

BMJ Open Propofol-based versus sevoflurane-based anaesthesia for deceased donor kidney transplantation: the VAPOR-2 study protocol for an international multicentre randomised controlled trial

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ABSTRACT

Introduction Ischaemia reperfusion injury (IRI) is inevitable in kidney transplantation and negatively affects patient and graft outcomes. Anaesthetic conditioning (AC) refers to the use of anaesthetic agents to mitigate IRI. AC is particularly associated with volatile anaesthetic (VA) agents and to a lesser extent to intravenous agents like propofol. VA like sevoflurane interferes with many of the processes underlying IRI and exerts renal protective properties in various models of injury and inflammation. We hypothesise that a sevoflurane-based anaesthesia is able to induce AC and thereby reduce post-transplant renal injury, reflected in improved graft and patient outcome, compared with a propofol-based anaesthesia in transplant recipients of a deceased donor kidney.

Methods and analysis Investigator-initiated, multicentre, randomised, controlled and prospective clinical trial with two parallel groups. The study will include 488 kidney transplant recipients from donation after brain death (DBD) or donation after circulatory death (DCD) donors. Participants are randomised in a 1:1 design to a sevoflurane (intervention) or propofol (control) group. The primary endpoint is the incidence of delayed graft function in recipients of DCD and DBD donor kidneys and/or 1-year biopsy-proven and treated acute rejection. Secondary endpoints include functional delayed graft function defined as failure of serum creatinine levels to decrease by at least 10% per day for three consecutive days; primary non-function is defined as a permanent lack of function of the allograft; length of hospital stay and postoperative complications of all kinds, estimated glomerular filtration rate at 1 week and 3 and 12 months calculated with the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula; readmissions at 3 and 12 months, graft survival and all-cause mortality at 12 months.

Ethics and dissemination The study is approved by the local ethical committees and national data security agencies. Results are expected to be published in 2025.

Trial registration number NCT02727296.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ This is a multicentre, randomised controlled trial comparing two routinely used anaesthetic strategies addressing a clinically relevant question.
- ⇒ Patient randomisation is stratified by study site and donor type to reduce allocation bias.
- ⇒ Standardised anaesthetic protocols ensure consistency across centres while maintaining clinical relevance.
- ⇒ Blinding of patients is implemented, but blinding of clinical staff is not feasible due to the nature of the interventions.
- ⇒ Sample size calculation is powered for two co-primary endpoints, with appropriate adjustments for multiple testing.

INTRODUCTION

During kidney donation and transplantation, several potentially harmful processes can impact graft viability. Until circulation is restored in the recipient, the donor kidney is subjected to a period of ischaemia. In deceased kidney donation, additional damage may occur prior to graft removal. In deceased brain dead (DBD) donors, systemic and local renal responses to brain death trigger pro-inflammatory and pro-coagulatory processes, whereas in deceased circulatory death (DCD) donors, extended warm ischaemia and hypoxia may impair post-transplant graft function and survival.¹ These combined factors lead to progressive kidney damage, which becomes evident when the kidney is reperfused during transplantation, a phenomenon known as ischaemia-reperfusion injury (IRI).

IRI is a complex pathophysiological process involving multiple molecular pathways, including mitochondrial dysfunction, particularly through disruption of the mitochondrial respiratory chain and uncontrolled reactive oxygen species production during reperfusion.² This triggers the opening of mitochondrial permeability transition pores (mPTP) and the release of danger-associated molecular patterns (DAMPs) into the intracellular and extracellular spaces.^{2–5} These processes activate injury pathways, including cell death mechanisms such as apoptosis and (regulated) necrosis, alongside endothelial dysfunction and glycocalyx loss, which promote leucocyte infiltration into the interstitial space. The DAMPs released exacerbate graft damage by binding to pattern recognition receptors, such as toll-like receptors and complement receptors, activating both the innate and adaptive immune responses.⁶ This increases the risk of T cell-mediated rejection, antibody-mediated rejection and interstitial fibrosis, contributing to chronic graft dysfunction. Simultaneously, protective cellular pathways, including hypoxia-inducible factors, are activated to support cell survival and angiogenesis.^{7,8}

