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List of abbreviations

DGF: delayed graft function

DSMB: Data Safety Monitoring Board

ECD: expanded criteria donor

eCRF: electronic case report form

ICU: intensive care unit

ITT: intention-to-treat

KR: kidney recipient

KTx: kidney transplantation

ABSTRACT

Introduction: Expanded-criteria donors (ECDs) are used to reduce the shortage of kidneys for transplantation. However, kidneys from ECDs are associated with an increased risk of delayed graft function (DGF). DGF is a risk factor for allograft loss and mortality. HYPOREME will be the first trial comparing targeted hypothermia to normothermia in ECDs. We hypothesize that targeted hypothermia will decrease the incidence of DFG in recipients of kidneys from ECDs.

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

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

presented during national and international scientific meetings.

Trial Registration: NCT03098706.

Strengths and limitations of this study

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

Keywords: Organ donor, kidney transplantation, hypothermia, renal replacement therapy, delayed graft function

BACKGROUND

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

Hypothermia may help to preserve renal function in donors (11). Experimental data have shown that mild hypothermia reduces cell metabolism, inflammation, and free-radical production (12). A randomized controlled trial conducted in the United States in 2015 found that targeted hypothermia (34 to 35°C) in deceased organ donors reduced the incidence of DGF in kidney recipients compared to normothermia (36.5 to 37.5°C), from 39.2% to 28.2% (P=0.02) (13). 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 designed a multicenter randomized controlled trial (HYPOREME) to test the safety and efficacy of targeted hypothermia compared to normothermia as part of the management of ECDs. We hypothesized that targeted hypothermia in ECDs would decrease the incidence of DFG in kidney recipients.

METHODS/DESIGN

Trial design and settings

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

Participants, interventions, outcomes

Participating units

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

Study population and recruitment modalities

This study involves two distinct populations:

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

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

included in the study.

Inclusion criteria for deceased ECDs

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

Inclusion criteria for kidney transplant recipients:

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

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

Exclusion criteria for deceased organ donors:

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

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

Exclusion criteria for kidney transplant recipients:

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

Study intervention

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

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

Targeted temperature protocol

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

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

General principles of management in both study arms

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

Study outcomes

Primary outcome measure

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

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

Secondary outcome measures

The secondary outcomes for the ECDs consist in comparing the following between the two arms:

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

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

- hospital length of stay after transplantation,
- kidney graft function (serum creatinine) at hospital discharge on days 7 and 28, and 3 months and 1 year after transplantation,
- persistent need for renal replacement therapy 28 days, 3 months, and 1 year after transplantation,
- reason for renal replacement therapy implementation (sepsis, acute rejection, oliguria, hyperkalemia),
- hospital mortality,
- day-28 (after transplantation) mortality,
- day-90 (after transplantation) mortality,
- day-365 (after transplantation) mortality.

Organization of the trial

Figure 1 is the study flowchart.

Recruitment modalities

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

Randomization

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

Blinding

The trial is open, since the nature of the intervention on the ECDs makes the blinding of the healthcare staff to group assignment impossible. However, the 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. The nephrologists in charge of the kidney recipients, who decide whether renal replacement therapy is needed during the first week after transplantation, are blinded to the intervention arm of the donor.

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.

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

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

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

Statistical analysis

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

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

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

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

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

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

Handling missing data

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

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

Data collection and follow-up

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

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

Data entry and monitoring

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

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

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

Confidentiality and source data archiving

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

Protocol amendments

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

Dissemination policy

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

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

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

Patient and public involvement

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

DISCUSSION

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

TRIAL STATUS

The first trial inclusion was on November 9, 2017. The protocol version is identified RC16_0041_Protocole HYPOREME V10.1 on December 12, 2020. The scheduled interim analysis was done on December 5, 2019, after the inclusion of 258 kidney recipients. The

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

DECLARATIONS

Ethics approval

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

Consent to participate

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

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

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

Access to data

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

Availability of data and materials

Not applicable

Competing Interests

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

Trial sponsor and Funding

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

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

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

Authors' contributions

NB and EC prepared the first draft of the manuscript.

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

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

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

NB and JR obtained funding for the study.

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

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

Acknowledgments

We thank Antoinette Wolfe, MD, for assistance in preparing and reviewing the manuscript; Carine Coffre and Frédérique Musset for managing the database; Manon Rouaud for coordinating the study; and Prof. Sylvie Chevret (Biostatistics and Medical Information Department, Hôpital Saint-Louis, Paris, France; Centre de Recherche en Épidémiologie et Statistiques [CRESS-INSERM-UMR1153], Paris, France; Epidemiology and Clinical Statistics for Tumor, Respiratory, and Resuscitation Assessments [ECSTRRA] Team, Paris, France; Université de Paris, Paris, France), Prof. Alain Combes (Medical ICU, La Pitié-Salpêtrière University Hospital, AP-HP, Paris, France), and Prof. Elie Azoulay (Medical ICU, Saint-Louis University Hospital, AP-HP, Paris, France) for constituting the independent data safety and monitoring board.

