Impact of targeted hypothermia in expanded-criteria organ donors on recipient kidney-graft function: study protocol for a multicentre randomised controlled trial (HYPOREME).

Noëlle Brulé, Emmanuel Canet, Morgane Péré, Fanny Feuillet, Maryvonne Hourmant, Karim Asehnoune, Bertrand Rozec, Agnes Duveau, Laurent Dube, Marc Pierrot, et al.

BMJ Open

Impact of targeted hypothermia in expanded-criteria organ donors on recipient kidney-graft function: study protocol for a multicentre randomised controlled trial (HYPOREME)

Noëlle Brulé,[1] Emmanuel Canet ,[1] Morgane Péré,[2] Fanny Feuillet,[2,3] Maryvonne Hourmant,[4] Karim Asehnoune,[5] Bertrand Rozec,[6] Agnes Duveau,[7] Laurent Dube,[8] Marc Pierrot,[9] Stanislas Humbert,[10] Patrice Tirot,[11] Jean-Marc Boyer,[12] Laurent Martin-Lefevre,[13] François Labadie,[14] René Robert ,[15,16] Thierry Benard,[17] Thomas Kerforne,[18] Antoine Thierry,[19] Olivier Lesieur,[20] Jean-François Vincent,[21] Mathieu Lesouhaitier,[22] Raphaelle Larmet,[23] Cecile Vigneau,[24] Angelique Goepp,[25] Pierre Bouju,[26] Charlotte Quentin,[27] Pierre-Yves Egreteau,[28] Olivier Huet,[29] Anne Renault,[30] Yannick Le Meur,[31] Jean-Christophe Venhard,[32] Mathias Buchler,[33] Olivier Michel,[34] Marie-Hélène Voellmy,[35] Fabien Herve,[36] David Schnell,[37] Anne Courte,[38] Denis Glotz,[39] Lucile Amrouche,[40] Marc Hazzan,[41] Nassim Kamar,[42] Valerie Moal,[43] Jeremy Bourenne,[44] Moglie Le Quintrec-Donnette,[45] Emmanuel Morelon,[46] Thierry Boulain ,[47] Philippe Grimbert,[48] Anne Elisabeth Heng,[49] Pierre Merville,[50] Aude Garin,[51] Christian Hiesse,[52] Brice Fermier,[53] Christiane Mousson,[54] Charlotte Guyot-Colosio,[55] Nicolas Bouvier,[56] Jean-Philippe Rerolle,[57] Antoine Durrbach,[58] Sarah Drouin,[59] Sophie Caillard,[60] Luc Frimat,[61] Sophie Girerd,[62] Laetitia Albano,[63] Lionel Rostaing,[64] Dominique Bertrand,[65] Alexandre Hertig,[66] Pierre-Francois Westeel,[67] Florent Montini,[68] Eric Delpierre,[69] Dider Dorez,[70] Eric Alamartine,[71] Carole Ouisse,[72] Veronique Sebille,[2,3] Jean Reignier [1]

To cite: Brulé N, Canet E, Péré M, *et al*. Impact of targeted hypothermia in expanded-criteria organ donors on recipient kidney-graft function: study protocol for a multicentre randomised controlled trial (HYPOREME). *BMJ Open* 2022;**12**:e052845. doi:10.1136/bmjopen-2021-052845

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2021-052845).

NB and EC are joint first authors.

Received 27 April 2021

For numbered affiliations see end of article.

Correspondence to
Emmanuel Canet;
emmanuel.canet@chu-nantes.fr

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 multicentre randomised 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 hypothesise that hypothermia will decrease the incidence of DGF.

Methods and analysis HYPOREME is a multicentre RCT comparing the effect on kidney function in recipients of targeted hypothermia (34°C–35°C) and normothermia (36.5°C–37.5°C) in the ECDs. The temperature intervention starts from randomisation and is maintained until aortic clamping in the operating room. We aim to enrol 289 ECDs in order to analyse the kidney function of 516 recipients in the 53 participating centres. The primary outcome is the occurrence of DGF in kidney recipients, defined as a requirement for renal replacement therapy within 7 days

Strengths and limitations of this study

- HYPOREME will be a large multicentre randomised controlled trial to evaluate the impact of targeted hypothermia on the function of kidneys from expanded-criteria donors after transplantation.
- All participating centres 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 onsite 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.

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 26 April 2016 and by the competent French authorities on 20 April 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 number NCT03098706.

