, EA, CO, VS
22 and JR contributed to acquire the study data.

23 All authors revised the manuscript for important intellectual content and read and
24 approved the final version of the manuscript.

25

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3 1 *Acknowledgments*
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5 2 We thank Antoinette Wolfe, MD, for assistance in preparing and reviewing the
6
7 3 manuscript; Carine Coffre and Frédérique Musset for managing the database; Manon Rouaud
8
9 4 for coordinating the study; and Prof. Sylvie Chevret (Biostatistics and Medical Information
10
11 5 Department, Hôpital Saint-Louis, Paris, France; Centre de Recherche en Épidémiologie et
12
13 6 Statistiques [CRESS-INSERM-UMR1153], Paris, France; Epidemiology and Clinical
14
15 7 Statistics for Tumor, Respiratory, and Resuscitation Assessments [ECSTRRA] Team, Paris,
16
17 8 France; Université de Paris, Paris, France), Prof. Alain Combes (Medical ICU, La Pitié-
18
19 9 Salpêtrière University Hospital, AP-HP, Paris, France), and Prof. Elie Azoulay (Medical
20
21 10 ICU, Saint-Louis University Hospital, AP-HP, Paris, France) for constituting the independent
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23 11 data safety and monitoring board.
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1 **FIGURE LEGENDS**

2 **Figure 1:** Study flowchart

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4

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1 TABLES

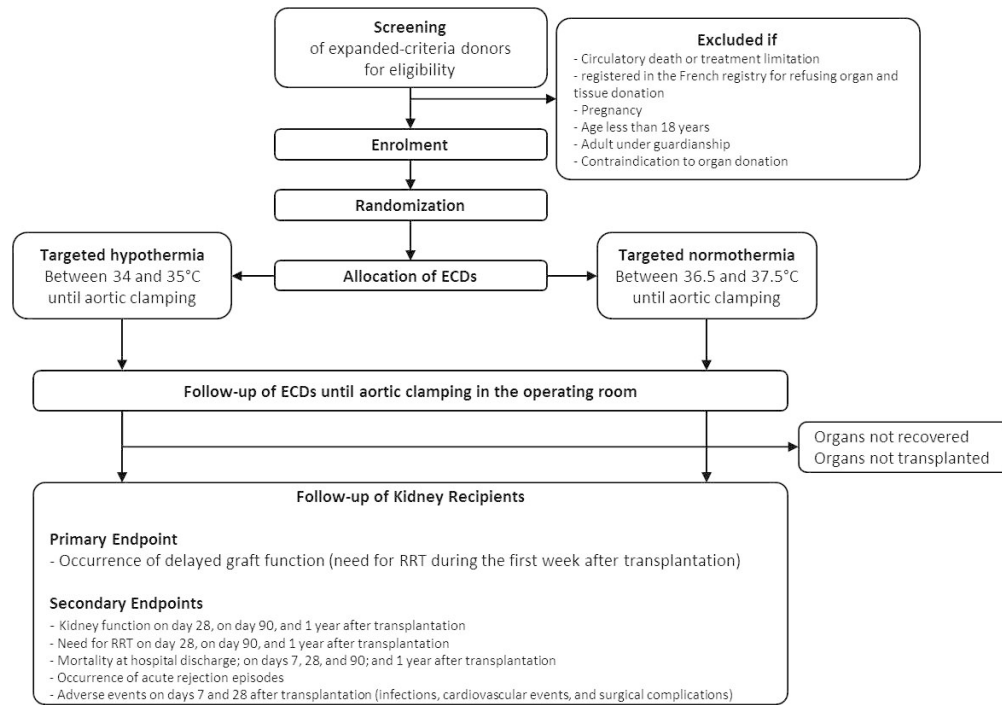
2
3 **Table 1: Flow-chart of patient follow-up**

	Inclusion	D0*	Operating room	Dx	D7**	D28**	D90*	One year End of follow-up**
	ECD			Kidney recipient				
Eligibility: check inclusion and exclusion criteria (for both ECD and KR)	X			DAY OF TRANSPLANTATION				
ECD: information of family/next of kin	X							
KR: information of the patient	X							
Randomization (ECD)		X						
Demographic characteristics		X						
Vital signs		X	X					
Laboratory tests		X	X			X	X	X
Body temperature		X	X					
Treatments		X	X			X		
Renal replacement therapy						X	X	X
Infectious complications						X	X	
Surgical complications						X	X	
Cardiovascular complications						X	X	
Acute rejection episodes						X	X	
Vital status					X	X	X	

5
6 * from time of inclusion to 11:59 pm

7 ** Day-7, day-28, day-90 and 1 year posttransplantation (Dx).

8 ECD, expanded criteria donor; KR, kidney recipient



Study flowchart

198x139mm (150 x 150 DPI)

Supplementary Appendix

Figure 1: Targeted temperature management protocol provided to each center

→ Targeted hypothermia (34-35°C) by internal cooling or warming device

The use of an intravenous bolus of cold (4°C) isotonic saline is not recommended.

→ Targeted hypothermia (34-35°C) by external cooling or warming with no specific device

- According to the local protocol or as an example:
 - Cooling can be obtained using one or more of the following methods:
 - Place 2 cold wet sheets (4°C) on the patient. Take care to keep the sheets wet to optimize cooling by convection.
 - Place ice packs wrapped in a towel on the following sites:
 - 1 on each side of the neck
 - 1 below each armpit
 - 2 on the abdomen
 - 1 on each groin
 - Place a fan with blades at the end of the bed directed towards the patient.

→ Targeted hypothermia (34-35°C) by internal or external cooling or warming with a specific device

- According to the local protocol or as an example:
 - Place the device on the patient and set the target temperature at 33°C.

Table 1: ICU management of deceased organ-donors*

Donor Management Goals	Parameters
General management	
Heart rate (bpm)	60-120
Mean arterial pressure (mmHg)	65-70
Hemoglobin (g/dL)	7-10
SpO ₂ (%)	≥95
PaO ₂ (mmHg)	>80
Urinary output (mL·kg ⁻¹ ·h ⁻¹)	0.5-3
Lactate (mmol/L)	<2
Metabolic disorders	
Serum sodium (mmol/L)	130-150
Serum glucose (mmol/L)	4-8
pH	7.35-7.45
Serum potassium, calcium, phosphate, magnesium	Maintain within normal range
Hemodynamic parameters**	
ScVO ₂ (%)	≥70
Cardiac index (L·min ⁻¹ ·m ²)	2.5-3
Central venous pressure (mmHg)	8-10
Pulmonary artery wedge pressure (mmHg)	6-10
Systemic vascular resistance (dynes·seconds·cm ⁻⁵)	800-1200

* From the following reference: Boulard G Ann Fr Anesth Reanim. 2005 Jul;24(7):836-43. doi: 10.1016/j.annfar.2005.05.020.

** If invasive monitoring is implemented (not mandatory)

SPIRIT Checklist for *Trials*

Complete this checklist by entering the page and line numbers where each of the items listed below can be found in your manuscript.

Your manuscript may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please state "n/a" and provide a short explanation. **Leaving an item blank or stating "n/a" without an explanation will lead to your manuscript being returned before review.**

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Reporting Item		Page and Line Number	Reason if not applicable
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Page 1, Lines 1-3
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	Page 23, Lines 11-14
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	Page 23, Lines 11-14
Protocol version	#3	Date and version identifier	Page 22, Lines 23-24
Funding	#4	Sources and types of financial, material, and other	Page 25, Lines 5-7

		support		
1 2 3 4 5	Roles and responsibilities: contributorship	#5a Names, affiliations, and roles of protocol contributors	Page 25, Lines 12-23	
6 7 8 9 10	Roles and responsibilities: sponsor contact information	#5b Name and contact information for the trial sponsor	Pages 1-6; Page 24, Lines 6-7	
11 12 13 14 15 16 17 18 19 20	Roles and responsibilities: sponsor and funder	#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	Page 25, Lines 5-10	
21 22 23 24 25 26 27 28 29	Roles and responsibilities: committees	#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)	Page 20, Lines 21-24; Page 21, Lines 1-6	
30 31	Introduction			
32 33 34 35 36 37 38 39 40	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	Page 10, Lines 2-22	
41 42 43 44	Background and rationale: choice of	#6b Explanation for choice of comparators	Page 10, Lines 17-20	

1	comparators			
2	Objectives	#7	Specific objectives or hypotheses	Page 10, Lines 22-25
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, non-inferiority, exploratory)	Page 10, Lines 22-25; Page 11, Lines 3-5; Page 17, Lines 8-10
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12	Methods: Participants, interventions, and outcomes			
13				
14	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	Page 11, Lines 3-12
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21	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)	Page 11, Lines 14-25 ; Page 12, Lines 1-25; Page 13, Lines 1-7
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28	Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	Page 13, Lines 9-18
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33	Interventions: modifications	#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. No harm can come to a deceased patient. Accordingly no intervention modifications are planned
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40	Interventions: adherence	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory	Not applicable. The intervention is applied to deceased patients
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		tests)		
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	Page 14, Lines 8-11	
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	Page 14, Lines 13-25 ; Page 15, Lines 1-25	
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)	Page 30, Table 1	
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	Page 17, Lines 2-15	
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	Page 16, Lines 5-11	
Methods: Assignment of interventions (for controlled trials)				
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of	Page 16, Lines 13-16	

		any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions		
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	Page 16, Lines 13-16	
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	Page 16, Lines 5-16	
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	Page 16, Lines 18-25	
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial		Not applicable. The intervention makes blinding of the healthcare staff impossible.
Methods: Data collection, management, and analysis				
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their	Page 20, Lines 5-18	

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1		reliability and validity, if known. Reference to		
2		where data collection forms can be found, if not in		
3		the protocol		
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5	Data collection plan:	#18b	Plans to promote participant retention and	Page 20, Lines 5-18
6	retention		complete follow-up, including list of any outcome	
7			data to be collected for participants who	
8			discontinue or deviate from intervention protocols	
9				
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11	Data management	#19	Plans for data entry, coding, security, and storage,	Page 20, Lines 20-24;
12			including any related processes to promote data	Page 21, Lines 1-15
13			quality (eg, double data entry; range checks for	
14			data values). Reference to where details of data	
15			management procedures can be found, if not in	
16			the protocol	
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21	Statistics: outcomes	#20a	Statistical methods for analysing primary and	Page 18, Lines 18-25
22			secondary outcomes. Reference to where other	
23			details of the statistical analysis plan can be found,	
24			if not in the protocol	
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28	Statistics: additional	#20b	Methods for any additional analyses (eg, subgroup	Page 19, Lines 5-18
29	analyses		and adjusted analyses)	
30				
31				
32	Statistics: analysis	#20c	Definition of analysis population relating to	Page 19, Lines 1-25
33	population and missing		protocol non-adherence (eg, as randomised	
34	data		analysis), and any statistical methods to handle	
35			missing data (eg, multiple imputation)	
36				
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38	Methods: Monitoring			
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40	Data monitoring: formal	#21a	Composition of data monitoring committee	Page 21, Lines 3-6
41	committee		(DMC); summary of its role and reporting	
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		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		
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	Page 18, Lines 1-4	
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		Not applicable. No harms can come to a deceased patient.
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	Page 18, Lines 1-4	
Ethics and dissemination				
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	Page 23, Lines 11-14	
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)	Page 21, Lines 17-23	
Consent or assent	#26a	Who will obtain informed consent or assent from	Page 23, Lines 16-25 ;	

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1		potential trial participants or authorised surrogates, and how (see Item 32)	Page 24, Lines 1-10	
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4	Consent or assent: ancillary studies	#26b Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable		Not applicable. No ancillary studies are planned at this stage
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9	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	Page 21, Lines 9-15	
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15	Declaration of interests	#28 Financial and other competing interests for principal investigators for the overall trial and each study site	Page 24, Lines 21-24	
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21	Data access	#29 Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	Page 24, Lines 12-16	
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26	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. No ancillary studies are planned at this stage
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31	Dissemination policy: trial results	#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	Page 22, Lines 1-6	
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42	Dissemination policy:	#31b Authorship eligibility guidelines and any intended	Page 22, Lines 7-9	
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1	authorship		use of professional writers		
2	Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Page 22, Lines 10-11	
3					
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5	Appendices				
6	Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	Page 24, Lines 9-10	
7					
8	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. No storage of biological specimens are planned for this study
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11 It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items.
12 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. This checklist can be completed online using <https://www.goodreports.org/> a tool made by the EQUATOR
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BMJ Open

Impact of Targeted Hypothermia in Expanded Criteria Organ Donors on Recipient Kidney-Graft Function: Study Protocol for a Multicenter Randomized Controlled Trial (HYPOREME)

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2021-052845.R2
Article Type:	Protocol
Date Submitted by the Author:	20-Oct-2021
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Primary Subject Heading:	Intensive care
Secondary Subject Heading:	Renal medicine
Keywords:	Renal transplantation < NEPHROLOGY, Dialysis < NEPHROLOGY, INTENSIVE & CRITICAL CARE

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Manuscripts

Note from the Editors: Instructions for reviewers of study protocols

Since launching in 2011, BMJ Open has published study protocols for planned or ongoing research studies. If data collection is complete, we will not consider the manuscript.

Publishing study protocols enables researchers and funding bodies to stay up to date in their fields by providing exposure to research activity that may not otherwise be widely publicised. This can help prevent unnecessary duplication of work and will hopefully enable collaboration. Publishing protocols in full also makes available more information than is currently required by trial registries and increases transparency, making it easier for others (editors, reviewers and readers) to see and understand any deviations from the protocol that occur during the conduct of the study.

The scientific integrity and the credibility of the study data depend substantially on the study design and methodology, which is why the study protocol requires a thorough peer-review.

BMJ Open will consider for publication protocols for any study design, including observational studies and systematic reviews.

Some things to keep in mind when reviewing the study protocol:

- Protocol papers should report planned or ongoing studies. The dates of the study should be included in the manuscript.
- Unfortunately we are unable to customize the reviewer report form for study protocols. As such, some of the items (i.e., those pertaining to results) on the form should be scored as Not Applicable (N/A).
- While some baseline data can be presented, there should be no results or conclusions present in the study protocol.
- For studies that are ongoing, it is generally the case that very few changes can be made to the methodology. As such, requests for revisions are generally clarifications for the rationale or details relating to the methods. If there is a major flaw in the study that would prevent a sound interpretation of the data, we would expect the study protocol to be rejected.