Clinically, IRI often manifests as delayed graft function (DGF), or in severe cases, primary non-function (PNF), when the kidney does not regain function. DGF and PNF are relevant clinical concerns, contributing to increased patient morbidity, anxiety, prolonged hospitalisation and higher diagnostic and treatment costs. Additionally, DGF is linked to a higher risk of acute rejection (AR), and when DGF and AR co-occur, they further reduce graft and patient survival.^{9–11}

Conditioning strategies aim to induce biochemical changes to reduce IRI. Based on the timing of application, these strategies are categorised as pre-conditioning (before ischaemia), per-conditioning (during ischaemia) or post-conditioning (immediately after reperfusion).^{12–14} Anaesthetic conditioning (AC) specifically refers to using anaesthetic agents to mitigate IRI. AC is particularly associated with volatile anaesthetic (VA) agents and to a lesser degree with intravenous agents like propofol. VA, including sevoflurane, have demonstrated the ability to reduce IRI in various organs, including the kidney, in both animal models and human studies.^{15–24} The protective effects of VAs against IRI involve several mechanisms, among others prevention of mPTP opening, preservation of the glycocalyx, upregulation and stabilisation of hypoxia-inducible factors and direct effects on circulating immune cells.²⁵

Given that general anaesthesia is integral to the transplant procedure and that sevoflurane is able to attenuate IRI, we designed the Volatile Anaesthetic Protection Of Renal transplants trial (VAPOR trial), a two-step study assessing the effect of sevoflurane or propofol on graft and patient outcome in kidney transplantation. As a first step, we conducted the VAPOR-1 (Medisch Etische Toetsings commissie (METc) 2009/334) trial, a single centre proof of concept study in living-donor kidney transplantation. Results of this study are published.²⁶ Consequently,

we initiated VAPOR-2 to compare the effects of a sevoflurane-based anaesthesia versus a propofol-based anaesthesia on graft and patient outcome in DCD and DBD donor kidney recipients. Findings from this study will potentially optimise graft and patient outcome and prevent DGF, rejection and graft failure. Reducing IRI at the time of transplantation might decrease DGF and other complications, shorten hospital admission times, reduce the incidence of AR and chronic graft dysfunction and improve survival. In addition, it may lower healthcare-associated costs for society. Finally, this project may enhance our understanding of renal IRI, including its impact on long-term graft fibrosis and adaptive immunity. We hypothesise that a sevoflurane-based anaesthesia is associated with improved graft and patient outcome compared with a propofol-based anaesthesia.

METHODS AND ANALYSIS

Study design

An investigator-initiated international multicentre, prospective randomised controlled clinical trial with two parallel groups. Patients are blinded to group assignment. The trial protocol is registered on ClinicalTrials.gov (NCT02727296). The study began on 1 April 2017, and reached primary completion in January 2025. An overview of the study design is shown in [figure 1](#).

Study population

Patients above 18 years of age scheduled for kidney transplantation with a kidney from a DBD/DCD donor (n=488) at the University Medical Centre Groningen, Groningen, the Netherlands; Aarhus University Hospital, Aarhus, Denmark; Oslo University Hospital, Oslo, Norway; Amsterdam University Medical Centre, Amsterdam, the Netherlands and Fundació Puigvert, Universitat Autònoma de Barcelona, Barcelona, Spain.

Donor and recipient selection will adhere to regional allocation programmes, Eurotransplant (Groningen, Amsterdam), Scandiatransplant (Aarhus and Oslo) and Organización Nacional de Trasplantes (Barcelona). Final recipient allocation and acceptance is based on local guidelines regarding immunological match, specified donor/recipient characteristics and kidney quality regardless of the VAPOR-2 protocol.

Eligibility criteria

Participants must be aged ≥ 18 years and provide written informed consent. Patients with a high immunological risk, as determined by local practice, or those with ABO-incompatibility are not eligible for inclusion. See [table 1](#) for details on the full inclusion and exclusion criteria for the study.