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 USA 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, optimising 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 randomised controlled trial conducted in the USA in 2015 found that targeted hypothermia (34°C–35°C) in deceased organ donors reduced the incidence of DGF in kidney recipients compared with normothermia (36.5°C–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 multicentre randomised controlled trial (HYPOREME) to test the safety and efficacy of targeted hypothermia compared with normothermia as part of the management of ECDs. We hypothesised that targeted hypothermia in ECDs would decrease the incidence of DFG in kidney recipients.

METHODS/DESIGN

Trial design and settings

HYPOREME is a multicentre, randomised, controlled, trial comparing two parallel groups of patients.

Participants, interventions and outcomes

Participating units

A total of 53 French intensive care units (ICUs) and transplant centres are participating in the study (30 university hospitals and 23 general hospitals). All participating centres 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 centre, 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>132 µmol/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 randomisation. 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 randomisation and continues until aortic clamping in the operating room. The objective is to reach the targeted temperature range within 4 hours after randomisation.

- In the targeted hypothermia group, ECDs have mild hypothermia (34°C–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

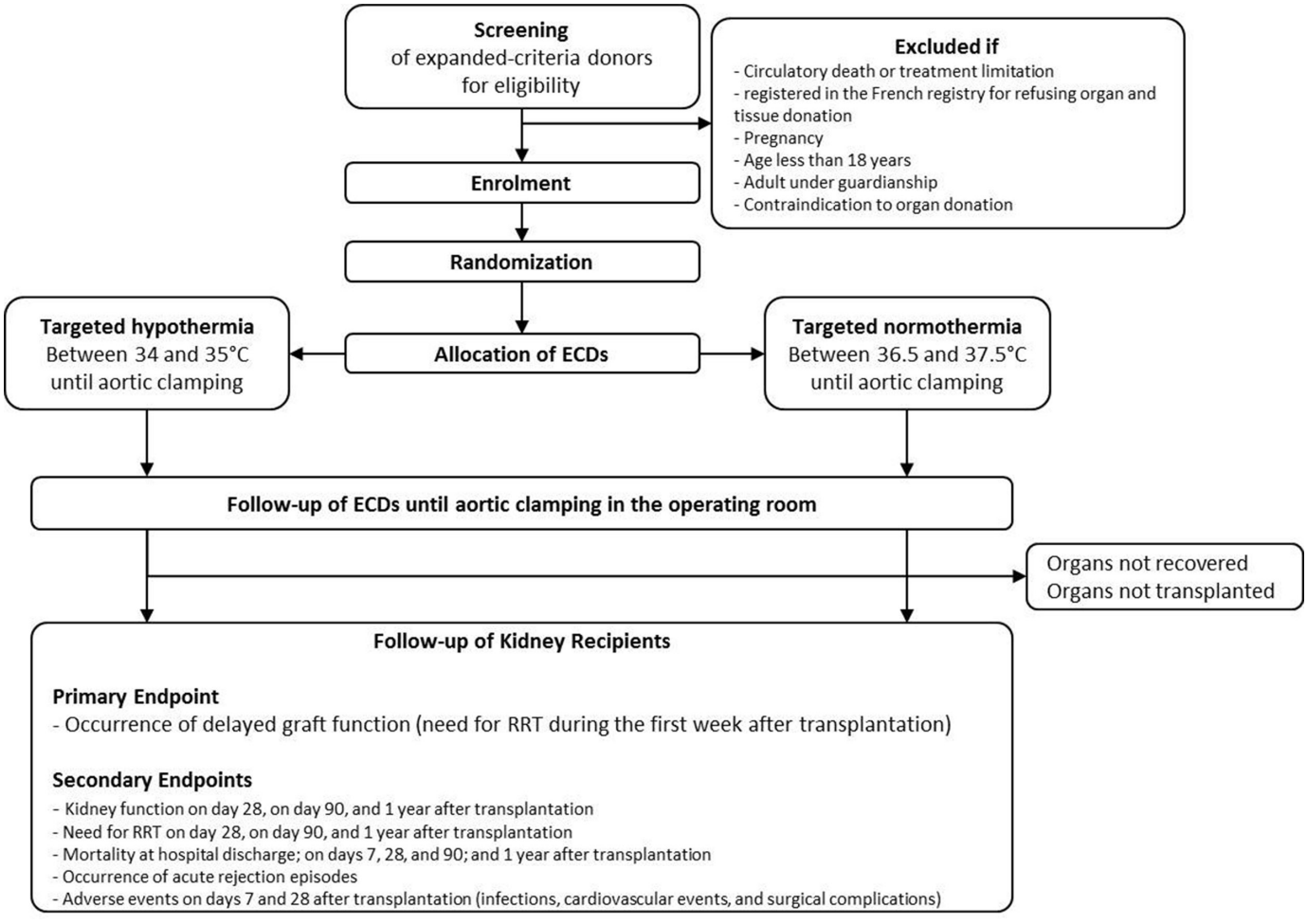

Figure 1 Study flowchart. ECDs, expanded-criteria donors; RRT, renal replacement therapy.