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3 **1 Impact of Targeted Hypothermia in Expanded Criteria Organ Donors on Recipient**
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5 **2 Kidney-Graft Function: Study Protocol for a Multicenter Randomized Controlled Trial**
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7 **3 (HYPOREME)**
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1 **List of abbreviations**

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3 DGF: delayed graft function

4 DSMB: Data Safety Monitoring Board

5 ECD: expanded criteria donor

6 eCRF: electronic case report form

7 ICU: intensive care unit

8 ITT: intention-to-treat

9 KR: kidney recipient

10 KTx: kidney transplantation

11 RCT: randomized controlled trial

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For peer review only

1
2
3 **1 ABSTRACT**
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8 **3 Introduction:** Expanded-criteria donors (ECDs) are used to reduce the shortage of kidneys
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10 for transplantation. However, kidneys from ECDs are associated with an increased risk of
11
12 delayed graft function (DGF). DGF is a risk factor for allograft loss and mortality.
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15 **6 HYPOREME** will be a large multicenter randomized controlled trial (RCT) comparing
16
17 targeted hypothermia to normothermia in ECDs. We hypothesize that targeted hypothermia
18
19 will decrease the incidence of DGF in recipients of kidneys from ECDs.
20

21 **9 Methods and analysis:** HYPOREME is a multicenter RCT comparing the effect on kidney
22
23 function in recipients of targeted hypothermia (34 to 35°C) and normothermia (36.5 to
24
25 37.5°C) in the ECDs. The temperature intervention starts from randomization (after legal
26
27 determination of death by neurologic criteria) and is maintained until aortic clamping in the
28
29 operating room. We aim to enroll 289 ECDs in order to analyze the kidney function of 516
30
31 recipients in the 53 participating centers. The primary outcome is the occurrence of DGF in
32
33 kidney recipients, defined as a requirement for renal replacement therapy within 7 days after
34
35 transplantation (not counting a single session for hyperkalemia during the first 24 hours).
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37 Secondary outcomes include the proportion of patients with individual organs transplanted in
38
39 each group; the number of organs transplanted from each ECD; and the vital status and
40
41 kidney function of the recipients 7 days, 28 days, 3 months, and 1 year after transplantation.
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47 An interim analysis is planned after the enrolment of 258 kidney recipients.
48

49 **21 Ethics and dissemination:** The trial was approved by the ethics committee of the French
50
51 Intensive Care Society (CE-SRLF-16-07) on April 26, 2016 and by the competent French
52
53 authorities on April 20, 2016 (Comité de Protection des Personnes - TOURS-Région Centre-
54
55 Ouest 1, registration #2016-S3). Findings will be published in peer-reviewed journals and
56
57 presented during national and international scientific meetings.
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3 1 **Trial Registration:** NCT03098706.
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8 3 **Strengths and limitations of this study**

- 9
10 4 • HYPOREME will be a large multicenter randomized controlled trial (RCT) to
11 evaluate the impact of targeted hypothermia on the function of kidneys from
12 expanded-criteria donors (ECDs) after transplantation.
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14 5
15 6
16 7 • All participating centers were selected based on their high level of experience and
17 expertise in organ transplantation.
18
19 8
20 9 • Assessors for both primary and secondary outcomes on kidney recipients are blinded
21 to the intervention arm of the donor.
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23 10
24 11 • Research assistants from the Research Division Promotion Department of the Nantes
25 University Hospital will regularly perform on-site checks of adherence to the protocol
26 and accuracy of the recorded data.
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28 12
29 13 • A minimal duration of targeted temperature management is not requested by the study
30 protocol
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18 **Keywords:** Organ donor, kidney transplantation, hypothermia, renal replacement therapy,
19 delayed graft function

1 BACKGROUND

2 Kidney transplantation (KTx) is the best therapeutic option for patients with end-stage
3 renal disease and improves both survival and quality of life (1). The use of expanded-criteria
4 donors (ECDs) in solid-organ transplantation was implemented in 2002 in the United States
5 to address the issue of organ donor shortage (2). In 2017 in France, half the KTxs were
6 performed with ECDs (3). Although the use of ECDs undoubtedly expands the pool of
7 deceased organ donors, it is associated with a significant risk of delayed graft function (DGF)
8 after transplantation (4,5). DGF is reported in up to 50% of kidney recipients (6) and is a
9 significant risk factor for allograft loss and mortality (7,8). Moreover, DGF is associated with
10 both acute rejection and worse long-term renal allograft function (9). Thus, developing new
11 strategies to reduce the risk of DGF is a major priority in KTx. Optimizing ECD management
12 from the confirmation of neurologic death to organ recovery in the operating room has been
13 shown to increase the organ yield per donor (10). Conceivably, better ECD management may
14 also improve renal allograft function after transplantation.

15 Hypothermia may help to preserve renal function in donors (11). Experimental data have
16 shown that mild hypothermia reduces cell metabolism, inflammation, and free-radical
17 production (12). A randomized controlled trial conducted in the United States in 2015 found
18 that targeted hypothermia (34 to 35°C) in deceased organ donors reduced the incidence of
19 DGF in kidney recipients compared to normothermia (36.5 to 37.5°C), from 39.2% to 28.2%
20 ($P=0.02$) (13). An a-priori defined stratum of patients from this trial suggested that kidney
21 recipients from ECDs benefited the most from donor targeted hypothermia. Therefore, we
22 designed a multicenter randomized controlled trial (HYPOREME) to test the safety and
23 efficacy of targeted hypothermia compared to normothermia as part of the management of
24 ECDs. We hypothesized that targeted hypothermia in ECDs would decrease the incidence of
25 DFG in kidney recipients.

1 1 **METHODS/DESIGN**

2

3 3 **Trial design and settings**

4 4 HYPOREME is a multicenter, randomized, controlled, trial comparing two parallel
5 groups of patients.

6 6 **Participants, interventions, outcomes**

7 7 ***Participating units***

8 8 A total of 53 French intensive care units (ICUs) and transplant centers are
9 participating in the study (30 university hospitals and 23 general hospitals). All participating
10 centers were carefully selected based on their high level of experience and expertise in the
11 management of organs donors, the process of organ transplantation, and clinical research. In
12 each participating center, a referring team for organ transplantation is identified to ensure
13 knowledge, training and compliance to the protocols edited by the French Biomedicine
14 Agency (national recommendation).

15 15 ***Study population and recruitment modalities***

16 16 This study involves two distinct populations:

- 17 17 • Deceased ECDs for whom the diagnosis of death is made based on neurologic
18 criteria in compliance with French law. ECDs are defined as deceased donors who
19 are older than 60 years or who are aged 50-59 years and have at least two other risk
20 factors (history of hypertension, creatinine >132 µmol/L, and/or cerebrovascular
21 cause of death). The study intervention (targeted temperature management) applies to
22 this population.
- 23 23 • Kidney recipients who receive a kidney allograft from the above-described ECDs.

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3 1 The effect of the study intervention is evaluated in this population based on allograft
4
5 2 function.

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8 3 Deceased ECDs and kidney recipients must fulfil all of the criteria listed below to be
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10 4 included in the study.

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12 5 *Inclusion criteria for deceased ECDs*

- 13
14 6 - Traumatic, vascular, or other brain injuries responsible for death defined by
15
16 neurologic criteria,
17
18 8 - Legal determination of death based on neurologic criteria in compliance with French
19
20 law,
21
22 9
23
24 10 - Organ donation procedure engaged in compliance with French law,
25
26 11 - Deceased ECD older than 60 years or aged 50-59 years with at least two other risk
27
28 factors (history of hypertension, creatinine >132µmol/L, and/or cerebrovascular cause
29
30 of death),
31
32 13
33 14 - Next of kin informed of the study.

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35 15 *Inclusion criteria for kidney transplant recipients:*

- 36
37 16 - Patient registered on the waiting list for KTx,
38
39 17 - Patient informed of the study,
40
41 18 - Age 18 years or older at the time of the pretransplantation evaluation,
42
43 19 - Patient covered by the statutory French health insurance.

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47 20 Deceased organ donors or kidney recipients fulfilling one or more of the following
48
49 21 criteria are not included in the study.

50
51 22 *Exclusion criteria for deceased organ donors:*

- 52
53 23 - Donors with circulatory death or donors who died after treatment limitation,
54
55 24 - Patient registered in the French registry for refusing organ and tissue donations,
56
57 25 - Pregnancy,
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- 1 - Age less than 18 years,
- 2 - Adult under guardianship,
- 3 - Contraindication to organ donation identified according to the current
- 4 recommendations of the French Biomedicine Agency (*Agence de la Biomédecine*).

5 *Exclusion criteria for kidney transplant recipients:*

- 6 - Refusal to participate in the study expressed by the patient,
- 7 - Pregnancy,
- 8 - Age less than 18 years,
- 9 - Adult under guardianship, or correctional facility inmate.

10

11 ***Study intervention***

12 The intervention is initiated after study inclusion and randomization. Deceased ECDs
13 are allocated at random to one of the two targeted temperature strategies (Figure 1). The
14 designated targeted temperature strategy is initiated as soon as possible after randomization
15 and continues until aortic clamping in the operating room. The objective is to reach the
16 targeted temperature range within 4 hours after randomization.

- 17 - In the targeted hypothermia group, ECDs have mild hypothermia (34°C to 35°C)
18 induced then maintained until aortic clamping in the operating room.
- 19 - In the targeted normothermia group, patients have normothermia (36.5°C-37.5°C)
20 induced and maintained until aortic clamping in the operating room.

21 Once the targeted temperature is reached, there is no request for a minimal duration of time
22 spent at the targeted temperature before the aortic clamping in the operating room.

23

24 ***Targeted temperature protocol***

1 No trial has demonstrated one method to be better than another for targeted
2 temperature management. Therefore, to induce and maintain the ECDs at 34°C-35°C or
3 36.5°C-37.5°C, each participating center uses its usual method and protocol. The method
4 may involve active internal cooling or warming using specific devices, active external
5 cooling or warming using specific devices, or active external cooling or warming without
6 specific devices. A standard protocol of targeted temperature management was provided to
7 each participating center (supplementary appendix, Figure 1). Body temperature is recorded
8 hourly from randomization to aortic clamping using invasive (intravascular catheter with a
9 temperature-sensing vascular probe placed in the femoral artery, Pulse Contour Cardiac
10 Output, PiCCO[®], or equivalent) or semi-invasive (esophageal probe, intra-rectal probe,
11 urinary probe) methods according to the device available and local protocol at each center.

12 13 ***General principles of management in both study arms***

14 The general management of deceased organ donors in the ICU and operating room
15 follows the standard protocol recommended by the French Biomedicine Agency in all
16 participating centers (supplementary appendix, Table 1) (14).

17 18 ***Study outcomes***

19 ***Primary outcome measure***

20 The primary outcome is the proportion of kidney recipients with DGF. DGF is
21 defined as a need for renal replacement therapy during the first week after transplantation
22 (not counting a single session of renal replacement therapy to treat hyperkalemia during the
23 first 24 hours after transplantation). DGF is determined for each kidney recipient at the
24 transplant center where the KTx was performed. The decision to commence renal
25 replacement therapy is left at the discretion of the nephrologist in charge.

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3 1 In the rare case of transplantation of both kidneys from a donor into a single recipient,
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5 2 that recipient is counted only once: the primary outcome measure is based on the presence or
6
7 absence of DGF in the kidney recipient.
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12 5 *Secondary outcome measures*
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14 6 The secondary outcomes for the ECDs consist of the following comparisons between the two
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16 arms:
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- 18
19 8 - number of organs recovered and number transplanted,
20
21 9 - body temperature recorded hourly from randomization to aortic clamping,
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23
24 10 - number of severe cardiac arrhythmia episodes,
25
26 11 - total volume of intravenous fluids administered,
27
28 12 - need for vasopressors and inotropes, including total dose and maximal dose,
29
30
31 13 - lowest and highest blood pressures,
32
33 14 - cardiac arrest leading to abortion of the organ-donation procedure,
34
35 15 - metabolic disturbances and coagulation disorders,
36
37 16 - kidney function of organ donors: last serum creatinine and creatinine clearance before
38
39 transfer to the operating room.
40
41

42 18 The secondary outcomes for the kidney recipients consist in comparing the following
43
44 between the two arms:
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- 46
47 20 - hospital length of stay after transplantation,
48
49 21 - kidney graft function (serum creatinine) at hospital discharge on days 7 and 28, and 3
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51 22 months and 1 year after transplantation,
52
53 23 - persistent need for renal replacement therapy 28 days, 3 months, and 1 year after
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55 transplantation,
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57 24
58 25 - reason for renal replacement therapy implementation (sepsis, acute rejection, oliguria,
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- 1
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3 1 hyperkalemia),
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5 2 - hospital mortality,
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8 3 - day-28 (after transplantation) mortality,
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10 4 - day-90 (after transplantation) mortality,
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12 5 - day-365 (after transplantation) mortality.
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7 **Organization of the trial**

8 Figure 1 is the study flowchart.
9

10 ***Recruitment modalities***

11 All patients with a confirmed diagnosis of death based on neurologic criteria in
12 compliance with French law and who meet the definition of ECDs will be screened for
13 eligibility by the ICU physicians and clinical research nurses, around the clock and 7 days a
14 week. Patients will be included after checking inclusion and non-inclusion criteria. A log of
15 patients considered for study participation will be kept and will include the reasons for non-
16 inclusion.
17

18 ***Randomization***

19 Randomization is centralized and performed using a secure, computer-generated,
20 interactive, web-response system available at each study center. Randomization is stratified
21 on study center with a 1:1 ratio.
22

23 ***Blinding***

24 The nature of the intervention on the ECDs makes the blinding of the ICU staff to
25 group assignment impossible. However, the assessors for both primary and secondary
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1 outcomes on kidney recipients are blinded to the intervention arm of the donor. Indeed, the
2 nephrologists in charge of the kidney recipients, who decide whether renal replacement
3 therapy is needed during the first week after transplantation, and the kidney recipients are
4 blinded to the intervention arm of the donor.

6 ***Sample size***

7 According to a recent randomized controlled trial conducted in the United States (13) the
8 proportion of recipients with DGF after kidney transplantation from ECDs was 56.5%. In our
9 local experience at the transplant center in Nantes (France), the proportion of recipients with
10 DGF after kidney transplantation from ECDs was 48%. In the US trial, the proportion with
11 DGF was 56.5% in the normothermia group and 31% in the hypothermia group (13).

12 Based on our local experience, we hypothesized that the rate of DGF after kidney
13 transplantation from ECDs would be 48%. We kept the hypothesis of the US trial of a 30%
14 relative difference in the rate of DGF between the study groups (13). To demonstrate a 14%
15 decrease in the proportion of recipients with DGF (from 48% in the normothermia group to
16 34% in the hypothermia group), a total of 516 kidney recipients are required (258 in each
17 group) to provide 90% power with a two-sided alpha risk of 5%. The analysis of 516 kidney
18 recipients theoretically requires 258 randomized ECDs. However, assuming an estimated
19 attrition rate of 12% (i.e., ECDs who are randomized but for whom organs are not recovered
20 or are recovered but not transplanted) and given that in rare cases both kidneys from a donor
21 are transplanted into a single recipient, our enrolment target is 289 randomized ECDs.

23 ***Interim analysis***

24 The sample size estimation is based on the primary outcome, i.e., the occurrence of
25 DGF. However, there is some uncertainty related to the limited amount of data available in

1 the literature. Accordingly, an interim analysis is planned after the enrolment of 258 kidney
2 recipients. The primary objective of this interim analysis is to reassess the sample size of the
3 study using the method proposed by Friede and Kieser (15,16). The probability of DGF will
4 be estimated from all treatment groups combined in order to preserve blindness. This method
5 makes it possible to maintain the initial clinical hypothesis (14% decrease in the frequency of
6 DGF) and to control the type I error.

7 The interim analysis will be conducted by an independent Data Safety Monitoring Board
8 (DSMB), whose members are not otherwise involved in the trial. This DSMB consists of one
9 methodologist and two intensivists. For the interim analysis, the DSMB will have access to
10 the following unblinded results:

- 11 • For the ECDs: number of patients enrolled, body temperature, mean arterial pressure,
12 total dose of vasopressors and inotropes, episodes of severe arrhythmia or cardiac
13 arrest, number of organs recovered from the donor, reason why organs were not
14 recovered (if applicable), use of machine perfusion for organ storage, and cold
15 ischemia time.
- 16 • For the recipients: occurrence of DGF, need for renal replacement therapy during the
17 first week posttransplantation, allograft lost by day 7, vital status on day 7, severe
18 posttransplantation complications, serum creatinine $<250 \mu\text{mol/L}$ on day 7, and
19 allograft function and vital status on day 28 posttransplantation.

20 The results of the interim analysis will not be disclosed unless they lead the DSMB to request
21 premature trial discontinuation.

23 ***Statistical analysis***

1 All analyses will be performed using SAS software (V.9.4). Analyses will be
2 conducted on data from the intention-to-treat (ITT) population as well as from the per-
3 protocol population.

4 For the primary analysis, sensitivity analyses will be performed with populations
5 defined as follows: first, the ITT population defined as all recipients who received kidneys
6 from the ECDs and, second, all donors, regardless of whether organs were recovered and
7 transplanted. The latter case (failure to recover organs) will be considered a failure for the
8 main outcome measure (occurrence of DGF).

9 In the per-protocol analysis, all randomized patients will be kept in the analysis
10 except those with one or more major protocol violations, such as failure to meet all the
11 inclusion criteria and none of the non-inclusion criteria, an inability to perform the surgical
12 procedure, or withdrawal of consent to participate in the study.

13 A statistical analysis report will be written to describe all the findings, according to
14 CONSORT Statement recommendations, while considering the specific features of the trial,
15 most notably the nonpharmacological nature of the intervention. The baseline features of the
16 groups established by randomization will be compared using descriptive statistics.
17 Continuous variables will be described as mean±SD if normally distributed and as median
18 [interquartile range] otherwise. Categorical data will be described as exact numbers and
19 percentages.

20 For the primary analysis, binary categorical data will be analyzed using random-effect
21 logistic regression adjusted to take into account the hierarchical structure of the data (kidneys
22 from the same donor) and variability across centers.

23 The number of organs transplanted per donor will be compared between the two
24 groups using Poisson regression model. Hospital length of stay will be compared between the
25 two groups using a generalized model with random effects models. Patient and graft

1 survivals will be compared using Cox regression models. All models will be adjusted on
2 centres and consider ECDs as random effects.

4 ***Handling missing data***

5 We expect no missing data for the primary outcome. Graft loss during the first week
6 after transplantation will be classified as DGF. Similarly, death within the first week after
7 transplantation will be classified as DGF. Surgical complications which do not require
8 resuming dialysis during the first week post transplantation will be classified as no DGF
9 while those which require resuming dialysis will be classified as DGF. If unexpectedly data
10 are missing for the primary outcome, sensitivity analyses will be performed using the worst-
11 case scenario (missing data considered the worst case for the hypothermia group) as well as
12 the best-case scenario (missing data considered the best case for the hypothermia group) and
13 the maximum bias scenario (missing data considered the best or worst case in the
14 normothermia and hypothermia groups respectively).