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FIGURE LEGENDS

Figure 1: Study flowchart

TABLES

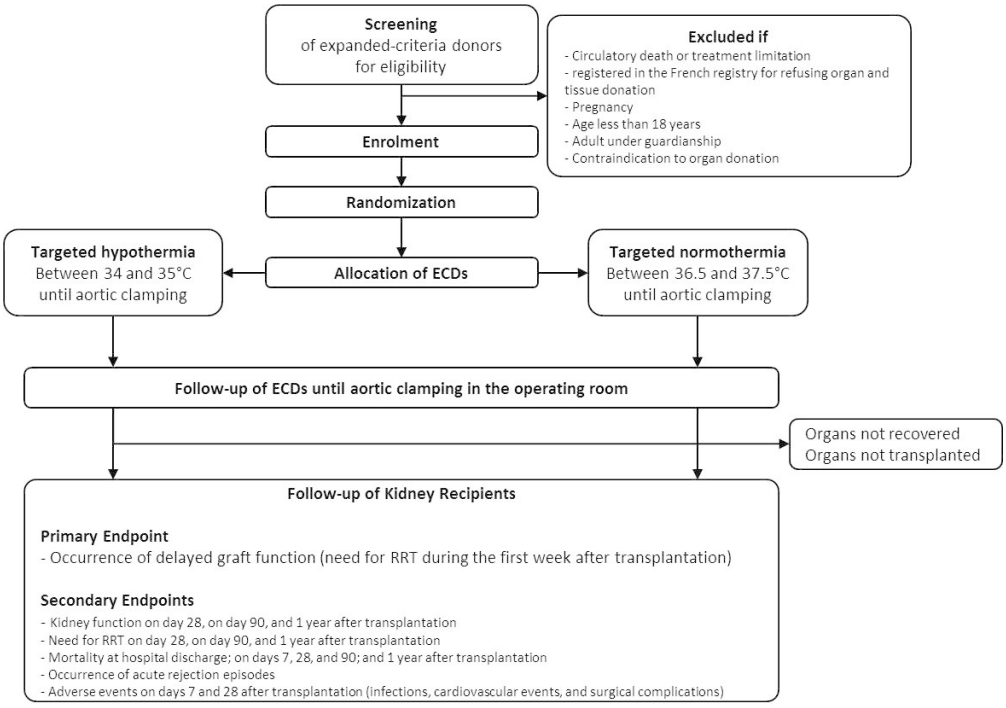
Table 1: Flow-chart of patient follow-up

	Inclu-sion	D0 *	Opera-ting 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

* from time of inclusion to 11:59 pm

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

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 ($mL \cdot kg^{-1} \cdot h^{-1}$)	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 ($L \cdot min^{-1} \cdot m^2$)	2.5-3
Central venous pressure (mmHg)	8-10
Pulmonary artery wedge pressure (mmHg)	6-10
Systemic vascular resistance ($dynes \cdot seconds \cdot cm^{-5}$)	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:

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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		
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	Page 25, Lines 12-23	
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	Pages 1-6; Page 24, Lines 6-7	
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	
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	
Introduction				
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	Page 10, Lines 2-22	
Background and rationale: choice of	#6b	Explanation for choice of comparators	Page 10, Lines 17-20	

comparators				
Objectives	#7	Specific objectives or hypotheses	Page 10, Lines 22-25	
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	
Methods: Participants, interventions, and outcomes				
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	Page 11, Lines 3-12	
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	
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	
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
Interventions: adherance	#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

		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	

		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	

		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 ;	

		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	

authorship		use of professional writers		
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	
Appendices				
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	Page 24, Lines 9-10	
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

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

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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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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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List of abbreviations

DGF: delayed graft function

DSMB: Data Safety Monitoring Board

ECD: expanded criteria donor

eCRF: electronic case report form

ICU: intensive care unit

ITT: intention-to-treat

KR: kidney recipient

KTx: kidney transplantation

RCT: randomized controlled trial

ABSTRACT

Introduction: Expanded-criteria donors (ECDs) are used to reduce the shortage of kidneys for transplantation. However, kidneys from ECDs are associated with an increased risk of delayed graft function (DGF). DGF is a risk factor for allograft loss and mortality. HYPOREME will be a large multicenter randomized controlled trial (RCT) comparing targeted hypothermia to normothermia in ECDs. We hypothesize that targeted hypothermia will decrease the incidence of DFG in recipients of kidneys from ECDs.

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

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

Trial Registration: NCT03098706.