36.5°C–37.5°C, each participating centre 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 centre (online supplemental appendix figure 1). Body temperature is recorded hourly from randomisation 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 (oesophageal probe, intra-rectal probe, urinary probe) methods according to the device available and local protocol at each centre.

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 centres (online supplemental 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 centre 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 randomisation 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 and oliguria hyperkalemia).
- Hospital mortality.
- Day-28 (after transplantation) mortality.
- Day-90 (after transplantation) mortality.
- Day-365 (after transplantation) mortality.

Organisation 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.

Randomisation

Randomisation is centralised and performed using a secure, computer-generated, interactive, web-response system available at each study centre. Randomisation is stratified on study centre 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 randomised controlled trial conducted in the USA,[13] the proportion of recipients with DGF after kidney transplantation from ECDs was 56.5%. In our local experience at the transplant centre 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 hypothesised 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 randomised ECDs. However, assuming an estimated attrition rate of 12% (ie, ECDs who are randomised 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 randomised ECDs.

Interim analysis

The sample size estimation is based on the primary outcome, that is, 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 ischaemia 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 post-transplantation.

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 randomised 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 Consolidated Standards of Reporting Trials statement recommendations, while considering the specific features of the trial, most notably the non-pharmacological nature of the intervention. The baseline features of the groups established by randomisation will be compared using descriptive statistics. Continuous variables will be described as mean±SD if normally distributed and as median (IQR) otherwise. Categorical data will be described as exact numbers and percentages.

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

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 generalised 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 hospitalised for a few hours or days at the most in the ICU. Kidney transplant recipients are admitted to the nephrology department. Few patients will be lost to follow-up, as hospitalisation 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 randomisation 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 (online supplemental 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 ischaemia time and vital status and graft function on days 7, 28 and 90 and after 1 year. Post-transplantation 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 centre. The eCRF is provided and managed by the biometrical unit of the Nantes University Hospital (EA 4275 SPHERE 'Methods for patient-centred 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 centre 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.

Table 1 Flowchart of patient follow-up

	Inclusion	D0*	Operating room	Dx	D7†	D28†	D90†	One year end of follow-up†
	ECD			Kidney recipient				
Eligibility: check inclusion and exclusion criteria (for both ECD and KR)	X			Day of transplantation				
ECD: information of family/ next of kin	X							
KR: information of the patient	X							
Randomisation (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 post-transplantation (Dx).
ECD, expanded-criteria donor; KR, kidney recipient.

Confidentiality and source data archiving

The medical data about each patient will be communicated only to the institution (ie, 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 randomised 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.

TRAIL 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 online supplemental 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 reportig 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.