15 The frequency of missing data should be low for the other outcomes as the ECDs
16 included in the study are hospitalized for a few hours or days at the most in the intensive care
17 unit. Kidney transplant recipients are admitted to the nephrology department. Few patients
18 will be lost to follow-up, as hospitalization after KTx lasts routinely about 10 days. Only
19 survival on day 28 and 3 months and 1 year after hospital discharge of recipients may be
20 missing. We will not use any technique to replace missing data. Missing data will be reported
21 for each treatment arm.

23 ***Data collection and follow-up***

24 The donor will be followed from randomization to aortic clamping in the operating
25 room. The following data will be recorded until aortic clamping in the operating room: date

1 and time of death based on neurologic criteria, demographic and clinical data, treatments
2 administered, laboratory tests, body temperature (recorded hourly), adverse events (mainly
3 cardiac arrhythmias, cardiac arrest, coagulopathy, and refractory shock), number of organs
4 recovered in the operating room, use of machine perfusion for organ storage, and number of
5 organs ultimately transplanted. In France, the use of machine perfusion for organ storage is a
6 national recommendation from the French Biomedicine Agency since 2011 for all organs
7 recovered from ECDs. The use of such device is part of the standard of care and it is
8 expected that almost all kidneys will be placed on machine perfusion. Detailed information
9 on machine perfusion settings are provided in the supplementary appendix (supplementary
10 appendix, Figure 2).

11 The kidney recipient will be followed from transplantation to 1 year after
12 transplantation. The following data will be recorded: demographic and clinical data,
13 treatments given, laboratory tests, cold ischemia time, and vital status and graft function on
14 days 7, 28, and 90 and after 1 year. Posttransplantation complications will be recorded during
15 the first 28 days following transplantation (mainly acute allograft rejection, cardiovascular
16 events, infections, and surgical complications). Table 1 is the flowchart of patient follow-up.

18 ***Data entry and monitoring***

19 An Internet-based data collection tool will be used to store the data of all the ECDs
20 and recipients. This electronic case-report form (eCRF) is a secure, interactive, web-response
21 system available at each study center. The eCRF is provided and managed by the biometrical
22 unit of the Nantes University Hospital (EA 4275 SPHERE “Methods for patient-centered
23 outcomes and health research”). Access to the eCRF will require only an Internet connection
24 and a browser.

1 Monitoring of the collected data and screening forms in each participating center will
2 be carried out by the Research Division Promotion Department of the Nantes University
3 Hospital. Research assistants will regularly perform on-site checks of adherence to the
4 protocol and accuracy of the recorded data. Newsletters about the study will be regularly sent
5 by email to all participants to provide support, information, and to recall key instructions.

7 ***Confidentiality and source data archiving***

8 The medical data about each patient will be communicated only to the institution (i.e.,
9 the sponsor) with which the chief investigator is affiliated or to a person appointed by the
10 chief investigator and the sponsor under conditions that ensure the confidentiality of the
11 patient data. During or at completion of the study, the data collected from the study
12 participants and communicated by the individuals involved in the study will be rendered
13 anonymous. The study investigators will archive all study data for at least 15 years after the
14 end of the study.

16 ***Protocol amendments***

17 Any modifications to the protocol will require a formal amendment to the protocol.
18 Such amendment will be reviewed by the Research Division Promotion Department of the
19 Nantes University Hospital and agreed by the competent French authorities (Comité de
20 Protection des Personnes - TOURS-Région Centre-Ouest 1) prior to implementation. Any
21 modifications to the protocol will be communicated without delay to relevant parties
22 (investigators and trial participants).

24 ***Patient and public involvement***

25 Neither the patients nor the public are involved in the study design.

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45 2 **DISCUSSION**
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8 3 HYPOREME will be a large randomized controlled trial to evaluate the impact of
9
10 4 targeted hypothermia on the function of kidneys received from ECDs. The results are
11
12 5 expected to provide intensivists with additional guidance about the optimal management of
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14 6 deceased organ donors.
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1819 8 **TRIAL STATUS**
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21 9 The first trial inclusion was on November 9, 2017. The protocol version is identified
22
23
24 10 RC16_0041_Protocole HYPOREME V10.1 on December 12, 2020. The scheduled interim
25
26 11 analysis was done on December 5, 2019, after the inclusion of 258 kidney recipients. The
27
28 12 interim analysis led the DSMB to recommend continuation of the study without modification
29
30 13 of the protocol and confirmed the initial goal of enrolling 516 kidney recipients. In addition,
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32 14 the DSMB suggested a second interim analysis after the inclusion of 350 kidney recipients.
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35 15 The second interim analysis was done on February 11, 2021, and led the DSMB to
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37 16 recommend continuation of the study without modification of the protocol. On February 11,
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39 17 2021, 349 kidney recipients had been included. The trial is expected to be completed in June
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42 18 2021.
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47 20 **ETHICS AND DISSEMINATION**
4849 21 ***Ethics approval***
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51 22 The HYPOREME trial was approved by the ethics committee of the French Intensive
52
53 23 Care Society (CE-SRLF-16-07) on April 26, 2016 and by the competent French authorities
54
55 24 on April 20, 2016 (Comité de Protection des Personnes - TOURS-Région Centre-Ouest 1,
56
57 25 registration #2016-S3) and was registered on ClinicalTrials (NCT03098706) in April 2017.
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2 ***Consent to participate***

3 In compliance with French law, at the time of declaration of death based on neurologic
4 criteria, the French registry of persons refusing organ and tissue donation is examined to
5 confirm that the deceased patient is not registered. In addition, families or next of kin are
6 interviewed to check that the patient had not expressed unwillingness to donate organs and/or
7 tissues. During the same meeting, information about the study is given orally and an
8 information letter is handed to the family. The information delivered is documented in the
9 donor's medical chart by the local investigator. Legal statutes do not require informed
10 consent from families or next of kin for study inclusion, given that no harm can come to a
11 deceased patient.

12 Prior to study initiation, all the participating transplant centers were contacted. Each
13 transplant center approved the study protocol. The allocation of organs to specific recipients
14 occurs based on the national regulations set forth by the French Agency of Biomedicine. The
15 transplant center that receives the organs from an included ECD is informed of the study
16 inclusion but blinded to the treatment arm. Kidney recipients are informed of the study orally
17 and via a written information sheet and are then asked to provide their written informed
18 consent to participation in the trial. That this information was delivered is documented in the
19 medical chart of the kidney recipient by the investigator.

20 Model consent form and other related documentation given to participants and
21 authorized surrogates are provided in the supplementary appendix.

22
23 ***Access to data***

24 Only the statisticians of the trial and the members of the DSMB have access to the
25 intra-study dataset in order to ensure that the results are not disclosed prior to the end of the

1 trial. After study completion, site investigators will have access to the full dataset if a formal
2 request is approved by the steering committee.

3 4 ***Dissemination policy***

5 The publication policy will comply with international recommendations (N Engl J
6 Med, 1997; 336:309-315) and the CONSORT statement (<http://www.consort-statement.org>).
7 Findings will be published in peer-reviewed journals and presented during national and
8 international scientific meetings. Communications and scientific reports relevant to this study
9 will be under the responsibility of the study coordinator (EC), who will obtain the approval
10 of the other investigators.

11 Substantive contributions of investigators, clinicians, researchers, and statisticians to
12 the design, conduct, interpretation, and reporting of the trial will be granted of authorship on
13 the final trial report.

14 Full protocol and participant-level dataset will be made available for scientific
15 purpose on reasonable request, after the agreement of the ethics and steering committee.

16 17 ***Availability of data and materials***

18 Not applicable

19 20 ***Competing Interests***

21 EC received fees for lectures and conference talks and had travel and accommodation
22 expenses related to attending scientific meetings covered by Gilead, Baxter and Sanofi-
23 Genzyme.

24 25 ***Trial sponsor and Funding***

1 The sponsor of the trial is the Centre Hospitalier Universitaire de Nantes (Direction de
2 la recherché et de l’Innovation – 5, allée de l’île Gloriette, 44093 Nantes cedex 01, France,
3 Phone : +33 253 482 835).

4 The HYPOREME trial received a grant from the French Ministry of Health in 2016
5 (Programme Hospitalier de Recherche Clinique Inter-Régional 2016; API16/N/033) and a
6 grant from the French Intensive Care Society in 2018.

7 Sponsor and funders had no role and no ultimate authority over the study design;
8 collection, management, analysis, and interpretation of data; writing of the report; and the
9 decision to submit the report for publication

11 ***Authors’ contributions***

12 NB and EC prepared the first draft of the manuscript.

13 JR, MP, NB, and EC wrote the manuscript.

14 JR, NB, MP, MH, and EC participated in designing the HYPOREME study.

15 MP and VS wrote the statistical analysis plan and performed the sample size
16 estimation.

17 NB and JR obtained funding for the study.

18 NB, EC, MP, MH, KA, BR, AD, LD, MP, SH, PT, JMB, LMM, FL, RR, TB, TK,
19 AT, OL, JFV, ML, RL, CV, AG, PB, CQ, PYE, OH, AR, YL, JCV, MB, OM, MHV, FH,
20 DS, AC, DG, LA, MH, NK, VM, JB, MLQD, EM, TB, PG, AEH, PM, AG, CH, BF, CM,
21 CGC, NB, JPR, AD, SD, SCO, LF, SG, LA, LR, DB, AH, PFW, FM, ED, DD, EA, CO, VS
22 and JR contributed to acquire the study data.

23 All authors revised the manuscript for important intellectual content and read and
24 approved the final version of the manuscript.

25

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3 1 *Acknowledgments*
4

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6
7 3 manuscript; Carine Coffre and Frédérique Musset for managing the database; Manon Rouaud
8
9 4 for coordinating the study; and Prof. Sylvie Chevret (Biostatistics and Medical Information
10
11 5 Department, Hôpital Saint-Louis, Paris, France; Centre de Recherche en Épidémiologie et
12
13 6 Statistiques [CRESS-INSERM-UMR1153], Paris, France; Epidemiology and Clinical
14
15 7 Statistics for Tumor, Respiratory, and Resuscitation Assessments [ECSTRRA] Team, Paris,
16
17 8 France; Université de Paris, Paris, France), Prof. Alain Combes (Medical ICU, La Pitié-
18
19 9 Salpêtrière University Hospital, AP-HP, Paris, France), and Prof. Elie Azoulay (Medical
20
21 10 ICU, Saint-Louis University Hospital, AP-HP, Paris, France) for constituting the independent
22
23 11 data safety and monitoring board.
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1 **FIGURE LEGENDS**

2 **Figure 1:** Study flowchart

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1 TABLES

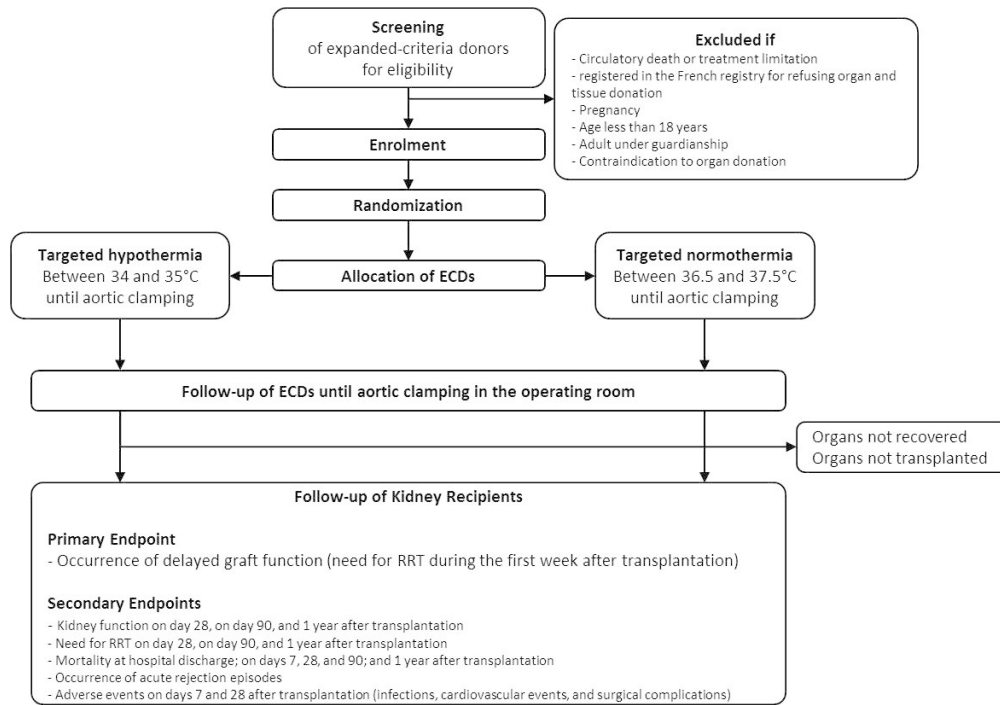
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3 **Table 1: Flow-chart of patient follow-up**

	Inclusion	D0*	Operating room	Dx	D7**	D28**	D90*	One year End of follow-up**	
	ECD			Kidney recipient					
Eligibility: check inclusion and exclusion criteria (for both ECD and KR)	X			DAY OF TRANSPLANTATION					
ECD: information of family/next of kin	X								
KR: information of the patient	X								
Randomization (ECD)		X							
Demographic characteristics		X							
Vital signs		X	X						
Laboratory tests		X	X			X	X	X	X
Body temperature		X	X						
Treatments		X	X			X			
Renal replacement therapy						X	X	X	X
Infectious complications						X	X		
Surgical complications						X	X		
Cardiovascular complications						X	X		
Acute rejection episodes						X	X		
Vital status					X	X	X	X	

5
6 * from time of inclusion to 11:59 pm

7 ** Day-7, day-28, day-90 and 1 year posttransplantation (Dx).

8 ECD, expanded criteria donor; KR, kidney recipient



Study flowchart

198x139mm (150 x 150 DPI)

Supplementary Appendix

Figure 1: Targeted temperature management protocol provided to each center

→ Targeted hypothermia (34-35°C) by internal cooling or warming device

The use of an intravenous bolus of cold (4°C) isotonic saline is not recommended.

→ Targeted hypothermia (34-35°C) by external cooling or warming with no specific device

- According to the local protocol or as an example:
 - Cooling can be obtained using one or more of the following methods:
 - Place 2 cold wet sheets (4°C) on the patient. Take care to keep the sheets wet to optimize cooling by convection.
 - Place ice packs wrapped in a towel on the following sites:
 - 1 on each side of the neck
 - 1 below each armpit
 - 2 on the abdomen
 - 1 on each groin
 - Place a fan with blades at the end of the bed directed towards the patient.

→ Targeted hypothermia (34-35°C) by internal or external cooling or warming with a specific device

- According to the local protocol or as an example:
 - Place the device on the patient and set the target temperature at 33°C.

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3 **Figure 2:** Hypothermic machine perfusion settings
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6 Two different machines are used in France for organ transportation: the ORS (Organ
7 Recovery Systems) LifePort® 2nd generation and the Waters Waves® machine. Both machines
8 are used for perfusion, delivering a pulsatile flow of preservation solution at 4°C, with no
9 changes in perfusion settings throughout the preservation period. The systolic perfusion
10 pressure is initially set at 30 mmHg, and can be temporarily increased to 35mmHg to open the
11 kidney. Thereafter, the perfusion pressure is set to target an intrarenal resistive index between
12 0.3 and 0.5 and a flow between 80 and 100ml/min. Pressure, flow, resistance and temperature
13 are recorded by both machines during the transport period.
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Table 1: ICU management of deceased organ-donors*

Donor Management Goals	Parameters
General management	
Heart rate (bpm)	60-120
Mean arterial pressure (mmHg)	65-70
Hemoglobin (g/dL)	7-10
SpO ₂ (%)	≥95
PaO ₂ (mmHg)	>80
Urinary output (mL·kg ⁻¹ ·h ⁻¹)	0.5-3
Lactate (mmol/L)	<2
Metabolic disorders	
Serum sodium (mmol/L)	130-150
Serum glucose (mmol/L)	4-8
pH	7.35-7.45
Serum potassium, calcium, phosphate, magnesium	Maintain within normal range
Hemodynamic parameters**	
ScVO ₂ (%)	≥70
Cardiac index (L·min ⁻¹ ·m ²)	2.5-3
Central venous pressure (mmHg)	8-10
Pulmonary artery wedge pressure (mmHg)	6-10
Systemic vascular resistance (dynes·seconds·cm ⁻⁵)	800-1200

* From the following reference: Boulard G Ann Fr Anesth Reanim. 2005 Jul;24(7):836-43. doi: 10.1016/j.annfar.2005.05.020.