Strengths and limitations of this study

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

Keywords: Organ donor, kidney transplantation, hypothermia, renal replacement therapy, delayed graft function

BACKGROUND

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

Hypothermia may help to preserve renal function in donors (11). Experimental data have shown that mild hypothermia reduces cell metabolism, inflammation, and free-radical production (12). A randomized controlled trial conducted in the United States in 2015 found that targeted hypothermia (34 to 35°C) in deceased organ donors reduced the incidence of DGF in kidney recipients compared to normothermia (36.5 to 37.5°C), from 39.2% to 28.2% (*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. Therefore, we designed a multicenter randomized controlled trial (HYPOREME) to test the safety and efficacy of targeted hypothermia compared to normothermia as part of the management of ECDs. We hypothesized that targeted hypothermia in ECDs would decrease the incidence of DFG in kidney recipients.

METHODS/DESIGN

Trial design and settings

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

Participants, interventions, outcomes

Participating units

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

Study population and recruitment modalities

This study involves two distinct populations:

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

The effect of the study intervention is evaluated in this population based on allograft function.

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

Inclusion criteria for deceased ECDs

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

Inclusion criteria for kidney transplant recipients:

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

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

Exclusion criteria for deceased organ donors:

- Donors with circulatory death or donors who died after treatment limitation,
- Patient registered in the French registry for refusing organ and tissue donations,
- Pregnancy,

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

Exclusion criteria for kidney transplant recipients:

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

Study intervention

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

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

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

Targeted temperature protocol

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

General principles of management in both study arms

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

Study outcomes

Primary outcome measure

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

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

Secondary outcome measures

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

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

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

- hospital length of stay after transplantation,
- kidney graft function (serum creatinine) at hospital discharge on days 7 and 28, and 3 months and 1 year after transplantation,
- persistent need for renal replacement therapy 28 days, 3 months, and 1 year after transplantation,
- reason for renal replacement therapy implementation (sepsis, acute rejection, oliguria,

hyperkalemia),

- hospital mortality,
- day-28 (after transplantation) mortality,
- day-90 (after transplantation) mortality,
- day-365 (after transplantation) mortality.

Organization of the trial

Figure 1 is the study flowchart.

Recruitment modalities

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

Randomization

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

Blinding

The nature of the intervention on the ECDs makes the blinding of the ICU 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. Indeed, the nephrologists in charge of the kidney recipients, 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%. In our local experience at the transplant center in Nantes (France), the proportion of recipients with DGF after kidney transplantation from ECDs was 48%. 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 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.

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

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

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

Statistical analysis

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

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

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

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

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

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

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

Handling missing data

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

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

Data collection and follow-up

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

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

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

Data entry and monitoring

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

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

protocol and accuracy of the recorded data. Newsletters about the study will be regularly sent by email to all participants to provide support, information, and to recall key instructions.

Confidentiality and source data archiving

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

Protocol amendments

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

Patient and public involvement

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

DISCUSSION

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

TRIAL STATUS

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

ETHICS AND DISSEMINATION

Ethics approval

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

Consent to participate

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

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

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

Access to data

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

Dissemination policy

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

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

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

Availability of data and materials

Not applicable

Competing Interests

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

Trial sponsor and Funding

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

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

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

Authors' contributions

NB and EC prepared the first draft of the manuscript.

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

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

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

NB and JR obtained funding for the study.

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

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

Acknowledgments

We thank Antoinette Wolfe, MD, for assistance in preparing and reviewing the manuscript; Carine Coffre and Frédérique Musset for managing the database; Manon Rouaud for coordinating the study; and Prof. Sylvie Chevret (Biostatistics and Medical Information Department, Hôpital Saint-Louis, Paris, France; Centre de Recherche en Épidémiologie et Statistiques [CRESS-INSERM-UMR1153], Paris, France; Epidemiology and Clinical Statistics for Tumor, Respiratory, and Resuscitation Assessments [ECSTRRA] Team, Paris, France; Université de Paris, Paris, France), Prof. Alain Combes (Medical ICU, La Pitié-Salpêtrière University Hospital, AP-HP, Paris, France), and Prof. Elie Azoulay (Medical ICU, Saint-Louis University Hospital, AP-HP, Paris, France) for constituting the independent data safety and monitoring board.