Author affiliations
[1]Service de Médecine Intensive Réanimation, Centre Hospitalier Universitaire de Nantes, Nantes, France
[2]Direction de la Recherche, Plateforme de Méthodologie et Biostatistique, Centre Hospitalier Universitaire de Nantes, Nantes, Pays de la Loire, France
[3]INSERM SPHERE U1246 Methods for Patient-centered Outcomes and Health Research, Université de Nantes, Université de Tours, Nantes, PAYS-DE-LA-LOIRE, France
[4]Service de Néphrologie et Immunologie Clinique, Centre Hospitalier Universitaire de Nantes, Nantes, France
[5]Service de Réanimation Chirurgicale, Centre Hospitalier Universitaire de Nantes, Nantes, France
[6]Service de Réanimation en Chirurgie Cardio-thoracique et Vasculaire, Centre Hospitalier Universitaire de Nantes, Nantes, France
[7]Service de Néphrologie, Centre Hospitalier Universitaire d'Angers, Angers, France
[8]Service de Coordination des prélèvements d'organe, Centre Hospitalier Universitaire d'Angers, Angers, France
[9]Service de Médecine Intensive Réanimation, Centre Hospitalier Universitaire d'Angers, Angers, France
[10]Service de Réanimation Polyvalente, Centre Hospitalier de Cholet, Cholet, France
[11]Service de Médecine Intensive Réanimation, Centre Hospitalier du Mans, Le Mans, Pays de la Loire, France
[12]Service de Réanimation, Centre Hospitalier de Laval, Laval, France
[13]Service de Médecine Intensive Réanimation, Centre Hospitalier Departemental Les Oudairies, La Roche-sur-Yon, Pays de la Loire, France
[14]Service de Médecine Intensive Réanimation, Centre Hospitalier de Saint Nazaire, Saint Nazaire, Pays de la Loire, France
[15]Médecine Intensive Réanimation, Centre Hospitalier Universitaire de Poitiers, Poitiers, France
[16]ALIVE Research Group, INSERM, University of Poitiers, Poitiers, Poitou-Charentes, France
[17]Service de Réanimation Neurochirurgicale, Centre Hospitalier Universitaire de Poitiers, Poitiers, France
[18]Service d'Anesthésie-Réanimation Cardio-Thoracique, Centre Hospitalier Universitaire de Poitiers, Poitiers, France
[19]Service de Néphrologie, Centre Hospitalier Universitaire de Poitiers, Poitiers, France
[20]Service de Réanimation, Centre Hospitalier de la Rochelle, La Rochelle, Nouvelle-Aquitaine, France
[21]Service de Réanimation, Centre Hospitalier de Saintes, Saintes, Poitou-Charentes, France
[22]Service des Maladies Infectieuses et Réanimation Médicale, Centre Hospitalier Universitaire de Rennes, Rennes, Bretagne, France
[23]Service de Réanimation Chirurgicale, Centre Hospitalier Universitaire de Rennes, Rennes, Bretagne, France
[24]Service de Néphrologie, Centre Hospitalier Universitaire de Rennes, Rennes, Bretagne, France
[25]Service de Réanimation, Centre Hospitalier Bretagne Atlantique de Vannes, Vannes, France
[26]Service de Réanimation, Centre Hospitalier de Bretagne Sud, Lorient, Lorient, France
[27]Service de Réanimation Polyvalente, Centre Hospitalier de Saint-Malo, Saint-Malo, Bretagne, France
[28]Service de Réanimation Polyvalente, Centre Hospitalier des Pays de Morlaix, Morlaix, France
[29]Service de Réanimation Chirurgicale, Hôpital La Cavale Blanche, CHU de Brest, Brest, France
[30]Service de Médecine Intensive Réanimation, CHRU de Brest, Brest, Bretagne, France
[31]Service de Néphrologie, Hôpital La Cavale Blanche, CHU de Brest, Brest, France
[32]Coordination des prélèvements d'organes et de tissus, Pôle Anesthésie Réanimations, Centre Hospitalier Régional Universitaire de Tours, Tours, Centre, France
[33]Service de Néphrologie, Centre Hospitalier Régional Universitaire de Tours, Tours, Centre, France
[34]Service de Réanimation Polyvalente, Centre Hospitalier Jacques Cœur, Bourges, Centre-Val de Loire, France
[35]Service de Coordination des prélèvements, Centre Hospitalier Jacques Cœur, Bourges, Centre-Val de Loire, France
[36]Service de Réanimation Polyvalente, Centre Hospitalier Intercommunal de Cornouaille, Quimper, France
[37]Service de Réanimation Polyvalente, Centre Hospitalier d'Angoulême, Angouleme, France
[38]Service de Réanimation Polyvalente, Centre Hospitalier de Saint Brieuc, Saint Brieuc, Bretagne, France
[39]Service de Néphrologie, Hôpital Saint-Louis, Université de Paris, Assistance Publique –Hôpitaux de Paris, Paris, France
[40]Service de Néphrologie, Hôpital Necker, Université de Paris, Assistance Publique–Hôpitaux de Paris, Paris, France
[41]University of Lille, Inserm, CHU Lille, U1286–Infinite–Institute for Translational Research in Inflammation, CHRU de Lille, Lille, Hauts-de-France, France
[42]Département de Néphrologie et Transplantation d'organes, Centre Hospitalier Universitaire de Toulouse, Université Paul Sabatier, Centre de Physiopathologie Toulouse Purpan, Inserm UMR 1043- CNRS 5282, Toulouse, France, Toulouse, Midi-Pyrénées, France
[43]Centre de Néphrologie et Transplantation Rénale, Aix-Marseille Université, Assistance Publique Hôpitaux de Marseille, Hôpital Conception, Marseille, France
[44]Médecine Intensive Réanimation, Réanimation des Urgences, Aix-Marseille Université, CHU La Timone 2, Marseille, France
[45]Service de Néphrologie et Transplantation, Centre Hospitalier Universitaire de Montpellier, Montpellier, Languedoc-Roussillon, France
[46]Service d'Urologie et de Chirurgie de la Transplantation, Pôle Chirurgie, Centre Hospitalier Universitaire de Lyon, Lyon, Rhône-Alpes, France
[47]Service de Médecine Intensive Réanimation, Centre Hospitalier Régional d'Orléans Hôpital de La Source, Orléans, France
[48]Service de Néphrologie et Transplantation, Hôpital Henri Mondor, Assistance Publique Hôpitaux de Paris, Créteil, Créteil, France
[49]Service de Néphrologie et Immunologie Clinique, Centre Hospitalier Universitaire de Clermont-Ferrand, Clermont-Ferrand, France
[50]Service de Nephrologie Transplantation Dialyse Aphérèses, Centre Hospitalier Universitaire de Bordeaux, Bordeaux, Aquitaine-Limousin-Poitou, France
[51]Service de Réanimation Polyvalente, Centre Hospitalier de Dreux, Dreux, France
[52]Service de Néphrologie, Hôpital Foch, Suresnes, Suresnes, France
[53]Service de Réanimation, Centre Hospitalier de Blois, Blois, Centre-Val de Loire, France
[54]Service de Néphrologie, Centre Hospitalier Universitaire de Dijon, Dijon, Bourgogne, France
[55]Service de Néphrologie, Centre Hospitalier Universitaire de Reims, Reims, Champagne-Ardenne, France
[56]Service de Néphrologie, Centre Hospitalier Universitaire de Caen, Caen, Basse-Normandie, France
[57]Service de Néphrologie, Centre Hospitalier Universitaire de Limoges, Limoges, Limousin, France
[58]Service de Néphrologie, Hôpital Kremlin-Bicêtre, Assistance Publique Hôpitaux de Paris, Le Kremlin-Bicêtre, France
[59]Service Médico-Chirurgical de Transplantation Rénale, APHP Sorbonne-Université, Hôpital Pitié-Salpêtrière, Paris, Île-de-France, France
[60]Service de Néphrologie et Transplantation, Centre Hospitalier Universitaire de Strasbourg, Strasbourg, Alsace, France
[61]Nephrology Department, CHRU Nancy, Université de Lorraine, Nancy, France
[62]Service de Néphrologie et Transplantation, Hôpital Brabois, Centre Hospitalier Régional Universitaire de Nancy, Nancy, France
[63]Service de Néphrologie et Transplantation, Centre Hospitalier Universitaire de Nice, Nice, Provence-Alpes-Côte d'Azur, France
[64]Service de Néphrologie, Hémodialyse, Aphérèses et Transplantation Rénale, CHU Grenoble Alpes, Grenoble, Rhône-Alpes, France
[65]Service de Néphrologie, Centre Hospitalier Universitaire de Rouen, Rouen, Normandie, France