** If invasive monitoring is implemented (not mandatory)

SPIRIT Checklist for *Trials*

Complete this checklist by entering the page and line numbers where each of the items listed below can be found in your manuscript.

Your manuscript may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please state "n/a" and provide a short explanation. **Leaving an item blank or stating "n/a" without an explanation will lead to your manuscript being returned before review.**

Upload your completed checklist as an additional file when you submit to *Trials*. You must reference this additional file in the main text of your protocol submission. The completed SPIRIT figure must be included within the main body of the protocol text and can be downloaded here: <http://www.spirit-statement.org/schedule-of-enrolment-interventions-and-assessments/>

In your methods section, please state that you used the SPIRIT reporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. *BMJ*. 2013;346:e7586

Reporting Item		Page and Line Number	Reason if not applicable
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Page 1, Lines 1-3
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	Page 23, Lines 11-14
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	Page 23, Lines 11-14
Protocol version	#3	Date and version identifier	Page 22, Lines 23-24
Funding	#4	Sources and types of financial, material, and other	Page 25, Lines 5-7

		support		
1 2 3 4 5	Roles and responsibilities: contributorship	#5a Names, affiliations, and roles of protocol contributors	Page 25, Lines 12-23	
6 7 8 9 10	Roles and responsibilities: sponsor contact information	#5b Name and contact information for the trial sponsor	Pages 1-6; Page 24, Lines 6-7	
11 12 13 14 15 16 17 18 19 20	Roles and responsibilities: sponsor and funder	#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	Page 25, Lines 5-10	
21 22 23 24 25 26 27 28 29	Roles and responsibilities: committees	#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)	Page 20, Lines 21-24; Page 21, Lines 1-6	
30 31	Introduction			
32 33 34 35 36 37 38 39 40	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	Page 10, Lines 2-22	
41 42 43 44	Background and rationale: choice of	#6b Explanation for choice of comparators	Page 10, Lines 17-20	

1	comparators			
2	Objectives	#7	Specific objectives or hypotheses	Page 10, Lines 22-25
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, non-inferiority, exploratory)	Page 10, Lines 22-25; Page 11, Lines 3-5; Page 17, Lines 8-10
5				
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12	Methods: Participants, interventions, and outcomes			
13				
14	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	Page 11, Lines 3-12
15				
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21	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)	Page 11, Lines 14-25 ; Page 12, Lines 1-25; Page 13, Lines 1-7
22				
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28	Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	Page 13, Lines 9-18
29				
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33	Interventions: modifications	#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. No harm can come to a deceased patient. Accordingly no intervention modifications are planned
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40	Interventions: adherence	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory	Not applicable. The intervention is applied to deceased patients
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		tests)		
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	Page 14, Lines 8-11	
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	Page 14, Lines 13-25 ; Page 15, Lines 1-25	
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)	Page 30, Table 1	
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	Page 17, Lines 2-15	
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	Page 16, Lines 5-11	
Methods: Assignment of interventions (for controlled trials)				
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of	Page 16, Lines 13-16	

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		any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions		
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	Page 16, Lines 13-16	
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	Page 16, Lines 5-16	
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	Page 16, Lines 18-25	
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial		Not applicable. The intervention makes blinding of the healthcare staff impossible.
Methods: Data collection, management, and analysis				
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their	Page 20, Lines 5-18	

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1		reliability and validity, if known. Reference to		
2		where data collection forms can be found, if not in		
3		the protocol		
4				
5	Data collection plan:	#18b	Plans to promote participant retention and	Page 20, Lines 5-18
6	retention		complete follow-up, including list of any outcome	
7			data to be collected for participants who	
8			discontinue or deviate from intervention protocols	
9				
10				
11	Data management	#19	Plans for data entry, coding, security, and storage,	Page 20, Lines 20-24;
12			including any related processes to promote data	Page 21, Lines 1-15
13			quality (eg, double data entry; range checks for	
14			data values). Reference to where details of data	
15			management procedures can be found, if not in	
16			the protocol	
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21	Statistics: outcomes	#20a	Statistical methods for analysing primary and	Page 18, Lines 18-25
22			secondary outcomes. Reference to where other	
23			details of the statistical analysis plan can be found,	
24			if not in the protocol	
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27				
28	Statistics: additional	#20b	Methods for any additional analyses (eg, subgroup	Page 19, Lines 5-18
29	analyses		and adjusted analyses)	
30				
31				
32	Statistics: analysis	#20c	Definition of analysis population relating to	Page 19, Lines 1-25
33	population and missing		protocol non-adherence (eg, as randomised	
34	data		analysis), and any statistical methods to handle	
35			missing data (eg, multiple imputation)	
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37				
38	Methods: Monitoring			
39				
40	Data monitoring: formal	#21a	Composition of data monitoring committee	Page 21, Lines 3-6
41	committee		(DMC); summary of its role and reporting	
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		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		
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	Page 18, Lines 1-4	
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		Not applicable. No harms can come to a deceased patient.
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	Page 18, Lines 1-4	
Ethics and dissemination				
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	Page 23, Lines 11-14	
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)	Page 21, Lines 17-23	
Consent or assent	#26a	Who will obtain informed consent or assent from	Page 23, Lines 16-25 ;	

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1		potential trial participants or authorised surrogates, and how (see Item 32)	Page 24, Lines 1-10	
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4	Consent or assent: ancillary studies	#26b Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable		Not applicable. No ancillary studies are planned at this stage
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9	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	Page 21, Lines 9-15	
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15	Declaration of interests	#28 Financial and other competing interests for principal investigators for the overall trial and each study site	Page 24, Lines 21-24	
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21	Data access	#29 Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	Page 24, Lines 12-16	
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26	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. No ancillary studies are planned at this stage
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31	Dissemination policy: trial results	#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	Page 22, Lines 1-6	
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42	Dissemination policy:	#31b Authorship eligibility guidelines and any intended	Page 22, Lines 7-9	
43				
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1	authorship		use of professional writers		
2	Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Page 22, Lines 10-11	
3					
4					
5	Appendices				
6	Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	Page 24, Lines 9-10	
7					
8	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. No storage of biological specimens are planned for this study
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11 It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items.
12 Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons “[Attribution-
13 NonCommercial-NoDerivs 3.0 Unported](#)” license. This checklist can be completed online using <https://www.goodreports.org/>, a tool made by the EQUATOR
14 Network in collaboration with Penelope.ai

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3 1 **Impact of Targeted Hypothermia in Expanded Criteria Organ Donors on Recipient**
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5 2 **Kidney-Graft Function: Study Protocol for a Multicenter Randomized Controlled Trial**
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7 3 **(HYPOREME)**
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1 **List of abbreviations**

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3 DGF: delayed graft function

4 DSMB: Data Safety Monitoring Board

5 ECD: expanded criteria donor

6 eCRF: electronic case report form

7 ICU: intensive care unit

8 ITT: intention-to-treat

9 KR: kidney recipient

10 KTx: kidney transplantation

11 [RCT: randomized controlled trial](#)

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1 ABSTRACT

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3 **Introduction:** Expanded-criteria donors (ECDs) are used to reduce the shortage of kidneys
4 for transplantation. However, kidneys from ECDs are associated with an increased risk of
5 delayed graft function (DGF). DGF is a risk factor for allograft loss and mortality.

6 HYPOREME will be [the first large multicenter randomized controlled trial \(RCT\)](#)
7 comparing targeted hypothermia to normothermia in ECDs. We hypothesize that targeted
8 hypothermia will decrease the incidence of DGF in recipients of kidneys from ECDs.

9 **Methods and analysis:** HYPOREME is a multicenter [RCT randomized controlled trial](#)
10 comparing the effect on kidney function in recipients of targeted hypothermia (34 to 35°C)
11 and normothermia (36.5 to 37.5°C) in the ECDs. The temperature intervention starts from
12 randomization (after legal determination of death by neurologic criteria) and is maintained
13 until aortic clamping in the operating room. We aim to enroll 289 ECDs in order to analyze
14 the kidney function of 516 recipients in the 53 participating centers. The primary outcome is
15 the occurrence of DGF in kidney recipients, defined as a requirement for renal replacement
16 therapy within 7 days after transplantation (not counting a single session for hyperkalemia
17 during the first 24 hours). Secondary outcomes include the proportion of patients with
18 individual organs transplanted in each group; the number of organs transplanted from each
19 ECD; and the vital status and kidney function of the recipients 7 days, 28 days, 3 months, and
20 1 year after transplantation. An interim analysis is planned after the enrolment of 258 kidney
21 recipients.

22 **Ethics and dissemination:** The trial was approved by the ethics committee of the French
23 Intensive Care Society (CE-SRLF-16-07) on April 26, 2016 and by the competent French
24 authorities on April 20, 2016 (Comité de Protection des Personnes - TOURS-Région Centre-
25 Ouest 1, registration #2016-S3). Findings will be published in peer-reviewed journals and

1 presented during national and international scientific meetings.

2 **Trial Registration:** NCT03098706.

4 **Strengths and limitations of this study**

- 5 • HYPOREME will be a large multicenter randomized controlled trial (RCT) to
6 evaluate the impact of targeted hypothermia on the function of kidneys from
7 expanded-criteria donors (ECDs) after transplantation.
- 8 • All participating centers were selected based on their high level of experience and
9 expertise in organ transplantation.
- 10 • Assessors for both primary and secondary outcomes on kidney recipients are blinded
11 to the intervention arm of the donor ICU staff will be aware of group assignments but
12 will not be involved in the assessment of the primary and secondary outcomes.
- 13 • Research assistants from the Research Division Promotion Department of the Nantes
14 University Hospital will regularly perform on-site checks of adherence to the protocol
15 and accuracy of the recorded data.
- 16 • A minimal duration of targeted temperature management is not requested by the study
17 protocol
- 18 • ~~HYPOREME will be the first large randomized controlled trial (RCT) to evaluate the~~
19 ~~impact of targeted hypothermia on the function of kidneys from expanded-criteria~~
20 ~~donors (ECDs) after transplantation.~~
- 21 • ~~The trial is open, since the nature of the intervention on the ECDs makes the blinding~~
22 ~~of the healthcare staff to group assignment impossible.~~
- 23 • ~~The results of this RCT are expected to provide intensivists with additional guidance~~
24 ~~about the optimal management of deceased organ donors.~~

1

2 **Keywords:** Organ donor, kidney transplantation, hypothermia, renal replacement therapy,

3 delayed graft function

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1 BACKGROUND

2 Kidney transplantation (KTx) is the best therapeutic option for patients with end-stage
3 renal disease and improves both survival and quality of life (1). The use of expanded-criteria
4 donors (ECDs) in solid-organ transplantation was implemented in 2002 in the United States
5 to address the issue of organ donor shortage (2). In 2017 in France, half the KTxs were
6 performed with ECDs (3). Although the use of ECDs undoubtedly expands the pool of
7 deceased organ donors, it is associated with a significant risk of delayed graft function (DGF)
8 after transplantation (4,5). DGF is reported in up to 50% of kidney recipients (6) and is a
9 significant risk factor for allograft loss and mortality (7,8). Moreover, DGF is associated with
10 both acute rejection and worse long-term renal allograft function (9). Thus, developing new
11 strategies to reduce the risk of DGF is a major priority in KTx. Optimizing ECD management
12 from the confirmation of neurologic death to organ recovery in the operating room has been
13 shown to increase the organ yield per donor (10). Conceivably, better ECD management may
14 also improve renal allograft function after transplantation.

15 Hypothermia may help to preserve renal function in donors (11). Experimental data have
16 shown that mild hypothermia reduces cell metabolism, inflammation, and free-radical
17 production (12). A randomized controlled trial conducted in the United States in 2015 found
18 that targeted hypothermia (34 to 35°C) in deceased organ donors reduced the incidence of
19 DGF in kidney recipients compared to normothermia (36.5 to 37.5°C), from 39.2% to 28.2%
20 ($P=0.02$) (13). [An a-priori defined stratum of patients from this trial suggested that kidney recipients from ECDs benefited the most from donor targeted hypothermia](#)
21 [A subgroup analysis from this trial suggested that kidney recipients from ECDs benefited the most from donor targeted hypothermia. However, this result needs to be confirmed.](#) Therefore, we
22 designed a multicenter randomized controlled trial (HYPOREME) to test the safety and
23 efficacy of targeted hypothermia compared to normothermia as part of the management of
24
25

1 ECDs. We hypothesized that targeted hypothermia in ECDs would decrease the incidence of
2 DFG in kidney recipients.

3 **METHODS/DESIGN**

5 **Trial design and settings**

6 HYPOREME is a multicenter, randomized, controlled, ~~open-label~~ trial comparing
7 two parallel groups of patients.

9 **Participants, interventions, outcomes**

10 ***Participating units***

11 A total of 53 French intensive care units (ICUs) and transplant centers are
12 participating in the study (30 university hospitals and 23 general hospitals). [All participating
13 centers were carefully selected based on their high level of experience and expertise in the
14 management of organs donors, the process of organ transplantation, and clinical research. In
15 each participating center, a referring team for organ transplantation is identified to ensure
16 knowledge, training and compliance to the protocols edited by the French Biomedicine
17 Agency \(national recommendation\)](#) ~~All participating ICU staff members are trained and
18 experienced in the procedures and protocols of organ donation and in the management of
19 deceased organ donors.~~

21 ***Study population and recruitment modalities***

22 This study involves two distinct populations:

- 23 • Deceased ECDs for whom the diagnosis of death is made based on neurologic
24 criteria in compliance with French law. ECDs are defined as deceased donors who
25 are older than 60 years or who are aged 50-59 years and have at least two other risk

1 factors (history of hypertension, creatinine >132 µmol/L, and/or cerebrovascular
2
3
4 1 factors (history of hypertension, creatinine >132 µmol/L, and/or cerebrovascular
5
6 2 cause of death). The study intervention (targeted temperature management) applies to
7
8 3 this population.

- 9
10 4 • Kidney recipients who receive a kidney allograft from the above-described ECDs.

11
12 5 The effect of the study intervention is evaluated in this population based on allograft
13
14 6 function.

15
16
17 7 Deceased ECDs and kidney recipients must fulfil all of the criteria listed below to be
18
19 8 included in the study.

20
21
22 9 *Inclusion criteria for deceased ECDs*

- 23
24 10 - Traumatic, vascular, or other brain injuries responsible for death defined by
25
26 11 neurologic criteria,
- 27
28 12 - Legal determination of death based on neurologic criteria in compliance with French
29
30 13 law,
- 31
32 14 - Organ donation procedure engaged in compliance with French law,
- 33
34 15 - Deceased ECD older than 60 years or aged 50-59 years with at least two other risk
35
36 16 factors (history of hypertension, creatinine >132µmol/L, and/or cerebrovascular cause
37
38 17 of death),
- 39
40 18 - Next of kin informed of the study.

41
42
43
44
45 19 *Inclusion criteria for kidney transplant recipients:*

- 46
47 20 - Patient registered on the waiting list for KTx,
- 48
49 21 - Patient informed of the study,
- 50
51 22 - Age 18 years or older at the time of the pretransplantation evaluation,
- 52
53 23 - Patient covered by the statutory French health insurance.

54
55
56 24 Deceased organ donors or kidney recipients fulfilling one or more of the following
57
58 25 criteria are not included in the study.