Informed consent

The nephrologist, anaesthesiologist or surgeon (as per local protocol) will provide and explain the study information. Due to the unscheduled nature of kidney

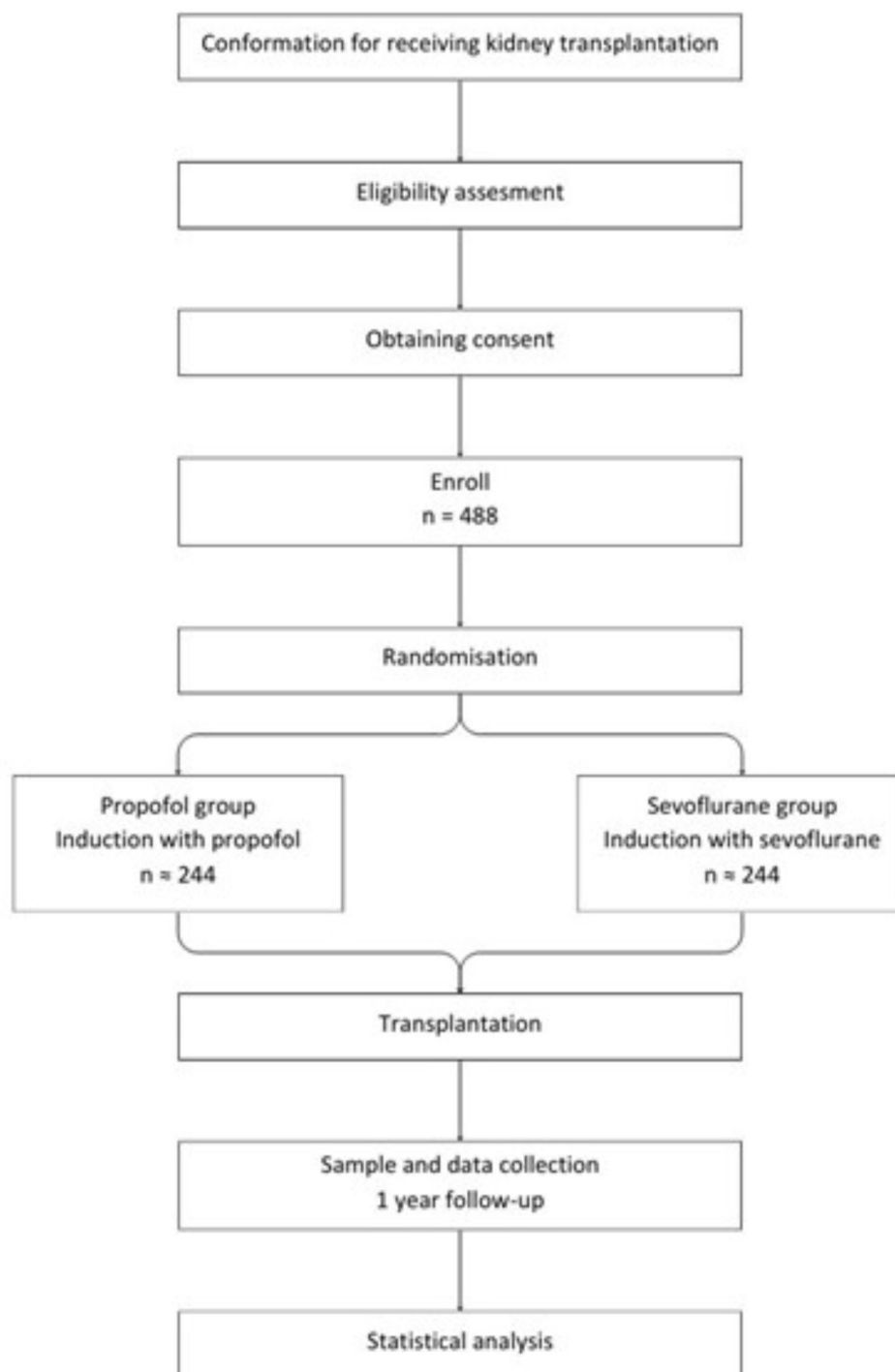


Figure 1 Flow chart illustrating the process of patient enrolment, randomisation, interventions and data collection. n, number.

transplantation, the standard 48-hour reflection period cannot be maintained; this will be clearly communicated to the patient. Patients will be informed that participation is voluntary, has no impact on their treatment and that they may withdraw at any time without consequences. Written informed consent will be obtained only after the patient has read and understood the study information. The form confirms that the patient:

1. Has read the information.
 2. Had the opportunity to ask questions.
 3. Received satisfactory answers.
 4. Had sufficient time to consider participation.
 5. Understands participation is voluntary and withdrawal is possible at any time without explanation.
 6. Is aware who may access their data.
 7. Consents to the use and 15-year storage of data and biological samples for study purposes.
- Specific consent will also be requested for:
- a. Storage of biological material for an additional 15 years for future research.