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FIGURE LEGENDS

Figure 1: Study flowchart

TABLES

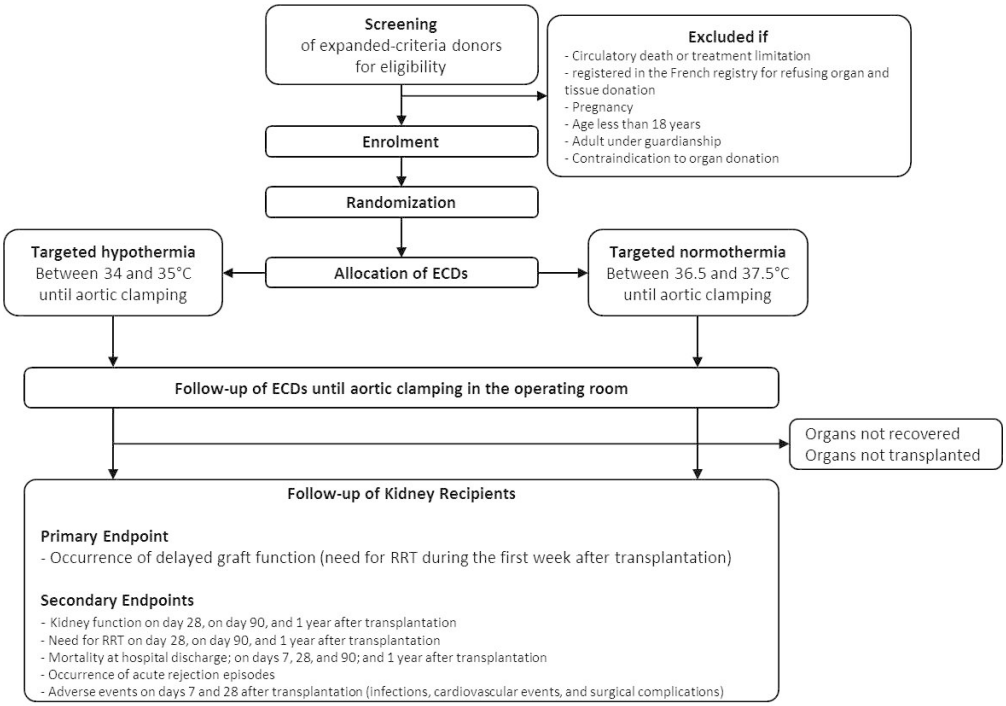
Table 1: Flow-chart of patient follow-up

	Inclu-sion	D0 *	Opera-ting 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

* from time of inclusion to 11:59 pm

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

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 ($mL \cdot kg^{-1} \cdot h^{-1}$)	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 ($L \cdot min^{-1} \cdot m^2$)	2.5-3
Central venous pressure (mmHg)	8-10
Pulmonary artery wedge pressure (mmHg)	6-10
Systemic vascular resistance ($dynes \cdot seconds \cdot cm^{-5}$)	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		
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	Page 25, Lines 12-23	
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	Pages 1-6; Page 24, Lines 6-7	
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	
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	
Introduction				
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	Page 10, Lines 2-22	
Background and rationale: choice of	#6b	Explanation for choice of comparators	Page 10, Lines 17-20	

comparators				
Objectives	#7	Specific objectives or hypotheses	Page 10, Lines 22-25	
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	
Methods: Participants, interventions, and outcomes				
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	Page 11, Lines 3-12	
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	
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	
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
Interventions: adherance	#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

		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	

		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	

		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 ;	

		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	

authorship		use of professional writers		
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	
Appendices				
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	Page 24, Lines 9-10	
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

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)

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Primary Subject Heading:	Intensive care
Secondary Subject Heading:	Renal medicine
Keywords:	Renal transplantation < NEPHROLOGY, Dialysis < NEPHROLOGY, INTENSIVE & CRITICAL CARE

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 scores 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.

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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List of abbreviations

DGF: delayed graft function

DSMB: Data Safety Monitoring Board

ECD: expanded criteria donor

eCRF: electronic case report form

ICU: intensive care unit

ITT: intention-to-treat

KR: kidney recipient

KTx: kidney transplantation

RCT: randomized controlled trial

ABSTRACT

Introduction: Expanded-criteria donors (ECDs) are used to reduce the shortage of kidneys for transplantation. However, kidneys from ECDs are associated with an increased risk of delayed graft function (DGF). DGF is a risk factor for allograft loss and mortality. HYPOREME will be a large multicenter randomized controlled trial (RCT) comparing targeted hypothermia to normothermia in ECDs. We hypothesize that targeted hypothermia will decrease the incidence of DFG in recipients of kidneys from ECDs.

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

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

Trial Registration: NCT03098706.

Strengths and limitations of this study

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

Keywords: Organ donor, kidney transplantation, hypothermia, renal replacement therapy, delayed graft function

BACKGROUND

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

Hypothermia may help to preserve renal function in donors (11). Experimental data have shown that mild hypothermia reduces cell metabolism, inflammation, and free-radical production (12). A randomized controlled trial conducted in the United States in 2015 found that targeted hypothermia (34 to 35°C) in deceased organ donors reduced the incidence of DGF in kidney recipients compared to normothermia (36.5 to 37.5°C), from 39.2% to 28.2% (*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. Therefore, we designed a multicenter randomized controlled trial (HYPOREME) to test the safety and efficacy of targeted hypothermia compared to normothermia as part of the management of ECDs. We hypothesized that targeted hypothermia in ECDs would decrease the incidence of DFG in kidney recipients.