[66]Service de Néphrologie, Hôpital Tenon, Université de Paris, Assistance Publique–Hôpitaux de Paris, Paris, France
[67]Service de Néphrologie, Centre Hospitalier Universitaire d'Amiens, Amiens, France
[68]Service de Réanimation, Centre Hospitalier Henri Duffaut, Avignon, France
[69]Service de Réanimation, Grand Hôpital de l'Est Francilien, Marne La vallée, France
[70]Service de Réanimation Polyvalente, Centre Hospitalier Annecy Genevois, Epagny Metz-Tessy, France
[71]Service de Néphrologie Dialyse et Transplantation Rénale, Centre Hospitalier Universitaire de Saint-Etienne, Saint-Etienne, Rhône-Alpes, France
[72]Service de Médecine Intensive Réanimation, Unité d'Investigation Clinique, Centre Hospitalier Universitaire de Nantes, Nantes, France

Twitter Emmanuel Canet @dremcanet

Acknowledgements 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 professor Sylvie Chevret (Biostatistics and Medical Information Department, Hôpital Saint-Louis, Paris, France; Centre de Recherche en Épidémiologie et Statistiques (CRESS-INSERM-UMR1153P), Paris, France; Epidemiology and Clinical Statistics for Tumor, Respiratory and Resuscitation Assessments (ECSTRRA) Team, Paris, France; Université de Paris, Paris, France), professor Alain Combes (Medical ICU, La Pitié-Salpêtrière University Hospital, AP-HP, Paris, France) and professor Elie Azoulay (Medical ICU, Saint-Louis University Hospital, AP-HP, Paris, France) for constituting the independent data safety and monitoring board.