Table 1 Immunosuppressive regimes

Induction regime	
Tacrolimus	0.1–0.15 mg/kg
Mycophenolate mofetil	750/2000 mg
Prednisolone	According to local practice
Basiliximab	20 mg at transplantation and day 4
Maintenance regime	
Tacrolimus	
Day 1–day 4	0.15–0.20 mg/kg per day
Day 5–week 6	8–12 µg/mL trough level
Week 7–6 months	6–10 µg/mL trough level
>6 months	4–6 µg/mL trough levels
Mycophenolate mofetil	
Day 1–week 2	750–1000 mg two times per day
Week 3–6 months	500–750 mg two times per day
6 months	500 mg two times per day
Prednisolone	According to local practice

kg, kilogram; mg, milligram; mL, millilitre; µg, microgram.

b. Potential recontact for follow-up studies.

Only patients providing written consent will be included. Full participant information is provided in online supplemental appendix 1: Subject Information VAPOR-2.

Participant withdrawal and adverse events

Participants may choose to leave the study at any time and for any reason, without any negative consequences. The investigator also holds the authority to withdraw a participant from the study for urgent medical reasons. If the actual kidney transplantation does not take place, participants who have already been randomised can be replaced. The randomisation number of the patient will be excluded and collected sample material (T0) will be destroyed. The same patient can be re-included if eligible, in which case they will undergo a new randomisation process with a new randomisation number.

If a patient is withdrawn from the study due to an adverse event, the adverse event will be followed until the patient has recovered with or without sequelae.

In the case of a serious adverse event (SAE), the investigator will report them to the sponsor without undue delay. The sponsor will report the SAEs through the web portal ToetsingOnline to the accredited METc that approved the protocol, within 7 days of first knowledge for SAEs that result in death or are life threatening, followed by a period of a maximum of 8 days to complete the initial preliminary report. All other SAEs will be reported within a period of maximum 15 days after the sponsor has first knowledge of the SAE.

Randomisation and blinding

Patients will be randomised by the study team to one of the following groups: group 1 PROP (control): propofol:

a propofol-remifentanyl based general anaesthesia; group 2 SEVO (intervention): sevoflurane: a sevoflurane-remifentanyl based general anaesthesia. The randomisation procedure will be performed using a web-based system (ALEA) stratified for donor type (DBD or DCD) and study site. If ALEA is unavailable and the randomisation of a patient cannot be postponed, manual randomisation using a standardised form will be used. The two treatment groups will be allocated in a 1:1 ratio, using a random-sized block design (block size minimum 4, maximum 8). The randomisation is blinded to the patient. Although blinding of clinical staff is not feasible due to the nature of the interventions, performance bias is mitigated through standardised perioperative and postoperative protocols, blinding of patients and outcome assessors and the use of centralised, objective definitions for primary outcomes.

Outcomes

Primary outcomes

The two co-primary endpoints are the incidence of DGF and 1-year acute rejection in recipients of DCD and DBD donor kidneys. DGF is defined as the need for dialysis within the first week after transplantation, excluding one-time dialysis for hyperkalaemia. Acute rejection is defined by the modified BANFF 2013 classification and must be associated with decline in kidney function and treatment.

Secondary outcomes

Functional delayed graft function (fDGF) is defined as the absence of a daily decrease of at least 10% in serum creatinine for at least three consecutive days; PNF is defined as a permanent lack of function of the allograft; length of hospital stay and postoperative complications of all kinds.²⁷ Estimated glomerular filtration rate (GFR) at 1 week and 3 and 12 months calculated with the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula; measured GFR employing iohexol (Oslo) at 12 months; readmissions at 3 and 12 months, graft survival and all-cause mortality at 12 months.