METHODS/DESIGN

Trial design and settings

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

Participants, interventions, outcomes

Participating units

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

Study population and recruitment modalities

This study involves two distinct populations:

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

The effect of the study intervention is evaluated in this population based on allograft function.

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

Inclusion criteria for deceased ECDs

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

Inclusion criteria for kidney transplant recipients:

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

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

Exclusion criteria for deceased organ donors:

- Donors with circulatory death or donors who died after treatment limitation,
- Patient registered in the French registry for refusing organ and tissue donations,
- Pregnancy,

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

Exclusion criteria for kidney transplant recipients:

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

Study intervention

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

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

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

Targeted temperature protocol

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

General principles of management in both study arms

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

Study outcomes

Primary outcome measure

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

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

Secondary outcome measures

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

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

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

- hospital length of stay after transplantation,
- kidney graft function (serum creatinine) at hospital discharge on days 7 and 28, and 3 months and 1 year after transplantation,
- persistent need for renal replacement therapy 28 days, 3 months, and 1 year after transplantation,
- reason for renal replacement therapy implementation (sepsis, acute rejection, oliguria,

hyperkalemia),

- hospital mortality,
- day-28 (after transplantation) mortality,
- day-90 (after transplantation) mortality,
- day-365 (after transplantation) mortality.

Organization of the trial

Figure 1 is the study flowchart.

Recruitment modalities

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

Randomization

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

Blinding

The nature of the intervention on the ECDs makes the blinding of the ICU 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. Indeed, the nephrologists in charge of the kidney recipients, 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%. In our local experience at the transplant center in Nantes (France), the proportion of recipients with DGF after kidney transplantation from ECDs was 48%. 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 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.

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

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

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

Statistical analysis

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

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

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

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

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

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

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

Handling missing data

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

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

Data collection and follow-up

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

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

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

Data entry and monitoring

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

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

Confidentiality and source data archiving

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

Protocol amendments

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

Patient and public involvement

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

DISCUSSION

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

TRIAL STATUS

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

ETHICS AND DISSEMINATION

Ethics approval

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

Consent to participate

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

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

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

Access to data

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

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

Dissemination policy

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

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

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

Availability of data and materials

Not applicable

Competing Interests

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

Trial sponsor and Funding

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

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

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

Authors' contributions

NB and EC prepared the first draft of the manuscript.

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

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

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

NB and JR obtained funding for the study.

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

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

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FIGURE LEGENDS

Figure 1: Study flowchart

TABLES

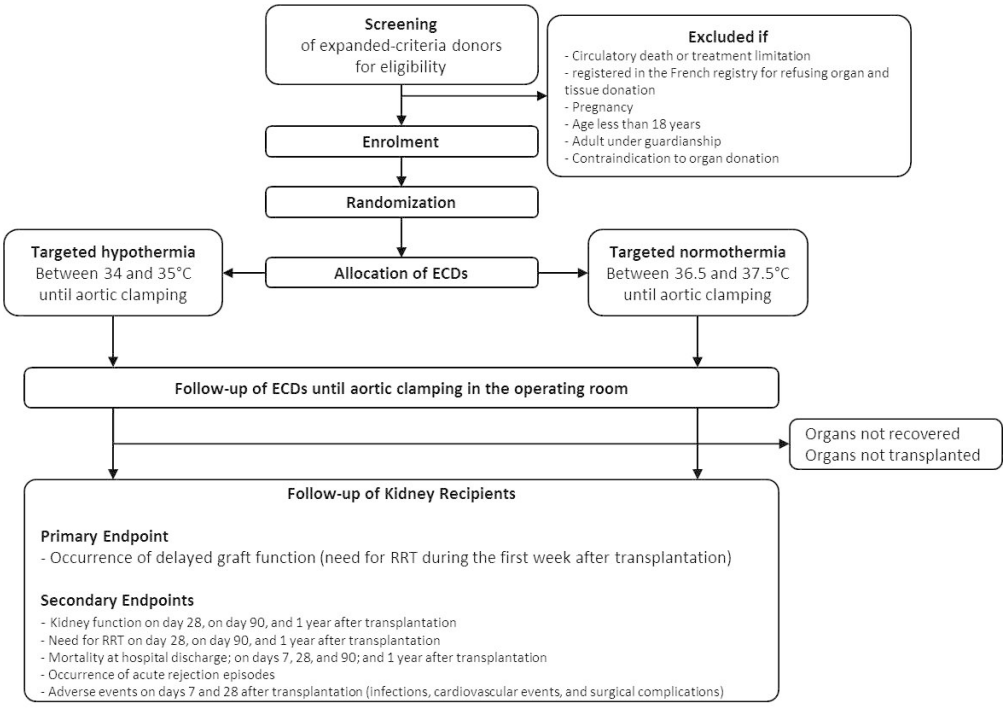
Table 1: Flow-chart of patient follow-up

	Inclu-sion	D0 *	Opera-ting 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

* from time of inclusion to 11:59 pm

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

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.