Contributors NoB and EC prepared the first draft of the manuscript. JR, MoP, NoB and EC wrote the manuscript. JR, NoB, MoP, MHo and EC participated in designing the HYPOREME study. MaP and VS wrote the statistical analysis plan and performed the sample size estimation. NiB and JR obtained funding for the study. NoB, EC, MoP, MHa, KA, BR, AgD, LD, MaP, SH, PT, J-MB, LM-L, FL, RR, TBe, TK, AT, OL, J-FV, ML, RL, CV, AGo, PB, CQ, P-YE, OH, AR, YLM, J-CV, MB, OM, M-HV, FH, DS, AC, DG, LAm, MHo, NK, VM, JB, MLQ-D, EM, TBo, PG, AEH, PM, AGa, CH, BF, CM, CG-C, NoB, J-PR, AnD, SD, SC, LF, SG, LAl, LR, DB, AH, P-FW, 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.

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.

Disclaimer 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.

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.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting or dissemination plans of this research.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iDs
Emmanuel Canet http://orcid.org/0000-0002-2143-8082
René Robert http://orcid.org/0000-0001-5989-5409
Thierry Boulain http://orcid.org/0000-0003-4664-3661
Jean Reignier http://orcid.org/0000-0002-3768-3496

REFERENCES

1 Tonelli M, Wiebe N, Knoll G, *et al*. Systematic review: kidney transplantation compared with dialysis in clinically relevant outcomes. *Am J Transplant* 2011;11:2093–109.
2 Port FK, Bragg-Gresham JL, Metzger RA, *et al*. Donor characteristics associated with reduced graft survival: an approach to expanding the pool of kidney donors. *Transplantation* 2002;74:1281–6.
3 Agence de la biomédecine - Le rapport annuel médical et scientifique 2017 [Internet]. Available: https://www.agence-biomedecine.fr/annexes/bilan2017/donnees/organes/06-rein/synthese.htm [Accessed 11 Jan 2021].
4 Irish WD, Ilsley JN, Schnitzler MA, *et al*. A risk prediction model for delayed graft function in the current era of deceased donor renal transplantation. *Am J Transplant* 2010;10:2279–86.
5 Yarlagadda SG, Coca SG, Garg AX, *et al*. Marked variation in the definition and diagnosis of delayed graft function: a systematic review. *Nephrol Dial Transplant* 2008;23:2995–3003.
6 Bahl D, Haddad Z, Datoo A, *et al*. Delayed graft function in kidney transplantation. *Curr Opin Organ Transplant* 2019;24:82–6.
7 Ojo AO, Wolfe RA, Held PJ, *et al*. Delayed graft function: risk factors and implications for renal allograft survival. *Transplantation* 1997;63:968–74.
8 Tapiawala SN, Tinckam KJ, Cardella CJ, *et al*. Delayed graft function and the risk for death with a functioning graft. *J Am Soc Nephrol* 2010;21:153–61.
9 de Sandes-Freitas TV, Felipe CR, Aguiar WF, *et al*. Prolonged delayed graft function is associated with inferior patient and kidney allograft survivals. *PLoS One* 2015;10:e0144188.
10 Patel MS, Zatarain J, De La Cruz S, *et al*. The impact of meeting donor management goals on the number of organs transplanted per expanded criteria donor: a prospective study from the UNOS region 5 donor management goals Workgroup. *JAMA Surg* 2014;149:969–75.
11 Schnuelle P, Mundt HM, Drüschler F, *et al*. Impact of spontaneous donor hypothermia on graft outcomes after kidney transplantation. *Am J Transplant* 2018;18:704–14.
12 Polderman KH. Mechanisms of action, physiological effects, and complications of hypothermia. *Crit Care Med* 2009;37:S186–202.
13 Niemann CU, Feiner J, Swain S, *et al*. Therapeutic hypothermia in deceased organ donors and kidney-graft function. *N Engl J Med* 2015;373:405–14.
14 Boulard G, Guiot P, Pottecher T, *et al*. [Management of subjects in a state of brain death and the preservation of organs]. *Ann Fr Anesth Reanim* 2005;24:836–43.
15 Friede T, Kieser M. Sample size recalculation in internal pilot study designs: a review. *Biom J* 2006;48:537–55.
16 Friede T, Kieser M. Sample size recalculation for binary data in internal pilot study designs. *Pharm Stat* 2004;3:269–79.