We predefined four substudies being: cardiac biomarkers in renal transplantation, volatile versus intravenous anaesthetic agent; predictive value of urinary biomarkers in a deceased donor kidney transplantation cohort to predict PNF, DGF, acute rejection and long-term graft function and outcome; association between intraoperative haemodynamics and vasopressor use and graft outcome; postoperative delirium, volatile versus intravenous anaesthetic agent (Groningen, Aarhus).

Interventions

Anaesthesia protocol

In the PROP group, anaesthesia will be induced and maintained with propofol (Target Controlled Infusion (TCI) Schnider model or mg/kg/hour).^{28 29} In the SEVO group, anaesthesia will be induced with propofol and maintained with sevoflurane. A Bispectral Index (BIS)

monitor will be used to monitor the depth of anaesthesia and a BIS value of 40–60 is considered an adequate depth. Dosage of anaesthetics will be adjusted to maintain this target. Analgesia will be managed with remifentanyl (TCI Minto model or $\mu\text{g}/\text{kg}/\text{min}$).^{30 31} During anaesthesia, the remifentanyl concentration will be increased or decreased at the discretion of the attending anaesthetist in order to maintain a stable blood pressure within 80% of baseline measures of the patient. In order to facilitate tracheal intubation, mechanical ventilation and surgical conditions, all patients will receive a bolus of cis-atracurium/rocuronium after loss of consciousness. During the procedure, muscle relaxation will be continued Train Of Four (TOF) guided (≤ 1) until skin closure or as specified by local institutional protocol.

Monitoring

Intraoperative monitoring will consist of: ECG, non-invasive blood pressure, continuous arterial blood pressure, oxygen saturation, BIS, end-tidal CO_2 , temperature.

Blood pressure management

In case of a mean arterial pressure (MAP) $< 80\%$ of patients baseline MAP, the depth of anaesthesia or analgesia is adjusted. Should this prove inadequate or not feasible, boluses of ephedrine (5 mg) or phenylephrine (100 μg) are administered. In the case of persistent hypotension, norepinephrine can be administered. In the case of hypertension, the depth of anaesthesia or analgesia is adjusted. If these adjustments are insufficient or not possible, 75–150 μg clonidine can be administered.

Fluid management

Fluid regimen during the procedure consists of balanced crystalloids (Ringers Lactate, Ringers Acetate, Plasma-lyte). No synthetic colloids are used intraoperatively or postoperatively. Intraoperative fluid administration will comprise 45–50 mL/kg body weight of the patient in which 50 kg and 120 kg will be the lower and upper body-weight, unless contraindicated in the patient. In the case of low body weight, 50 kg will be used and in the case of obesity, 120 kg will be used. Postoperative fluid management is according to local standardised practice.

Pain management

Preoperatively, patients will receive 1000 mg paracetamol. Postoperative pain will be managed with paracetamol and morphine/fentanyl/oxycodone according to the local protocol.

Other medication

Antibiotics will be given according to local standard institutional guidelines. Before reperfusion, mannitol 30 g is given. Hyperkalaemia occurring during the intraoperative or immediate postoperative period will be treated according to local standard institutional protocol. Diuretics can be administered according to local standard institutional protocol. Postoperative nausea and vomiting will be treated with ondansetron and droperidol

according to local standard institutional protocol. Bladder spasms will be treated with oxybutynin 5 mg.

Kidney preservation

Kidneys will be preserved using either static cold storage (Oslo, Aarhus, Barcelona) or hypothermic machine perfusion (Groningen, Amsterdam, Oslo). Preservation solution consists of SPS-1 (University of Wisconsin solution, Organ Recovery Systems, Itasca, Illinois, USA), IGL-1 (Institut Georges Lopez, Lissieu, France) or Custodiol HTK (Essential Pharmaceuticals, Raleigh, North Carolina, USA).

Transplant procedure

The transplantation procedure will be performed according to local protocol.

Immunosuppressive regimen

The immunosuppressive regimen is shown in [table 2](#) and consists of induction with tacrolimus, mycophenolate mofetil, prednisolone and basiliximab. Maintenance immunosuppressive regime consists of tacrolimus, mycophenolate mofetil and prednisolone.