Figure 2: Hypothermic machine perfusion settings

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

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 ($mL \cdot kg^{-1} \cdot h^{-1}$)	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 ($L \cdot min^{-1} \cdot m^2$)	2.5-3
Central venous pressure (mmHg)	8-10
Pulmonary artery wedge pressure (mmHg)	6-10
Systemic vascular resistance ($dynes \cdot seconds \cdot cm^{-5}$)	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.

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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		
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	Page 25, Lines 12-23	
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	Pages 1-6; Page 24, Lines 6-7	
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	
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	
Introduction				
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	Page 10, Lines 2-22	
Background and rationale: choice of	#6b	Explanation for choice of comparators	Page 10, Lines 17-20	

comparators				
Objectives	#7	Specific objectives or hypotheses	Page 10, Lines 22-25	
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	
Methods: Participants, interventions, and outcomes				
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	Page 11, Lines 3-12	
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	
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	
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
Interventions: adherance	#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

		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	

		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	

		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 ;	

		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	

authorship		use of professional writers		
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	
Appendices				
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	Page 24, Lines 9-10	
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

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

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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Manuscript Word Count (body of text only): ~~3426~~ 3981

Abstract Word Count: 297~~8~~

List of abbreviations

DGF: delayed graft function

DSMB: Data Safety Monitoring Board

ECD: expanded criteria donor

eCRF: electronic case report form

ICU: intensive care unit

ITT: intention-to-treat

KR: kidney recipient

KTx: kidney transplantation

RCT: randomized controlled trial

ABSTRACT

Introduction: Expanded-criteria donors (ECDs) are used to reduce the shortage of kidneys for transplantation. However, kidneys from ECDs are associated with an increased risk of delayed graft function (DGF). DGF is a risk factor for allograft loss and mortality. HYPOREME will be ~~the first~~a large multicenter randomized controlled trial (RCT) comparing targeted hypothermia to normothermia in ECDs. We hypothesize that targeted hypothermia will decrease the incidence of DFG in recipients of kidneys from ECDs.

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

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

presented during national and international scientific meetings.

Trial Registration: NCT03098706.

Strengths and limitations of this study

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

Keywords: Organ donor, kidney transplantation, hypothermia, renal replacement therapy, delayed graft function

BACKGROUND

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

Hypothermia may help to preserve renal function in donors (11). Experimental data have shown that mild hypothermia reduces cell metabolism, inflammation, and free-radical production (12). A randomized controlled trial conducted in the United States in 2015 found that targeted hypothermia (34 to 35°C) in deceased organ donors reduced the incidence of DGF in kidney recipients compared to normothermia (36.5 to 37.5°C), from 39.2% to 28.2% (*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~~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 designed a multicenter randomized controlled trial (HYPOREME) to test the safety and efficacy of targeted hypothermia compared to normothermia as part of the management of

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

METHODS/DESIGN

Trial design and settings

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

Participants, interventions, outcomes

Participating units

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

Study population and recruitment modalities

This study involves two distinct populations:

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

factors (history of hypertension, creatinine >132 µmol/L, and/or cerebrovascular cause of death). The study intervention (targeted temperature management) applies to this population.

- Kidney recipients who receive a kidney allograft from the above-described ECDs. The effect of the study intervention is evaluated in this population based on allograft function.

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

Inclusion criteria for deceased ECDs

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

Inclusion criteria for kidney transplant recipients:

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

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

Exclusion criteria for deceased organ donors:

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

Exclusion criteria for kidney transplant recipients:

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

Study intervention

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

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

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

Targeted temperature protocol

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

General principles of management in both study arms

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

Study outcomes

Primary outcome measure

The primary outcome is the proportion of kidney recipients with DGF. DGF is defined as a need for renal replacement therapy during the first week after transplantation

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

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

Secondary outcome measures

The secondary outcomes for the ECDs consist of ~~in comparing~~ the following comparisons between the two arms:

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

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

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

months and 1 year after transplantation,

- persistent need for renal replacement therapy 28 days, 3 months, and 1 year after transplantation,
- reason for renal replacement therapy implementation (sepsis, acute rejection, oliguria, hyperkalemia),
- hospital mortality,
- day-28 (after transplantation) mortality,
- day-90 (after transplantation) mortality,
- day-365 (after transplantation) mortality.