1
2
3 1 *Exclusion criteria for deceased organ donors:*

- 4
5 2 - Donors with circulatory death or donors who died after treatment limitation,
6
7 3 - Patient registered in the French registry for refusing organ and tissue donations,
8
9 4 - Pregnancy,
10
11 5 - Age less than 18 years,
12
13 6 - Adult under guardianship,
14
15 7 - Contraindication to organ donation identified according to the current
16
17 8 recommendations of the French Biomedicine Agency (*Agence de la Biomédecine*).
18
19

20
21 9 *Exclusion criteria for kidney transplant recipients:*

- 22
23
24 10 - Refusal to participate in the study expressed by the patient,
25
26 11 - Pregnancy,
27
28 12 - Age less than 18 years,
29
30 13 - Adult under guardianship, or correctional facility inmate.
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35 15 ***Study intervention***

36
37 16 The intervention is initiated after study inclusion and randomization. Deceased ECDs
38
39 17 are allocated at random to one of the two targeted temperature strategies (Figure 1). The
40
41 18 designated targeted temperature strategy is initiated as soon as possible after randomization
42
43 19 and continues until aortic clamping in the operating room. The objective is to reach the
44
45 20 targeted temperature range within 4 hours after randomization.
46
47

- 48
49 21 - In the targeted hypothermia group, ECDs have mild hypothermia (34°C to 35°C)
50
51 22 induced then maintained until aortic clamping in the operating room.
52
53
54 23 - In the targeted normothermia group, patients have normothermia (36.5°C-37.5°C)
55
56 24 induced and maintained until aortic clamping in the operating room.
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- 1
2
3 1 - [Once the targeted temperature is reached, there is no request for a minimal duration of](#)
4
5 2 [time spent at the targeted temperature before the aortic clamping in the operating room.](#)
6
7
8 3
9

10 4 ***Targeted temperature protocol***

11
12 5 No trial has demonstrated one method to be better than another for targeted
13
14 6 temperature management. Therefore, to induce and maintain the ECDs at 34°C-35°C or
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16 7 36.5°C-37.5°C, each participating center uses its usual method and protocol. The method
17
18 8 may involve active internal cooling or warming using specific devices, active external
19
20 9 cooling or warming using specific devices, or active external cooling or warming without
21
22 10 specific devices. A standard protocol of targeted temperature management was provided to
23
24 11 each participating center (supplementary appendix, Figure 1). Body temperature is recorded
25
26 12 hourly from randomization to aortic clamping using invasive (intravascular catheter with a
27
28 13 temperature-sensing vascular probe placed in the femoral artery, Pulse Contour Cardiac
29
30 14 Output, PiCCO®, or equivalent) or semi-invasive (esophageal probe, intra-rectal probe,
31
32 15 urinary probe) methods according to the device available and local protocol at each center.
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40 17 ***General principles of management in both study arms***

41
42 18 The general management of deceased organ donors in the ICU and operating room
43
44 19 follows the standard protocol recommended by the French Biomedicine Agency in all
45
46 20 participating centers (supplementary appendix, Table 1) (14).
47
48
49
50

51 22 ***Study outcomes***

52 23 ***Primary outcome measure***

53
54 24 The primary outcome is the proportion of kidney recipients with DGF. DGF is
55
56 25 defined as a need for renal replacement therapy during the first week after transplantation
57
58
59
60

1 (not counting a single session of renal replacement therapy to treat hyperkalemia during the
2 first 24 hours after transplantation). DGF is determined for each kidney recipient at the
3 transplant center where the KTx was performed. The decision to commence renal
4 replacement therapy is left at the discretion of the nephrologist in charge.

5 In the rare case of transplantation of both kidneys from a donor into a single recipient,
6 that recipient is counted only once: the primary outcome measure is based on the presence or
7 absence of DGF in the kidney recipient.

8 *Secondary outcome measures*

9 The secondary outcomes for the ECDs consist ~~of -in comparing-~~ the following [comparisons](#)
10 between the two arms:

- 11 - number of organs recovered and number transplanted,
- 12 - body temperature recorded hourly from randomization to aortic clamping,
- 13 - number of severe cardiac arrhythmia episodes,
- 14 - total volume of intravenous fluids administered,
- 15 - need for vasopressors and inotropes, including total dose and maximal dose,
- 16 - lowest and highest blood pressures,
- 17 - cardiac arrest leading to abortion of the organ-donation procedure,
- 18 - metabolic disturbances and coagulation disorders,
- 19 - kidney function of organ donors: last serum creatinine and creatinine clearance before
20 transfer to the operating room.

21 The secondary outcomes for the kidney recipients consist in comparing the following
22 between the two arms:

- 23 - hospital length of stay after transplantation,
- 24 - kidney graft function (serum creatinine) at hospital discharge on days 7 and 28, and 3

- 1 months and 1 year after transplantation,
- 2
- 3 1 months and 1 year after transplantation,
- 4
- 5 2 - persistent need for renal replacement therapy 28 days, 3 months, and 1 year after
- 6
- 7 transplantation,
- 8 3
- 9
- 10 4 - reason for renal replacement therapy implementation (sepsis, acute rejection, oliguria,
- 11
- 12 hyperkalemia),
- 13 5
- 14 - hospital mortality,
- 15 6
- 16 - day-28 (after transplantation) mortality,
- 17 7
- 18 - day-90 (after transplantation) mortality,
- 19 8
- 20 - day-365 (after transplantation) mortality.
- 21 9
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- 23
- 24 10
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26 11 **Organization of the trial**

27 Figure 1 is the study flowchart.

28

29

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33 14 ***Recruitment modalities***

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35 All patients with a confirmed diagnosis of death based on neurologic criteria in

36

37 compliance with French law and who meet the definition of ECDs will be screened for

38 16

39 eligibility by the ICU physicians and clinical research nurses, around the clock and 7 days a

40 17

41 week. Patients will be included after checking inclusion and non-inclusion criteria. A log of

42 18

43 patients considered for study participation will be kept and will include the reasons for non-

44 19

45 inclusion.

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51 22 ***Randomization***

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53 Randomization is centralized and performed using a secure, computer-generated,

54 23

55 interactive, web-response system available at each study center. Randomization is stratified

56 24

57 on study center with a 1:1 ratio.

58 25

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Blinding

~~The trial is open, T since~~ the nature of the intervention on the ECDs makes the blinding of the ~~ICU healthcare~~ staff to group assignment impossible. However, the assessors for both primary and secondary outcomes on kidney recipients are blinded to the intervention arm of the donor~~absence of blinding cannot have an impact on assessment of the primary outcome. Indeed, the primary outcome (the occurrence of DGF) is analyzed in another population of patients, namely kidney recipients. Indeed, t~~The nephrologist~~s~~ in charge of the kidney recipient~~s~~, who decide whether renal replacement therapy is needed during the first week after transplantation, and the kidney recipients are blinded to the intervention arm of the donor.

Sample size

According to a recent randomized controlled trial conducted in the United States (13) the proportion of recipients with DGF after kidney transplantation from ECDs was 56.5%. and to ~~o~~In our local experience at the transplant center in Nantes (France), the proportions of recipients with ~~renal~~ DGF after kidney transplantation from ECDs ~~were 56.5% and was~~ 48%, ~~respectively~~. In the US trial, the proportion with DGF was 56.5% in the normothermia group and 31% in the hypothermia group (13).

Based on our local experience, we hypothesized that the rate of DGF after kidney transplantation from ECDs would be 48%. We kept the hypothesis of the US trial of a 30% relative difference in the rate of DGF between the study groups (13). To demonstrate a 14% decrease in the proportion of recipients with DGF (from 48% in the normothermia group to 34% in the hypothermia group), a total of 516 kidney recipients are required (258 in each group) to provide 90% power with a two-sided alpha risk of 5%. The analysis of 516 kidney

1 recipients theoretically requires 258 randomized ECDs. However, assuming an estimated
2 attrition rate of 12% (i.e., ECDs who are randomized but for whom organs are not recovered
3 or are recovered but not transplanted) and given that in rare cases both kidneys from a donor
4 are transplanted into a single recipient, our enrolment target is 289 randomized ECDs.

6 *Interim analysis*

7 The sample size estimation is based on the primary outcome, i.e., the occurrence of
8 DGF. However, there is some uncertainty related to the limited amount of data available in
9 the literature. Accordingly, an interim analysis is planned after the enrolment of 258 kidney
10 recipients. The primary objective of this interim analysis is to reassess the sample size of the
11 study using the method proposed by Friede and Kieser (15,16). The probability of DGF will
12 be estimated from all treatment groups combined in order to preserve blindness. This method
13 makes it possible to maintain the initial clinical hypothesis (14% decrease in the frequency of
14 DGF) and to control the type I error.

15 The interim analysis will be conducted by an independent Data Safety Monitoring Board
16 (DSMB), whose members are not otherwise involved in the trial. This DSMB consists of one
17 methodologist and two intensivists. For the interim analysis, the DSMB will have access to
18 the following unblinded results:

- 19 • For the ECDs: number of patients enrolled, body temperature, mean arterial pressure,
20 total dose of vasopressors and inotropes, episodes of severe arrhythmia or cardiac
21 arrest, number of organs recovered from the donor, reason why organs were not
22 recovered (if applicable), use of machine perfusion for organ storage, and cold
23 ischemia time.
- 24 • For the recipients: occurrence of DGF, need for renal replacement therapy during the
25 first week posttransplantation, allograft lost by day 7, vital status on day 7, severe

1 posttransplantation complications, serum creatinine <250 µmol/L on day 7, and
2 allograft function and vital status on day 28 posttransplantation.

3 The results of the interim analysis will not be disclosed unless they lead the DSMB to request
4 premature trial discontinuation.

6 ***Statistical analysis***

7 All analyses will be performed using SAS software (V.9.4). Analyses will be
8 conducted on data from the intention-to-treat (ITT) population as well as from the per-
9 protocol population.

10 For the primary analysis, sensitivity analyses will be performed with populations
11 defined as follows: first, the ITT population defined as all recipients who received kidneys
12 from the ECDs and, second, all donors, regardless of whether organs were recovered and
13 transplanted. The latter case (failure to recover organs) will be considered a failure for the
14 main outcome measure (occurrence of DGF).

15 In the per-protocol analysis, all randomized patients will be kept in the analysis
16 except those with one or more major protocol violations, such as failure to meet all the
17 inclusion criteria and none of the non-inclusion criteria, an inability to perform the surgical
18 procedure, or withdrawal of consent to participate in the study.

19 A statistical analysis report will be written to describe all the findings, according to
20 CONSORT Statement recommendations, while considering the specific features of the trial,
21 most notably the nonpharmacological nature of the intervention. The baseline features of the
22 groups established by randomization will be compared using descriptive statistics.

23 Continuous variables will be described as mean±SD if normally distributed and as median
24 [interquartile range] otherwise. Categorical data will be described as exact numbers and
25 percentages.

1 For the primary analysis, binary categorical data will be analyzed using random-effect
2 logistic regression adjusted to take into account the hierarchical structure of the data (kidneys
3 from the same donor) and variability across centers.

4 The number of organs transplanted per donor will be compared between the two
5 groups using Poisson regression model. Hospital length of stay will be compared between the
6 two groups using a generalized model with random effects models. Patient and graft
7 survivals will be compared using Cox regression models. All models will be adjusted on
8 centres and consider ECDs as random effects.

10 ***Handling missing data***

11 We ~~expect no~~expect no missing data for the primary outcome. Graft loss during the
12 first week after transplantation will be classified as DGF. Similarly, death within the first
13 week after transplantation will be classified as DGF. Surgical complications which do not
14 require resuming dialysis during the first week post transplantation will be classified as no
15 DGF while those which require resuming dialysis will be classified as DGF. If unexpectedly
16 data are missing for the primary outcome, sensitivity analyses will be performed using the
17 worst-case scenario (missing data considered the worst case for the hypothermia group) as
18 well as the best-case scenario (missing data considered the best case for the hypothermia
19 group) and the maximum bias scenario (missing data considered the best or worst case in the
20 normothermia and hypothermia groups respectively).

21 The frequency of missing data should be low for the other outcomes as the ECDs
22 included in the study are hospitalized for a few hours or days at the most in the intensive care
23 unit. Kidney transplant recipients are admitted to the nephrology department. Few patients
24 will be lost to follow-up, as hospitalization after KTx lasts routinely about 10 days. Only
25 survival on day 28 and 3 months and 1 year after hospital discharge of recipients may be

1 missing. We will not use any technique to replace missing data. Missing data will be reported
2 for each treatment arm.

3 4 ***Data collection and follow-up***

5 The donor will be followed from randomization to aortic clamping in the operating
6 room. The following data will be recorded until aortic clamping in the operating room: date
7 and time of death based on neurologic criteria, demographic and clinical data, treatments
8 administered, laboratory tests, body temperature ([recorded hourly](#)), adverse events (mainly
9 cardiac arrhythmias, cardiac arrest, coagulopathy, and refractory shock), number of organs
10 recovered in the operating room, use of machine perfusion for organ storage, and number of
11 organs ultimately transplanted. [In France, the use of machine perfusion for organ storage is a
12 national recommendation from the French Biomedicine Agency since 2011 for all organs
13 recovered from ECDs. The use of such device is part of the standard of care and it is
14 expected that almost all kidneys will be placed on machine perfusion. Detailed information
15 on machine perfusion settings are provided in the supplementary appendix \(supplementary
16 appendix, Figure 2\).](#)

17 The kidney recipient will be followed from transplantation to 1 year after
18 transplantation. The following data will be recorded: demographic and clinical data,
19 treatments given, laboratory tests, cold ischemia time, and vital status and graft function on
20 days 7, 28, and 90 and after 1 year. Posttransplantation complications will be recorded during
21 the first 28 days following transplantation (mainly acute allograft rejection, cardiovascular
22 events, infections, and surgical complications). Table 1 is the flowchart of patient follow-up.

23 24 ***Data entry and monitoring***

1 An Internet-based data collection tool will be used to store the data of all the ECDs
2 and recipients. This electronic case-report form (eCRF) is a secure, interactive, web-response
3 system available at each study center. The eCRF is provided and managed by the biometrical
4 unit of the Nantes University Hospital (EA 4275 SPHERE “Methods for patient-centered
5 outcomes and health research”). Access to the eCRF will require only an Internet connection
6 and a browser.

7 Monitoring of the collected data and screening forms in each participating center will
8 be carried out by the Research Division Promotion Department of the Nantes University
9 Hospital. Research assistants will regularly perform on-site checks of adherence to the
10 protocol and accuracy of the recorded data. [Newsletters about the study will be regularly sent
11 by email to all participants to provide support, information, and to recall key instructions.](#)

13 ***Confidentiality and source data archiving***

14 The medical data about each patient will be communicated only to the institution (i.e.,
15 the sponsor) with which the chief investigator is affiliated or to a person appointed by the
16 chief investigator and the sponsor under conditions that ensure the confidentiality of the
17 patient data. During or at completion of the study, the data collected from the study
18 participants and communicated by the individuals involved in the study will be rendered
19 anonymous. The study investigators will archive all study data for at least 15 years after the
20 end of the study.

22 ***Protocol amendments***

23 Any modifications to the protocol will require a formal amendment to the protocol.
24 Such amendment will be reviewed by the Research Division Promotion Department of the
25 Nantes University Hospital and agreed by the competent French authorities (Comité de

1 Protection des Personnes - TOURS-Région Centre-Ouest 1) prior to implementation. Any
2 modifications to the protocol will be communicated without delay to relevant parties
3 (investigators and trial participants).

4 ~~*Dissemination policy*~~

5 ~~The publication policy will comply with international recommendations (N Engl J~~
6 ~~Med, 1997; 336:309-315) and the CONSORT statement (<http://www.consort-statement.org>).~~
7 ~~Findings will be published in peer-reviewed journals and presented during national and~~
8 ~~international scientific meetings. Communications and scientific reports relevant to this study~~
9 ~~will be under the responsibility of the study coordinator (EC), who will obtain the approval~~
10 ~~of the other investigators.~~

11 ~~Substantive contributions of investigators, clinicians, researchers, and statisticians to~~
12 ~~the design, conduct, interpretation, and reporting of the trial will be granted of authorship on~~
13 ~~the final trial report.~~

14 ~~Full protocol and participant-level dataset will be made available for scientific~~
15 ~~purpose on reasonable request, after the agreement of the ethics and steering committee.~~

16 *Patient and public involvement*

17 Neither the patients nor the public are involved in the ~~conduct of the study~~ design.

18 **DISCUSSION**

19 HYPOREME will be ~~the first~~ large randomized controlled trial to evaluate the
20 impact of targeted hypothermia on the function of kidneys received from ECDs. The results
21 are expected to provide intensivists with additional guidance about the optimal management
22 of deceased organ donors.

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3 1
45 2 **TRIAL STATUS**
6

7
8 3 The first trial inclusion was on November 9, 2017. The protocol version is identified
9
10 4 RC16_0041_Protocol HYPOREME V10.1 on December 12, 2020. The scheduled interim
11
12 5 analysis was done on December 5, 2019, after the inclusion of 258 kidney recipients. The
13
14 6 interim analysis led the DSMB to recommend continuation of the study without modification
15
16 7 of the protocol and confirmed the initial goal of enrolling 516 kidney recipients. In addition,
17
18 8 the DSMB suggested a second interim analysis after the inclusion of 350 kidney recipients.
19
20 9 The second interim analysis was done on February 11, 2021, and led the DSMB to
21
22 10 recommend continuation of the study without modification of the protocol. On February 11,
23
24 11 2021, 349 kidney recipients had been included. The trial is expected to be completed in June
25
26 12 2021.
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33 14 **ETHICS AND DISSEMINATION DECLARATIONS**
3435 15 ***Ethics approval***
36

37
38 16 The HYPOREME trial was approved by the ethics committee of the French Intensive
39
40 17 Care Society (CE-SRLF-16-07) on April 26, 2016 and by the competent French authorities
41
42 18 on April 20, 2016 (Comité de Protection des Personnes - TOURS-Région Centre-Ouest 1,
43
44 19 registration #2016-S3) and was registered on ClinicalTrials (NCT03098706) in April 2017.
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49 21 ***Consent to participate***
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51 22 In compliance with French law, at the time of declaration of death based on neurologic
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53 23 criteria, the French registry of persons refusing organ and tissue donation is examined to
54
55 24 confirm that the deceased patient is not registered. In addition, families or next of kin are
56
57 25 interviewed to check that the patient had not expressed unwillingness to donate organs and/or
58
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1 tissues. During the same meeting, information about the study is given orally and an
2 information letter is handed to the family. ~~The~~^{at this} information ~~was~~ delivered is
3 documented in the donor's medical chart by the local investigator. Legal statutes do not
4 require informed consent from families or next of kin for study inclusion, given that no harm
5 can come to a deceased patient.