Sample collection

Urine and blood samples are collected at standardised time points, as shown in [figure 2](#). At T0, a time window of 24 hours is allowed. At T1, a time window of 10 min is allowed. At T2, a time window of 30 min is allowed. At T3–9, time windows of 8 hours are allowed. At T10 (3 months), a time window of 1 month is allowed. At T11 (1 year), a time window of 2 months is allowed. Per sample, 15 mL of urine and 13.5 mL of blood (10 mL of EDTA and 3.5 mL of citrate) are collected. Biopsies taken according to local standardised protocol will be used for analysis. No additional biopsies will be taken for this trial. Samples are processed within 3 hours after collection. The samples are stored at -80°C . In the event of a patient withdrawal, biomaterial will be destroyed.

Data collection, storage and monitoring

Data collection includes donor, kidney, procedure and recipient characteristics as shown in [table 2](#). Specification of each variable is shown in online supplemental appendix 2: table S1. Data will be stored in an electronic case report form in REDCap (Research Electronic Data Capture). Continuous data recorded during the transplant procedure such as blood pressure, heart rate, depth of anaesthesia, oxygenation, end tidal CO_2 , ventilator settings and medication, will be retrieved from the electronic health record. All study data will be recorded under a unique study number ensuring strict confidentiality. All research and medical data will be kept strictly confidential. Only the principal investigators and research office coordinator who are involved in this study will have access to the coding system and will be able to identify a participant. Monitoring of the data is carried out annually by a certified study monitor who is independent from the sponsor and has no competing interests.

Table 2 Data collection

Donor characteristics	Transplantation characteristics	Recipient characteristics	Post-transplantation
Gender	First warm ischaemia	Gender	PACU/ICU
Age	Cold ischaemia	Age	Time/date admission
Height	Second warm ischaemia	Height	Time/date discharge
Weight	Kidney (left/right)	Weight	PONV
Ethnicity	Number of arteries	Ethnicity	Blood pressure
Smoking	Arteries fused	Smoking	Hypertensive medication
Blood type	Artery sacrificed	Blood type	Hypotensive medication
Comorbidity	Preservation fluid	Comorbidity	Pain medication
Viral status	Kidney preservation procedure	Primary kidney disease diagnosis	Diuresis
Donor type (DBD/DCD)	Time anaesthesia	Current dialysis treatment	Diuretics
Date and time of death	Time reperfusion	Residual diuresis	Fluid administration
Cause of death	Time end of surgery	Prior kidney transplantations	Complications Delirium (RASS/CAM scores)
Type of donation file	Blood pressure	Viral status	Day 1–7 after transplantation
Copy present of donation file	Induction	Number of mismatches at HLA	Blood pressure
Last plasma creatinine	Reperfusion	Panel reactive antibodies	Heart rate
Last plasma urea	End of surgery	Donor specific antibodies	Diuresis
CPR performed	Heart rate	Crossmatch performed	Graft function
Hypotensive periods	Induction	General medication use	Blood products administration
Inotropic/vasopressor support	Reperfusion	Preoperative medication	Immunosuppression
	End of surgery		Dialysis
	Blood loss		DGF Delirium (RASS/CAM scores)
	Blood products administration		Hospital discharge
	Fluid administration		Blood pressure
	Medication administration		Heart rate
	Depth of anaesthesia		Diuresis
	Biopsies		Biopsies
	Complications		Rejection
			Dialysis
			DGF
			Immunosuppression
			Medication use
			Complications during admission
			Month 3 and 12 after transplantation
			Blood pressure
			Heart rate
			PNF (month 3)
			Biopsies
			Rejection
			Dialysis
			Graft loss

Continued

Table 2 Continued

Donor characteristics	Transplantation characteristics	Recipient characteristics	Post-transplantation
			Immunosuppression
			Medication use
			Recent hospital admission
			Recent complications
CAM, Confusion Assessment Method; CPR, cardiopulmonary resuscitation; DBD, donation after brain death; DCD, donation after circulatory death; DGF, delayed graft function; HLA, human leucocyte antigens; ICU, intensive care unit; PACU, post anaesthesia care unit; PNF, primary non-function; PONV, postoperative nausea and vomiting; RASS, Richmond Agitation-Sedation Scale.			