Organization of the trial

Figure 1 is the study flowchart.

Recruitment modalities

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

Randomization

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

Blinding

~~The trial is open,~~T ~~since t~~he 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~~T~~he nephrologist~~s~~s in charge of the kidney recipient~~s~~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 proportion~~s~~ 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

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.

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

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

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

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

Statistical analysis

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

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

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

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

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

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

Handling missing data

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

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

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

Data collection and follow-up

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

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

Data entry and monitoring

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

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

Confidentiality and source data archiving

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

Protocol amendments

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

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

~~***Dissemination policy***~~

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

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

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

Patient and public involvement

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

DISCUSSION

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

TRIAL STATUS

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

ETHICS AND DISSEMINATION~~DECLARATIONS~~

Ethics approval

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

Consent to participate

In compliance with French law, at the time of declaration of death based on neurologic criteria, the French registry of persons refusing organ and tissue donation is examined to confirm that the deceased patient is not registered. In addition, families or next of kin are interviewed to check that the patient had not expressed unwillingness to donate organs and/or

tissues. During the same meeting, information about the study is given orally and an information letter is handed to the family. Theat this information was delivered is documented in the donor's medical chart by the local investigator. Legal statutes do not require informed consent from families or next of kin for study inclusion, given that no harm can come to a deceased patient.

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

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

Access to data

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

Dissemination policy

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

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

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

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

Availability of data and materials

Not applicable

Competing Interests

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

Trial sponsor and Funding

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

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

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

Authors' contributions

NB and EC prepared the first draft of the manuscript.

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

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

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

NB and JR obtained funding for the study.

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

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

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FIGURE LEGENDS

Figure 1: Study flowchart

TABLES

Table 1: Flow-chart of patient follow-up

	Inclu-sion	D0 *	Opera-ting 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

* from time of inclusion to 11:59 pm

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

ECD, expanded criteria donor; KR, kidney recipient

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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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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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List of abbreviations

DGF: delayed graft function

DSMB: Data Safety Monitoring Board

ECD: expanded criteria donor

eCRF: electronic case report form

ICU: intensive care unit

ITT: intention-to-treat

KR: kidney recipient

KTx: kidney transplantation

RCT: randomized controlled trial

ABSTRACT

Introduction: Expanded-criteria donors (ECDs) are used to reduce the shortage of kidneys for transplantation. However, kidneys from ECDs are associated with an increased risk of delayed graft function (DGF), a risk factor for allograft loss and mortality. HYPOREME will be a multicenter randomized controlled trial (RCT) comparing targeted hypothermia to normothermia in ECDs, in a country where the use of machine perfusion for organ storage is the standard of care. We hypothesize that hypothermia will decrease the incidence of DGF.

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

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

Trial Registration: NCT03098706.

Strengths and limitations of this study

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

Keywords: Organ donor, kidney transplantation, hypothermia, renal replacement therapy, delayed graft function

BACKGROUND

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

Hypothermia may help to preserve renal function in donors (11). Experimental data have shown that mild hypothermia reduces cell metabolism, inflammation, and free-radical production (12). A randomized controlled trial conducted in the United States in 2015 found that targeted hypothermia (34 to 35°C) in deceased organ donors reduced the incidence of DGF in kidney recipients compared to normothermia (36.5 to 37.5°C), from 39.2% to 28.2% (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. Therefore, we designed a multicenter randomized controlled trial (HYPOREME) to test the safety and efficacy of targeted hypothermia compared to normothermia as part of the management of

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

METHODS/DESIGN

Trial design and settings

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

Participants, interventions, outcomes

Participating units

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

Study population and recruitment modalities

This study involves two distinct populations:

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

cause of death). The study intervention (targeted temperature management) applies to this population.

- Kidney recipients who receive a kidney allograft from the above-described ECDs. The effect of the study intervention is evaluated in this population based on allograft function.

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

Inclusion criteria for deceased ECDs

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

Inclusion criteria for kidney transplant recipients:

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

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

Exclusion criteria for deceased organ donors:

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

Exclusion criteria for kidney transplant recipients:

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

Study intervention

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

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

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

Targeted temperature protocol

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

General principles of management in both study arms

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

Study outcomes

Primary outcome measure

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

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

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

Secondary outcome measures

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

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

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

- hospital length of stay after transplantation,
- kidney graft function (serum creatinine) at hospital discharge on days 7 and 28, and 3 months and 1 year after transplantation,
- persistent need for renal replacement therapy 28 days, 3 months, and 1 year after

transplantation,

- reason for renal replacement therapy implementation (sepsis, acute rejection, oliguria, hyperkalemia),
- hospital mortality,
- day-28 (after transplantation) mortality,
- day-90 (after transplantation) mortality,
- day-365 (after transplantation) mortality.

Organization of the trial

Figure 1 is the study flowchart.