6 Prior to study initiation, all the participating transplant centers were contacted. Each
7 transplant center approved the study protocol. The allocation of organs to specific recipients
8 occurs based on the national regulations set forth by the French Agency of Biomedicine. The
9 transplant center that receives the organs from an included ECD is informed of the study
10 inclusion but blinded to the treatment arm. Kidney recipients are informed of the study orally
11 and via a written information sheet and are then asked to provide their written informed
12 consent to participation in the trial. That this information was delivered is documented in the
13 medical chart of the kidney recipient by the investigator.

14 Model consent form and other related documentation given to participants and
15 authorized surrogates are provided in the supplementary appendix.

17 *Access to data*

18 Only the statisticians of the trial and the members of the DSMB have access to the
19 intra-study dataset in order to ensure that the results are not disclosed prior ^{to} the end of the
20 trial. After study completion, site investigators will have access to the full dataset if a formal
21 request is approved by the steering committee.

23 Dissemination policy

24 The publication policy will comply with international recommendations (N Engl J
25 Med, 1997; 336:309-315) and the CONSORT statement (<http://www.consort-statement.org>).

1 [Findings will be published in peer-reviewed journals and presented during national and](#)
2 [international scientific meetings. Communications and scientific reports relevant to this study](#)
3 [will be under the responsibility of the study coordinator \(EC\), who will obtain the approval](#)
4 [of the other investigators.](#)

5 [Substantive contributions of investigators, clinicians, researchers, and statisticians to](#)
6 [the design, conduct, interpretation, and reporting of the trial will be granted of authorship on](#)
7 [the final trial report.](#)

8 [Full protocol and participant-level dataset will be made available for scientific](#)
9 [purpose on reasonable request, after the agreement of the ethics and steering committee.](#)

12 ***Availability of data and materials***

13 Not applicable

15 ***Competing Interests***

16 EC received fees for lectures and conference talks and had travel and accommodation
17 expenses related to attending scientific meetings covered by Gilead, Baxter and Sanofi-
18 Genzyme.

20 ***Trial sponsor and Funding***

21 The sponsor of the trial is the Centre Hospitalier Universitaire de Nantes (Direction de
22 la recherché et de l'Innovation – 5, allée de l'île Gloriette, 44093 Nantes cedex 01, France,
23 Phone : +33 253 482 835).

1 The HYPOREME trial received a grant from the French Ministry of Health in 2016
2
3
4
5 2 (Programme Hospitalier de Recherche Clinique Inter-Régional 2016; API16/N/033) and a
6
7
8 3 grant from the French Intensive Care Society in 2018.

9
10 4 Sponsor and funders had no role and no ultimate authority over the study design;
11
12 5 collection, management, analysis, and interpretation of data; writing of the report; and the
13
14 6 decision to submit the report for publication

19 8 *Authors' contributions*

21 9 NB and EC prepared the first draft of the manuscript.

23 10 JR, MP, NB, and EC wrote the manuscript.

25 11 JR, NB, MP, MH, and EC participated in designing the HYPOREME study.

27 12 MP and VS wrote the statistical analysis plan and performed the sample size
28
29 13 estimation.

31 14 NB and JR obtained funding for the study.

33 15 NB, EC, MP, MH, KA, BR, AD, LD, MP, SH, PT, JMB, LMM, FL, RR, TB, TK,
34
35 16 AT, OL, JFV, ML, RL, CV, AG, PB, CQ, PYE, OH, AR, YL, JCV, MB, OM, MHV, FH,
36
37 17 DS, AC, DG, LA, MH, NK, VM, JB, MLQD, EM, TB, PG, AEH, PM, AG, CH, BF, CM,
38
39 18 CGC, NB, JPR, AD, SD, SCO, LF, SG, LA, LR, DB, AH, PFW, FM, ED, DD, EA, CO, VS
40
41 19 and JR contributed to acquire the study data.

42 20 All authors revised the manuscript for important intellectual content and read and
43
44 21 approved the final version of the manuscript.

53 23 *Acknowledgments*

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55
56 25 manuscript; Carine Coffre and Frédérique Musset for managing the database; Manon Rouaud
57
58
59
60

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2 Department, Hôpital Saint-Louis, Paris, France; Centre de Recherche en Épidémiologie et
3 Statistiques [CRESS-INSERM-UMR1153], Paris, France; Epidemiology and Clinical
4 Statistics for Tumor, Respiratory, and Resuscitation Assessments [ECSTRRA] Team, Paris,
5 France; Université de Paris, Paris, France), Prof. Alain Combes (Medical ICU, La Pitié-
6 Salpêtrière University Hospital, AP-HP, Paris, France), and Prof. Elie Azoulay (Medical
7 ICU, Saint-Louis University Hospital, AP-HP, Paris, France) for constituting the independent
8 data safety and monitoring board.

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1 **FIGURE LEGENDS**

2 **Figure 1:** Study flowchart

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1 TABLES

2
3 **Table 1: Flow-chart of patient follow-up**

	Inclusion	D0*	Operating room	Dx	D7**	D28**	D90*	One year End of follow-up**	
	ECD			Kidney recipient					
Eligibility: check inclusion and exclusion criteria (for both ECD and KR)	X			DAY OF TRANSPLANTATION					
ECD: information of family/next of kin	X								
KR: information of the patient	X								
Randomization (ECD)		X							
Demographic characteristics		X							
Vital signs		X	X						
Laboratory tests		X	X			X	X	X	X
Body temperature		X	X						
Treatments		X	X			X			
Renal replacement therapy						X	X	X	X
Infectious complications						X	X		
Surgical complications						X	X		
Cardiovascular complications						X	X		
Acute rejection episodes						X	X		
Vital status					X	X	X	X	

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6 * from time of inclusion to 11:59 pm

7 ** Day-7, day-28, day-90 and 1 year posttransplantation (Dx).

8 ECD, expanded criteria donor; KR, kidney recipient

BMJ Open

Impact of Targeted Hypothermia in Expanded Criteria Organ Donors on Recipient Kidney-Graft Function: Study Protocol for a Multicenter Randomized Controlled Trial (HYPOREME)

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Manuscripts

1 **Impact of Targeted Hypothermia in Expanded Criteria Organ Donors on Recipient**
 2 **Kidney-Graft Function: Study Protocol for a Multicenter Randomized Controlled Trial**
 3 **(HYPOREME)**

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3 **1 List of abbreviations**
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8 3 DGF: delayed graft function
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10 4 DSMB: Data Safety Monitoring Board
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12 5 ECD: expanded criteria donor
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14 6 eCRF: electronic case report form
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16 7 ICU: intensive care unit
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18 8 ITT: intention-to-treat
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20 9 KR: kidney recipient
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22 10 KTx: kidney transplantation
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24 11 RCT: randomized controlled trial
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3 **1 ABSTRACT**
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8 **3 Introduction:** Expanded-criteria donors (ECDs) are used to reduce the shortage of kidneys
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10 for transplantation. However, kidneys from ECDs are associated with an increased risk of
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12 delayed graft function (DGF), a risk factor for allograft loss and mortality. HYPOREME will
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14 be a multicenter randomized controlled trial (RCT) comparing targeted hypothermia to
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16 normothermia in ECDs, in a country where the use of machine perfusion for organ storage is
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18 the standard of care. We hypothesize that hypothermia will decrease the incidence of DGF.
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21 **9 Methods and analysis:** HYPOREME is a multicenter RCT comparing the effect on kidney
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23 function in recipients of targeted hypothermia (34 to 35°C) and normothermia (36.5 to
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25 37.5°C) in the ECDs. The temperature intervention starts from randomization and is
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27 maintained until aortic clamping in the operating room. We aim to enroll 289 ECDs in order
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29 to analyze the kidney function of 516 recipients in the 53 participating centers. The primary
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31 outcome is the occurrence of DGF in kidney recipients, defined as a requirement for renal
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33 replacement therapy within 7 days after transplantation (not counting a single session for
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35 hyperkalemia during the first 24 hours). Secondary outcomes include the proportion of
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37 patients with individual organs transplanted in each group; the number of organs transplanted
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39 from each ECD; and the vital status and kidney function of the recipients 7 days, 28 days, 3
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41 months, and 1 year after transplantation. An interim analysis is planned after the enrolment of
42
43 258 kidney recipients.
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48
49 **21 Ethics and dissemination:** The trial was approved by the ethics committee of the French
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51 Intensive Care Society (CE-SRLF-16-07) on April 26, 2016 and by the competent French
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53 authorities on April 20, 2016 (Comité de Protection des Personnes - TOURS-Région Centre-
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55 Ouest 1, registration #2016-S3). Findings will be published in peer-reviewed journals and
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57 presented during national and international scientific meetings.
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1 **Trial Registration:** NCT03098706.

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3 **Strengths and limitations of this study**

- 4 • HYPOREME will be a large multicenter randomized controlled trial (RCT) to
5 evaluate the impact of targeted hypothermia on the function of kidneys from
6 expanded-criteria donors (ECDs) after transplantation.
- 7 • All participating centers were selected based on their high level of experience and
8 expertise in organ transplantation.
- 9 • Assessors for both primary and secondary outcomes on kidney recipients are blinded
10 to the intervention arm of the donor.
- 11 • Research assistants from the Research Division Promotion Department of the Nantes
12 University Hospital will regularly perform on-site checks of adherence to the protocol
13 and accuracy of the recorded data.
- 14 • A minimal duration of targeted temperature management is not requested by the study
15 protocol

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18 **Keywords:** Organ donor, kidney transplantation, hypothermia, renal replacement therapy,

19 delayed graft function

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1 BACKGROUND

2 Kidney transplantation (KTx) is the best therapeutic option for patients with end-stage
3 renal disease and improves both survival and quality of life (1). The use of expanded-criteria
4 donors (ECDs) in solid-organ transplantation was implemented in 2002 in the United States
5 to address the issue of organ donor shortage (2). In 2017 in France, half the KTxs were
6 performed with ECDs (3). Although the use of ECDs undoubtedly expands the pool of
7 deceased organ donors, it is associated with a significant risk of delayed graft function (DGF)
8 after transplantation (4,5). DGF is reported in up to 50% of kidney recipients (6) and is a
9 significant risk factor for allograft loss and mortality (7,8). Moreover, DGF is associated with
10 both acute rejection and worse long-term renal allograft function (9). Thus, developing new
11 strategies to reduce the risk of DGF is a major priority in KTx. One of them is the use of
12 machine perfusion for organ storage, which is a national recommendation from the French
13 Biomedicine Agency since 2011 for all organs recovered from ECDs. Moreover, optimizing
14 ECD management from the confirmation of neurologic death to organ recovery in the
15 operating room has been shown to increase the organ yield per donor (10). Conceivably,
16 better ECD management may also improve renal allograft function after transplantation.

17 Hypothermia may help to preserve renal function in donors (11). Experimental data have
18 shown that mild hypothermia reduces cell metabolism, inflammation, and free-radical
19 production (12). A randomized controlled trial conducted in the United States in 2015 found
20 that targeted hypothermia (34 to 35°C) in deceased organ donors reduced the incidence of
21 DGF in kidney recipients compared to normothermia (36.5 to 37.5°C), from 39.2% to 28.2%
22 ($P=0.02$) (13). An a-priori defined stratum of patients from this trial suggested that kidney
23 recipients from ECDs benefited the most from donor targeted hypothermia. Therefore, we
24 designed a multicenter randomized controlled trial (HYPOREME) to test the safety and
25 efficacy of targeted hypothermia compared to normothermia as part of the management of

1 ECDs. We hypothesized that targeted hypothermia in ECDs would decrease the incidence of
2 DFG in kidney recipients.

4 **METHODS/DESIGN**

6 **Trial design and settings**

7 HYPOREME is a multicenter, randomized, controlled, trial comparing two parallel
8 groups of patients.

10 **Participants, interventions, outcomes**

11 *Participating units*

12 A total of 53 French intensive care units (ICUs) and transplant centers are
13 participating in the study (30 university hospitals and 23 general hospitals). All participating
14 centers were carefully selected based on their high level of experience and expertise in the
15 management of organs donors, the process of organ transplantation, and clinical research. In
16 each participating center, a referring team for organ transplantation is identified to ensure
17 knowledge, training and compliance to the protocols edited by the French Biomedicine
18 Agency (national recommendation).

20 *Study population and recruitment modalities*

21 This study involves two distinct populations:

- 22 • Deceased ECDs for whom the diagnosis of death is made based on neurologic
23 criteria in compliance with French law. ECDs are defined as deceased donors who
24 are older than 60 years or who are aged 50-59 years and have at least two other risk
25 factors (history of hypertension, creatinine >132 µmol/L, and/or cerebrovascular

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3 1 cause of death). The study intervention (targeted temperature management) applies to
4
5 2 this population.

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8 3 • Kidney recipients who receive a kidney allograft from the above-described ECDs.

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10 4 The effect of the study intervention is evaluated in this population based on allograft
11
12 5 function.

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14 6 Deceased ECDs and kidney recipients must fulfil all of the criteria listed below to be
15
16
17 7 included in the study.

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19 8 *Inclusion criteria for deceased ECDs*

- 20
21 9 - Traumatic, vascular, or other brain injuries responsible for death defined by
22
23 10 neurologic criteria,
24
25 11 - Legal determination of death based on neurologic criteria in compliance with French
26
27 12 law,
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29 13 - Organ donation procedure engaged in compliance with French law,
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31 14 - Deceased ECD older than 60 years or aged 50-59 years with at least two other risk
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33 15 factors (history of hypertension, creatinine >132µmol/L, and/or cerebrovascular cause
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35 16 of death),
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37 17 - Next of kin informed of the study.

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42 18 *Inclusion criteria for kidney transplant recipients:*

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44 19 - Patient registered on the waiting list for KTx,
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46 20 - Patient informed of the study,
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48 21 - Age 18 years or older at the time of the pretransplantation evaluation,
49
50 22 - Patient covered by the statutory French health insurance.

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53 23 Deceased organ donors or kidney recipients fulfilling one or more of the following
54
55 24 criteria are not included in the study.

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58 25 *Exclusion criteria for deceased organ donors:*

- 1 - Donors with circulatory death or donors who died after treatment limitation,
- 2 - Patient registered in the French registry for refusing organ and tissue donations,
- 3 - Pregnancy,
- 4 - Age less than 18 years,
- 5 - Adult under guardianship,
- 6 - Contraindication to organ donation identified according to the current
- 7 recommendations of the French Biomedicine Agency (*Agence de la Biomédecine*).

8 *Exclusion criteria for kidney transplant recipients:*

- 9 - Refusal to participate in the study expressed by the patient,
- 10 - Pregnancy,
- 11 - Age less than 18 years,
- 12 - Adult under guardianship, or correctional facility inmate.

13
14 ***Study intervention***

15 The intervention is initiated after study inclusion and randomization. Deceased ECDs
16 are allocated at random to one of the two targeted temperature strategies (Figure 1). The
17 designated targeted temperature strategy is initiated as soon as possible after randomization
18 and continues until aortic clamping in the operating room. The objective is to reach the
19 targeted temperature range within 4 hours after randomization.

- 20 - In the targeted hypothermia group, ECDs have mild hypothermia (34°C to 35°C)
21 induced then maintained until aortic clamping in the operating room.
- 22 - In the targeted normothermia group, patients have normothermia (36.5°C-37.5°C)
23 induced and maintained until aortic clamping in the operating room.

24 Once the targeted temperature is reached, there is no request for a minimal duration of time
25 spent at the targeted temperature before the aortic clamping in the operating room.