Recruitment modalities

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

Randomization

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

Blinding

The nature of the intervention on the ECDs makes the blinding of the ICU 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. Indeed, the nephrologists in charge of the kidney recipients, 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%. In our local experience at the transplant center in Nantes (France), the proportion of recipients with DGF after kidney transplantation from ECDs was 48%. 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 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.

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

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

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

Statistical analysis

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

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

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

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

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

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

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

Handling missing data

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

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

Data collection and follow-up

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

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

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

Data entry and monitoring

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

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

Confidentiality and source data archiving

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

Protocol amendments

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

Patient and public involvement

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

DISCUSSION

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

TRIAL STATUS

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

ETHICS AND DISSEMINATION

Ethics approval

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

Consent to participate

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

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

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

Access to data

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

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

Dissemination policy

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

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

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

Availability of data and materials

Not applicable

Competing Interests

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

Trial sponsor and Funding

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

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

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

Authors' contributions

NB and EC prepared the first draft of the manuscript.

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

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

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

NB and JR obtained funding for the study.

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

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

Acknowledgments

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FIGURE LEGENDS

Figure 1: Study flowchart

TABLES

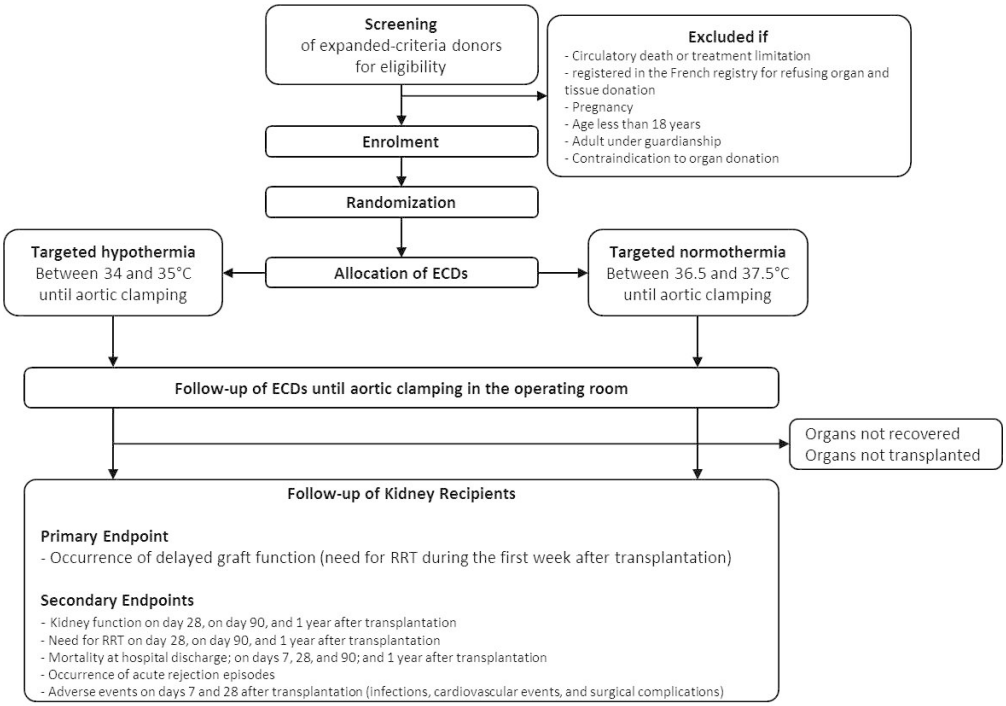
Table 1: Flow-chart of patient follow-up

	Inclu-sion	D0 *	Opera-ting 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

* from time of inclusion to 11:59 pm

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

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.

Figure 2: Hypothermic machine perfusion settings

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

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 ($mL \cdot kg^{-1} \cdot h^{-1}$)	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 ($L \cdot min^{-1} \cdot m^2$)	2.5-3
Central venous pressure (mmHg)	8-10
Pulmonary artery wedge pressure (mmHg)	6-10
Systemic vascular resistance ($dynes \cdot seconds \cdot cm^{-5}$)	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/

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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		
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	Page 25, Lines 12-23	
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	Pages 1-6; Page 24, Lines 6-7	
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	
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	
Introduction				
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	Page 10, Lines 2-22	
Background and rationale: choice of	#6b	Explanation for choice of comparators	Page 10, Lines 17-20	

comparators				
Objectives	#7	Specific objectives or hypotheses	Page 10, Lines 22-25	
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	
Methods: Participants, interventions, and outcomes				
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	Page 11, Lines 3-12	
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	
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	
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
Interventions: adherance	#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

		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	

		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	

		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 ;	

		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	

authorship		use of professional writers		
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	
Appendices				
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	Page 24, Lines 9-10	
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

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