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6 2***Targeted temperature protocol***

3 No trial has demonstrated one method to be better than another for targeted
4 temperature management. Therefore, to induce and maintain the ECDs at 34°C-35°C or
5 36.5°C-37.5°C, each participating center uses its usual method and protocol. The method
6 may involve active internal cooling or warming using specific devices, active external
7 cooling or warming using specific devices, or active external cooling or warming without
8 specific devices. A standard protocol of targeted temperature management was provided to
9 each participating center (supplementary appendix, Figure 1). Body temperature is recorded
10 hourly from randomization to aortic clamping using invasive (intravascular catheter with a
11 temperature-sensing vascular probe placed in the femoral artery, Pulse Contour Cardiac
12 Output, PiCCO®, or equivalent) or semi-invasive (esophageal probe, intra-rectal probe,
13 urinary probe) methods according to the device available and local protocol at each center.

14

General principles of management in both study arms

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16 The general management of deceased organ donors in the ICU and operating room
17 follows the standard protocol recommended by the French Biomedicine Agency in all
18 participating centers (supplementary appendix, Table 1) (14).

19

Study outcomes***Primary outcome measure***

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22 The primary outcome is the proportion of kidney recipients with DGF. DGF is
23 defined as a need for renal replacement therapy during the first week after transplantation
24 (not counting a single session of renal replacement therapy to treat hyperkalemia during the
25 first 24 hours after transplantation). DGF is determined for each kidney recipient at the

1 transplant center where the KTx was performed. The decision to commence renal
2 replacement therapy is left at the discretion of the nephrologist in charge.

3 In the rare case of transplantation of both kidneys from a donor into a single recipient,
4 that recipient is counted only once: the primary outcome measure is based on the presence or
5 absence of DGF in the kidney recipient.

6 *Secondary outcome measures*

7 The secondary outcomes for the ECDs consist of the following comparisons between the two
8 arms:

- 9 - number of organs recovered and number transplanted,
- 10 - body temperature recorded hourly from randomization to aortic clamping,
- 11 - number of severe cardiac arrhythmia episodes,
- 12 - total volume of intravenous fluids administered,
- 13 - need for vasopressors and inotropes, including total dose and maximal dose,
- 14 - lowest and highest blood pressures,
- 15 - cardiac arrest leading to abortion of the organ-donation procedure,
- 16 - metabolic disturbances and coagulation disorders,
- 17 - kidney function of organ donors: last serum creatinine and creatinine clearance before
18 transfer to the operating room.

19 The secondary outcomes for the kidney recipients consist in comparing the following
20 between the two arms:

- 21 - hospital length of stay after transplantation,
- 22 - kidney graft function (serum creatinine) at hospital discharge on days 7 and 28, and 3
23 months and 1 year after transplantation,
- 24 - persistent need for renal replacement therapy 28 days, 3 months, and 1 year after
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3 1 transplantation,
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5 2 - reason for renal replacement therapy implementation (sepsis, acute rejection, oliguria,
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7 hyperkalemia),
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10 4 - hospital mortality,
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12 5 - day-28 (after transplantation) mortality,
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14 6 - day-90 (after transplantation) mortality,
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16 7 - day-365 (after transplantation) mortality.
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23 9 **Organization of the trial**

24 10 Figure 1 is the study flowchart.
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29 12 **Recruitment modalities**

30 13 All patients with a confirmed diagnosis of death based on neurologic criteria in
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32 compliance with French law and who meet the definition of ECDs will be screened for
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34 eligibility by the ICU physicians and clinical research nurses, around the clock and 7 days a
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36 week. Patients will be included after checking inclusion and non-inclusion criteria. A log of
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38 patients considered for study participation will be kept and will include the reasons for non-
39 17
40 inclusion.
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47 20 **Randomization**

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49 21 Randomization is centralized and performed using a secure, computer-generated,
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51 22 interactive, web-response system available at each study center. Randomization is stratified
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53 23 on study center with a 1:1 ratio.
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58 25 **Blinding** 59 60

1 The nature of the intervention on the ECDs makes the blinding of the ICU staff to
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6 group assignment impossible. However, the assessors for both primary and secondary
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8 outcomes on kidney recipients are blinded to the intervention arm of the donor. Indeed, the
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10 nephrologists in charge of the kidney recipients, who decide whether renal replacement
11
12 therapy is needed during the first week after transplantation, and the kidney recipients are
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14 blinded to the intervention arm of the donor.
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17 18 19 **Sample size**

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21 According to a recent randomized controlled trial conducted in the United States (13) the
22
23 proportion of recipients with DGF after kidney transplantation from ECDs was 56.5%. In our
24
25 local experience at the transplant center in Nantes (France), the proportion of recipients with
26
27 DGF after kidney transplantation from ECDs was 48%. In the US trial, the proportion with
28
29 DGF was 56.5% in the normothermia group and 31% in the hypothermia group (13).
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33 Based on our local experience, we hypothesized that the rate of DGF after kidney
34
35 transplantation from ECDs would be 48%. We kept the hypothesis of the US trial of a 30%
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37 relative difference in the rate of DGF between the study groups (13). To demonstrate a 14%
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39 decrease in the proportion of recipients with DGF (from 48% in the normothermia group to
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41 34% in the hypothermia group), a total of 516 kidney recipients are required (258 in each
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43 group) to provide 90% power with a two-sided alpha risk of 5%. The analysis of 516 kidney
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45 recipients theoretically requires 258 randomized ECDs. However, assuming an estimated
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47 attrition rate of 12% (i.e., ECDs who are randomized but for whom organs are not recovered
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49 or are recovered but not transplanted) and given that in rare cases both kidneys from a donor
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51 are transplanted into a single recipient, our enrolment target is 289 randomized ECDs.
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56 **Interim analysis**

1 The sample size estimation is based on the primary outcome, i.e., the occurrence of
2 DGF. However, there is some uncertainty related to the limited amount of data available in
3 the literature. Accordingly, an interim analysis is planned after the enrolment of 258 kidney
4 recipients. The primary objective of this interim analysis is to reassess the sample size of the
5 study using the method proposed by Friede and Kieser (15,16). The probability of DGF will
6 be estimated from all treatment groups combined in order to preserve blindness. This method
7 makes it possible to maintain the initial clinical hypothesis (14% decrease in the frequency of
8 DGF) and to control the type I error.

9 The interim analysis will be conducted by an independent Data Safety Monitoring Board
10 (DSMB), whose members are not otherwise involved in the trial. This DSMB consists of one
11 methodologist and two intensivists. For the interim analysis, the DSMB will have access to
12 the following unblinded results:

- 13 • For the ECDs: number of patients enrolled, body temperature, mean arterial pressure,
14 total dose of vasopressors and inotropes, episodes of severe arrhythmia or cardiac
15 arrest, number of organs recovered from the donor, reason why organs were not
16 recovered (if applicable), use of machine perfusion for organ storage, and cold
17 ischemia time.
- 18 • For the recipients: occurrence of DGF, need for renal replacement therapy during the
19 first week posttransplantation, allograft lost by day 7, vital status on day 7, severe
20 posttransplantation complications, serum creatinine <250 µmol/L on day 7, and
21 allograft function and vital status on day 28 posttransplantation.

22 The results of the interim analysis will not be disclosed unless they lead the DSMB to request
23 premature trial discontinuation.

24 25 ***Statistical analysis***

1 All analyses will be performed using SAS software (V.9.4). Analyses will be
2 conducted on data from the intention-to-treat (ITT) population as well as from the per-
3 protocol population.

4 For the primary analysis, sensitivity analyses will be performed with populations
5 defined as follows: first, the ITT population defined as all recipients who received kidneys
6 from the ECDs and, second, all donors, regardless of whether organs were recovered and
7 transplanted. The latter case (failure to recover organs) will be considered a failure for the
8 main outcome measure (occurrence of DGF).

9 In the per-protocol analysis, all randomized patients will be kept in the analysis
10 except those with one or more major protocol violations, such as failure to meet all the
11 inclusion criteria and none of the non-inclusion criteria, an inability to perform the surgical
12 procedure, or withdrawal of consent to participate in the study.

13 A statistical analysis report will be written to describe all the findings, according to
14 CONSORT Statement recommendations, while considering the specific features of the trial,
15 most notably the nonpharmacological nature of the intervention. The baseline features of the
16 groups established by randomization will be compared using descriptive statistics.
17 Continuous variables will be described as mean±SD if normally distributed and as median
18 [interquartile range] otherwise. Categorical data will be described as exact numbers and
19 percentages.

20 For the primary analysis, binary categorical data will be analyzed using random-effect
21 logistic regression adjusted to take into account the hierarchical structure of the data (kidneys
22 from the same donor) and variability across centers.

23 The number of organs transplanted per donor will be compared between the two
24 groups using Poisson regression model. Hospital length of stay will be compared between the
25 two groups using a generalized model with random effects models. Patient and graft

1 survivals will be compared using Cox regression models. All models will be adjusted on
2 centres and consider ECDs as random effects.

3 4 ***Handling missing data***

5 We expect no missing data for the primary outcome. Graft loss during the first week
6 after transplantation will be classified as DGF. Similarly, death within the first week after
7 transplantation will be classified as DGF. Surgical complications which do not require
8 resuming dialysis during the first week post transplantation will be classified as no DGF
9 while those which require resuming dialysis will be classified as DGF. If unexpectedly data
10 are missing for the primary outcome, sensitivity analyses will be performed using the worst-
11 case scenario (missing data considered the worst case for the hypothermia group) as well as
12 the best-case scenario (missing data considered the best case for the hypothermia group) and
13 the maximum bias scenario (missing data considered the best or worst case in the
14 normothermia and hypothermia groups respectively).

15 The frequency of missing data should be low for the other outcomes as the ECDs
16 included in the study are hospitalized for a few hours or days at the most in the intensive care
17 unit. Kidney transplant recipients are admitted to the nephrology department. Few patients
18 will be lost to follow-up, as hospitalization after KTx lasts routinely about 10 days. Only
19 survival on day 28 and 3 months and 1 year after hospital discharge of recipients may be
20 missing. We will not use any technique to replace missing data. Missing data will be reported
21 for each treatment arm.

22 23 ***Data collection and follow-up***

24 The donor will be followed from randomization to aortic clamping in the operating
25 room. The following data will be recorded until aortic clamping in the operating room: date

1 and time of death based on neurologic criteria, demographic and clinical data, treatments
2 administered, laboratory tests, body temperature (recorded hourly), adverse events (mainly
3 cardiac arrhythmias, cardiac arrest, coagulopathy, and refractory shock), number of organs
4 recovered in the operating room, use of machine perfusion for organ storage, and number of
5 organs ultimately transplanted. In France, the use of machine perfusion for organ storage is a
6 national recommendation from the French Biomedicine Agency since 2011 for all organs
7 recovered from ECDs. The use of such device is part of the standard of care and it is
8 expected that almost all kidneys will be placed on machine perfusion. Detailed information
9 on machine perfusion settings are provided in the supplementary appendix (supplementary
10 appendix, Figure 2).

11 The kidney recipient will be followed from transplantation to 1 year after
12 transplantation. The following data will be recorded: demographic and clinical data,
13 treatments given, laboratory tests, cold ischemia time, and vital status and graft function on
14 days 7, 28, and 90 and after 1 year. Posttransplantation complications will be recorded during
15 the first 28 days following transplantation (mainly acute allograft rejection, cardiovascular
16 events, infections, and surgical complications). Table 1 is the flowchart of patient follow-up.

18 ***Data entry and monitoring***

19 An Internet-based data collection tool will be used to store the data of all the ECDs
20 and recipients. This electronic case-report form (eCRF) is a secure, interactive, web-response
21 system available at each study center. The eCRF is provided and managed by the biometrical
22 unit of the Nantes University Hospital (EA 4275 SPHERE “Methods for patient-centered
23 outcomes and health research”). Access to the eCRF will require only an Internet connection
24 and a browser.

1 Monitoring of the collected data and screening forms in each participating center will
2
3 be carried out by the Research Division Promotion Department of the Nantes University
4
5 Hospital. Research assistants will regularly perform on-site checks of adherence to the
6
7 protocol and accuracy of the recorded data. Newsletters about the study will be regularly sent
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9 by email to all participants to provide support, information, and to recall key instructions.
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17 ***Confidentiality and source data archiving***

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19 The medical data about each patient will be communicated only to the institution (i.e.,
20
21 the sponsor) with which the chief investigator is affiliated or to a person appointed by the
22
23 chief investigator and the sponsor under conditions that ensure the confidentiality of the
24
25 patient data. During or at completion of the study, the data collected from the study
26
27 participants and communicated by the individuals involved in the study will be rendered
28
29 anonymous. The study investigators will archive all study data for at least 15 years after the
30
31 end of the study.
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38 ***Protocol amendments***

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40 Any modifications to the protocol will require a formal amendment to the protocol.
41
42 Such amendment will be reviewed by the Research Division Promotion Department of the
43
44 Nantes University Hospital and agreed by the competent French authorities (Comité de
45
46 Protection des Personnes - TOURS-Région Centre-Ouest 1) prior to implementation. Any
47
48 modifications to the protocol will be communicated without delay to relevant parties
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51
52 (investigators and trial participants).
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56 ***Patient and public involvement***

57
58 Neither the patients nor the public are involved in the study design.
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2 **DISCUSSION**

3 HYPOREME will be a large randomized controlled trial to evaluate the impact of
4 targeted hypothermia on the function of kidneys received from ECDs. The results are
5 expected to provide intensivists with additional guidance about the optimal management of
6 deceased organ donors.

8 **TRIAL STATUS**

9 The first trial inclusion was on November 9, 2017. The protocol version is identified
10 RC16_0041_Protocole HYPOREME V10.1 on December 12, 2020. The scheduled interim
11 analysis was done on December 5, 2019, after the inclusion of 258 kidney recipients. The
12 interim analysis led the DSMB to recommend continuation of the study without modification
13 of the protocol and confirmed the initial goal of enrolling 516 kidney recipients. In addition,
14 the DSMB suggested a second interim analysis after the inclusion of 350 kidney recipients.
15 The second interim analysis was done on February 11, 2021, and led the DSMB to
16 recommend continuation of the study without modification of the protocol. On February 11,
17 2021, 349 kidney recipients had been included. The trial is expected to be completed in June
18 2021.

20 **ETHICS AND DISSEMINATION**

21 *Ethics approval*

22 The HYPOREME trial was approved by the ethics committee of the French Intensive
23 Care Society (CE-SRLF-16-07) on April 26, 2016 and by the competent French authorities
24 on April 20, 2016 (Comité de Protection des Personnes - TOURS-Région Centre-Ouest 1,
25 registration #2016-S3) and was registered on ClinicalTrials (NCT03098706) in April 2017.

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6 2***Consent to participate***

3 In compliance with French law, at the time of declaration of death based on neurologic
4 criteria, the French registry of persons refusing organ and tissue donation is examined to
5 confirm that the deceased patient is not registered. In addition, families or next of kin are
6 interviewed to check that the patient had not expressed unwillingness to donate organs and/or
7 tissues. During the same meeting, information about the study is given orally and an
8 information letter is handed to the family. The information delivered is documented in the
9 donor's medical chart by the local investigator. Legal statutes do not require informed
10 consent from families or next of kin for study inclusion, given that no harm can come to a
11 deceased patient.

12 Prior to study initiation, all the participating transplant centers were contacted. Each
13 transplant center approved the study protocol. The allocation of organs to specific recipients
14 occurs based on the national regulations set forth by the French Agency of Biomedicine. The
15 transplant center that receives the organs from an included ECD is informed of the study
16 inclusion but blinded to the treatment arm. Kidney recipients are informed of the study orally
17 and via a written information sheet and are then asked to provide their written informed
18 consent to participation in the trial. That this information was delivered is documented in the
19 medical chart of the kidney recipient by the investigator.

20 Model consent form and other related documentation given to participants and
21 authorized surrogates are provided in the supplementary appendix.

22

Access to data

23
24 Only the statisticians of the trial and the members of the DSMB have access to the
25 intra-study dataset in order to ensure that the results are not disclosed prior to the end of the

1 trial. After study completion, site investigators will have access to the full dataset if a formal
2 request is approved by the steering committee.

3 4 ***Dissemination policy***

5 The publication policy will comply with international recommendations (N Engl J
6 Med, 1997; 336:309-315) and the CONSORT statement (<http://www.consort-statement.org>).
7 Findings will be published in peer-reviewed journals and presented during national and
8 international scientific meetings. Communications and scientific reports relevant to this study
9 will be under the responsibility of the study coordinator (EC), who will obtain the approval
10 of the other investigators.

11 Substantive contributions of investigators, clinicians, researchers, and statisticians to
12 the design, conduct, interpretation, and reporting of the trial will be granted of authorship on
13 the final trial report.

14 Full protocol and participant-level dataset will be made available for scientific
15 purpose on reasonable request, after the agreement of the ethics and steering committee.

16 17 ***Availability of data and materials***

18 Not applicable

19 20 ***Competing Interests***

21 EC received fees for lectures and conference talks and had travel and accommodation
22 expenses related to attending scientific meetings covered by Gilead, Baxter and Sanofi-
23 Genzyme.

24 25 ***Trial sponsor and Funding***

1 The sponsor of the trial is the Centre Hospitalier Universitaire de Nantes (Direction de
2 la recherché et de l'Innovation – 5, allée de l'île Gloriette, 44093 Nantes cedex 01, France,
3 Phone : +33 253 482 835).

4 The HYPOREME trial received a grant from the French Ministry of Health in 2016
5 (Programme Hospitalier de Recherche Clinique Inter-Régional 2016; API16/N/033) and a
6 grant from the French Intensive Care Society in 2018.

7 Sponsor and funders had no role and no ultimate authority over the study design;
8 collection, management, analysis, and interpretation of data; writing of the report; and the
9 decision to submit the report for publication

10

11 *Authors' contributions*

12 NB and EC prepared the first draft of the manuscript.

13 JR, MP, NB, and EC wrote the manuscript.

14 JR, NB, MP, MH, and EC participated in designing the HYPOREME study.

15 MP and VS wrote the statistical analysis plan and performed the sample size
16 estimation.

17 NB and JR obtained funding for the study.

18 NB, EC, MP, MH, KA, BR, AD, LD, MP, SH, PT, JMB, LMM, FL, RR, TB, TK,
19 AT, OL, JFV, ML, RL, CV, AG, PB, CQ, PYE, OH, AR, YL, JCV, MB, OM, MHV, FH,
20 DS, AC, DG, LA, MH, NK, VM, JB, MLQD, EM, TB, PG, AEH, PM, AG, CH, BF, CM,
21 CGC, NB, JPR, AD, SD, SCO, LF, SG, LA, LR, DB, AH, PFW, FM, ED, DD, EA, CO, VS
22 and JR contributed to acquire the study data.

23 All authors revised the manuscript for important intellectual content and read and
24 approved the final version of the manuscript.

25

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3 1 *Acknowledgments*
4

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6
7 3 manuscript; Carine Coffre and Frédérique Musset for managing the database; Manon Rouaud
8
9 4 for coordinating the study; and Prof. Sylvie Chevret (Biostatistics and Medical Information
10
11 5 Department, Hôpital Saint-Louis, Paris, France; Centre de Recherche en Épidémiologie et
12
13 6 Statistiques [CRESS-INSERM-UMR1153], Paris, France; Epidemiology and Clinical
14
15 7 Statistics for Tumor, Respiratory, and Resuscitation Assessments [ECSTRRA] Team, Paris,
16
17 8 France; Université de Paris, Paris, France), Prof. Alain Combes (Medical ICU, La Pitié-
18
19 9 Salpêtrière University Hospital, AP-HP, Paris, France), and Prof. Elie Azoulay (Medical
20
21 10 ICU, Saint-Louis University Hospital, AP-HP, Paris, France) for constituting the independent
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23 11 data safety and monitoring board.
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1 **FIGURE LEGENDS**

2 **Figure 1:** Study flowchart

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1 TABLES

2
3 **Table 1: Flow-chart of patient follow-up**

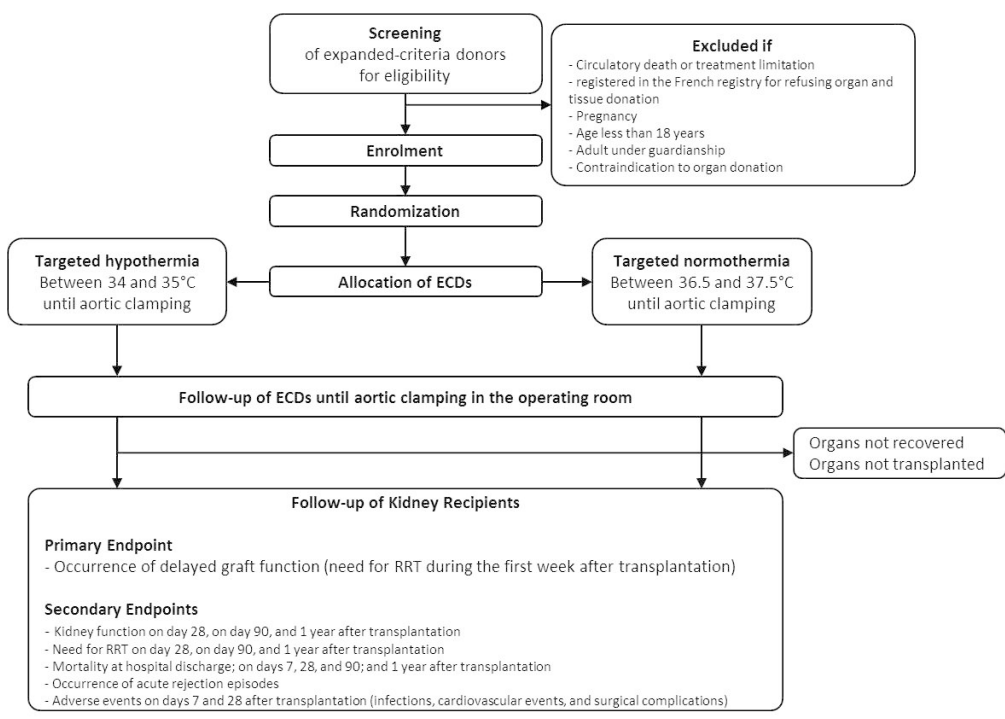
	Inclusion	D0*	Operating room	Dx	D7**	D28**	D90*	One year End of follow-up**
	ECD			Kidney recipient				
Eligibility: check inclusion and exclusion criteria (for both ECD and KR)	X			DAY OF TRANSPLANTATION				
ECD: information of family/next of kin	X							
KR: information of the patient	X							
Randomization (ECD)		X						
Demographic characteristics		X						
Vital signs		X	X					
Laboratory tests		X	X		X	X	X	X
Body temperature		X	X					
Treatments		X	X		X			
Renal replacement therapy					X	X	X	X
Infectious complications					X	X		
Surgical complications					X	X		
Cardiovascular complications					X	X		
Acute rejection episodes					X	X		
Vital status				X	X	X	X	

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6 * from time of inclusion to 11:59 pm

7 ** Day-7, day-28, day-90 and 1 year posttransplantation (Dx).

8 ECD, expanded criteria donor; KR, kidney recipient

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Study flowchart

198x139mm (150 x 150 DPI)

Supplementary Appendix

Figure 1: Targeted temperature management protocol provided to each center

→ Targeted hypothermia (34-35°C) by internal cooling or warming device

The use of an intravenous bolus of cold (4°C) isotonic saline is not recommended.

→ Targeted hypothermia (34-35°C) by external cooling or warming with no specific device

- According to the local protocol or as an example:
 - Cooling can be obtained using one or more of the following methods:
 - Place 2 cold wet sheets (4°C) on the patient. Take care to keep the sheets wet to optimize cooling by convection.
 - Place ice packs wrapped in a towel on the following sites:
 - 1 on each side of the neck
 - 1 below each armpit
 - 2 on the abdomen
 - 1 on each groin
 - Place a fan with blades at the end of the bed directed towards the patient.

→ Targeted hypothermia (34-35°C) by internal or external cooling or warming with a specific device

- According to the local protocol or as an example:
 - Place the device on the patient and set the target temperature at 33°C.

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3 **Figure 2:** Hypothermic machine perfusion settings
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6 Two different machines are used in France for organ transportation: the ORS (Organ
7 Recovery Systems) LifePort® 2nd generation and the Waters Waves® machine. Both machines
8 are used for perfusion, delivering a pulsatile flow of preservation solution at 4°C, with no
9 changes in perfusion settings throughout the preservation period. The systolic perfusion
10 pressure is initially set at 30 mmHg, and can be temporarily increased to 35mmHg to open the
11 kidney. Thereafter, the perfusion pressure is set to target an intrarenal resistive index between
12 0.3 and 0.5 and a flow between 80 and 100ml/min. Pressure, flow, resistance and temperature
13 are recorded by both machines during the transport period.
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Table 1: ICU management of deceased organ-donors*

Donor Management Goals	Parameters
General management	
Heart rate (bpm)	60-120
Mean arterial pressure (mmHg)	65-70
Hemoglobin (g/dL)	7-10
SpO ₂ (%)	≥95
PaO ₂ (mmHg)	>80
Urinary output (mL·kg ⁻¹ ·h ⁻¹)	0.5-3
Lactate (mmol/L)	<2
Metabolic disorders	
Serum sodium (mmol/L)	130-150
Serum glucose (mmol/L)	4-8
pH	7.35-7.45
Serum potassium, calcium, phosphate, magnesium	Maintain within normal range
Hemodynamic parameters**	
ScVO ₂ (%)	≥70
Cardiac index (L·min ⁻¹ ·m ²)	2.5-3
Central venous pressure (mmHg)	8-10
Pulmonary artery wedge pressure (mmHg)	6-10
Systemic vascular resistance (dynes·seconds·cm ⁻⁵)	800-1200

* From the following reference: Boulard G Ann Fr Anesth Reanim. 2005 Jul;24(7):836-43. doi: 10.1016/j.annfar.2005.05.020.

** If invasive monitoring is implemented (not mandatory)

136/bmjopen-2021-052845 on 28 March 2022. Downloaded from <http://bmjopen.bmj.com/> on April 19, 2024 by guest. Protected by copyright.

SPIRIT Checklist for *Trials*

Complete this checklist by entering the page and line numbers where each of the items listed below can be found in your manuscript.

Your manuscript may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please state "n/a" and provide a short explanation. **Leaving an item blank or stating "n/a" without an explanation will lead to your manuscript being returned before review.**

Upload your completed checklist as an additional file when you submit to *Trials*. You must reference this additional file in the main text of your protocol submission. The completed SPIRIT figure must be included within the main body of the protocol text and can be downloaded here: <http://www.spirit-statement.org/schedule-of-enrolment-interventions-and-assessments/>

In your methods section, please state that you used the SPIRIT reporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. *BMJ*. 2013;346:e7586

Reporting Item		Page and Line Number	Reason if not applicable
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Page 1, Lines 1-3
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	Page 23, Lines 11-14
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	Page 23, Lines 11-14
Protocol version	#3	Date and version identifier	Page 22, Lines 23-24
Funding	#4	Sources and types of financial, material, and other	Page 25, Lines 5-7

		support		
1 2 3 4 5	Roles and responsibilities: contributorship	#5a Names, affiliations, and roles of protocol contributors	Page 25, Lines 12-23	
6 7 8 9 10	Roles and responsibilities: sponsor contact information	#5b Name and contact information for the trial sponsor	Pages 1-6; Page 24, Lines 6-7	
11 12 13 14 15 16 17 18 19 20	Roles and responsibilities: sponsor and funder	#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	Page 25, Lines 5-10	
21 22 23 24 25 26 27 28 29	Roles and responsibilities: committees	#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)	Page 20, Lines 21-24; Page 21, Lines 1-6	
30 31	Introduction			
32 33 34 35 36 37 38 39 40	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	Page 10, Lines 2-22	
41 42 43 44	Background and rationale: choice of	#6b Explanation for choice of comparators	Page 10, Lines 17-20	

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1	comparators			
2	Objectives	#7	Specific objectives or hypotheses	Page 10, Lines 22-25
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, non-inferiority, exploratory)	Page 10, Lines 22-25; Page 11, Lines 3-5; Page 17, Lines 8-10
5				
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11				
12	Methods: Participants, interventions, and outcomes			
13				
14	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	Page 11, Lines 3-12
15				
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21	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)	Page 11, Lines 14-25 ; Page 12, Lines 1-25; Page 13, Lines 1-7
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28	Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	Page 13, Lines 9-18
29				
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33	Interventions: modifications	#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. No harm can come to a deceased patient. Accordingly no intervention modifications are planned
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40	Interventions: adherence	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory	Not applicable. The intervention is applied to deceased patients
41				
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		tests)		
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	Page 14, Lines 8-11	
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	Page 14, Lines 13-25 ; Page 15, Lines 1-25	
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)	Page 30, Table 1	
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	Page 17, Lines 2-15	
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	Page 16, Lines 5-11	
Methods: Assignment of interventions (for controlled trials)				
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of	Page 16, Lines 13-16	

1		any factors for stratification. To reduce		
2		predictability of a random sequence, details of any		
3		planned restriction (eg, blocking) should be		
4		provided in a separate document that is		
5		unavailable to those who enrol participants or		
6		assign interventions		
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10	Allocation concealment	#16b Mechanism of implementing the allocation	Page 16, Lines 13-16	
11	mechanism	sequence (eg, central telephone; sequentially		
12		numbered, opaque, sealed envelopes), describing		
13		any steps to conceal the sequence until		
14		interventions are assigned		
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18	Allocation:	#16c Who will generate the allocation sequence, who	Page 16, Lines 5-16	
19	implementation	will enrol participants, and who will assign		
20		participants to interventions		
21				
22				
23	Blinding (masking)	#17a Who will be blinded after assignment to	Page 16, Lines 18-25	
24		interventions (eg, trial participants, care providers,		
25		outcome assessors, data analysts), and how		
26				
27				
28	Blinding (masking):	#17b If blinded, circumstances under which unblinding		Not applicable. The intervention makes
29	emergency unblinding	is permissible, and procedure for revealing a		blinding of the healthcare staff impossible.
30		participant's allocated intervention during the trial		
31				
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33	Methods: Data collection, management, and analysis			
34				
35	Data collection plan	#18a Plans for assessment and collection of outcome,	Page 20, Lines 5-18	
36		baseline, and other trial data, including any		
37		related processes to promote data quality (eg,		
38		duplicate measurements, training of assessors)		
39		and a description of study instruments (eg,		
40		questionnaires, laboratory tests) along with their		
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		reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol		
Data collection plan: retention	#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	Page 20, Lines 5-18	
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	Page 20, Lines 20-24; Page 21, Lines 1-15	
Statistics: outcomes	#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	Page 18, Lines 18-25	
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	Page 19, Lines 5-18	
Statistics: analysis population and missing data	#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)	Page 19, Lines 1-25	
Methods: Monitoring				
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting	Page 21, Lines 3-6	

1		structure; statement of whether it is independent		
2		from the sponsor and competing interests; and		
3		reference to where further details about its		
4		charter can be found, if not in the protocol.		
5		Alternatively, an explanation of why a DMC is not		
6		needed		
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10	Data monitoring: interim	#21b	Description of any interim analyses and stopping	Page 18, Lines 1-4
11	analysis		guidelines, including who will have access to these	
12			interim results and make the final decision to	
13			terminate the trial	
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16	Harms	#22	Plans for collecting, assessing, reporting, and	Not applicable. No harms can come to a
17			managing solicited and spontaneously reported	deceased patient.
18			adverse events and other unintended effects of	
19			trial interventions or trial conduct	
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23	Auditing	#23	Frequency and procedures for auditing trial	Page 18, Lines 1-4
24			conduct, if any, and whether the process will be	
25			independent from investigators and the sponsor	
26				
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28	Ethics and dissemination			
29				
30	Research ethics approval	#24	Plans for seeking research ethics committee /	Page 23, Lines 11-14
31			institutional review board (REC / IRB) approval	
32				
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34	Protocol amendments	#25	Plans for communicating important protocol	Page 21, Lines 17-23
35			modifications (eg, changes to eligibility criteria,	
36			outcomes, analyses) to relevant parties (eg,	
37			investigators, REC / IRBs, trial participants, trial	
38			registries, journals, regulators)	
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42	Consent or assent	#26a	Who will obtain informed consent or assent from	Page 23, Lines 16-25 ;
43				
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		potential trial participants or authorised surrogates, and how (see Item 32)	Page 24, Lines 1-10	
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable		Not applicable. No ancillary studies are planned at this stage
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	Page 21, Lines 9-15	
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	Page 24, Lines 21-24	
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	Page 24, Lines 12-16	
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. No ancillary studies are planned at this stage
Dissemination policy: trial results	#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	Page 22, Lines 1-6	
Dissemination policy:	#31b	Authorship eligibility guidelines and any intended	Page 22, Lines 7-9	

1	authorship		use of professional writers		
2	Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Page 22, Lines 10-11	
3					
4					
5	Appendices				
6	Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	Page 24, Lines 9-10	
7					
8	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. No storage of biological specimens are planned for this study
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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](https://creativecommons.org/licenses/by-nc-nd/4.0/)” license. This checklist can be completed online using <https://www.goodreports.org/> a tool made by the EQUATOR Network in collaboration with Penelope.ai