The research office coordinator also monitors the trial on a regular basis. Monitoring will include checking if the collected data are consistent with adherence to the trial protocol, CRFs are completed by authorised personnel, no key data are missing, validating the data (ie, range and consistency checks) and reviewing of recruitment rates, withdrawals and losses to follow-up. Given the low risk nature of the study, comparing two standards of care in anaesthesia, a data safety monitoring board was not installed. For a complete overview of all data collected, we refer to online supplemental appendix 2: table S1. The final dataset is managed by the Principal Investigator (PI) and the sponsor of the study and stored on a secured server. All sample material will be transported to and stored at the Central Freezer Facility of the University Medical Centre of Groningen, the Netherlands. A scientific steering committee is installed and consists of the PI and the local PI's of each participating centre. All investigators involved can propose substudies. A substudy can be proposed by filling in an application form consisting of research question, background analysis, aims and hypothesis, study design, outcome measures and requested data/samples. The steering board will review the request and, when approved, data and samples will be shared with the investigator.

Sample size calculation

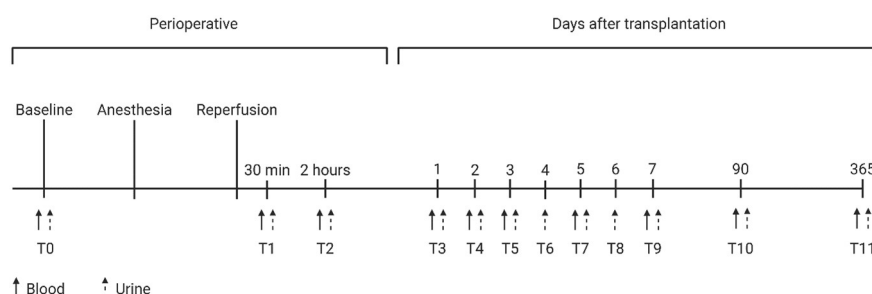
Sample size calculation was conducted using SPSS V.28 (IBM Statistics) by testing two proportions using the two-sided Z-test with pooled variance with normal approximation. DGF incidences reported in literature vary between 15% and 40% in case of kidneys retrieved from DBD donors and between 40% and 70% in case of kidneys

retrieved from DCD donors.^{32–35} An incidence of 40% was taken for a combination of the two donor types and a reduction of 30% was determined clinically relevant. A sample size of 488 recipients of deceased donor kidneys (244 patients/group) was calculated to achieve adequate power to detect a reduction in DGF from 40% to 28% (power of 80% and a 5% significance level). The incidence of 1-year AR in the VAPOR-1 study was 31% in patients receiving propofol and 8% in patients receiving sevoflurane. A sample size of 398 recipients of deceased donor kidneys (199 patients/group) was calculated to achieve adequate power to detect a reduction in 1-year AR from 20% to 10% (power of 80% and a 5% significance level). Stratification was not taken into account. Missing data and dropouts are expected to be minimal and unrelated to treatment, as all patients undergo transplantation and follow-up is part of standard clinical care, ensuring consistent data collection, as demonstrated in a comparable study in a similar patient population.³⁶

Statistical plan

The primary null hypotheses to be tested are H1: the proportion of DGF incidence in the PROP group is equal to that of the SEVO group. H2: the proportion of AR incidence in the PROP group is equal to that of the SEVO group at week 52. The Hochberg's step-up procedure will be used to test the null hypotheses.³⁷ Which will imply the least significant outcome to be tested at the 5% level, and if it can be rejected, reject both hypotheses. If not, the remaining hypothesis will be tested at the 2.5% level.

The primary statistical analysis is stratified for study site and donor type. The primary analysis is unadjusted for known covariates like donor age, ischaemia times and

**Figure 2** Sample collection time points.

Propofol- versus sevoflurane-based anaesthesia for deceased donor kidney transplantation; The Volatile Anaesthetic Protection of Renal transplant (VAPOR)-2 study.

Multicentre randomised controlled clinical trial with two parallel groups including 488 patients above 18 years of age scheduled for kidney transplantation with a kidney from a deceased brain death (DBD) or deceased circulatory death donor (DCD) donor in 5 European Transplant Centres

Hypothesis: A Sevoflurane-based anaesthesia is able to attenuate transplant procedure associated ischemia-reperfusion injury and therefore associated with improved graft and patient outcome compared to a Propofol-based anaesthesia

Inclusion criteria: ≥ 18 years, transplantation with a DBD/DCD kidney

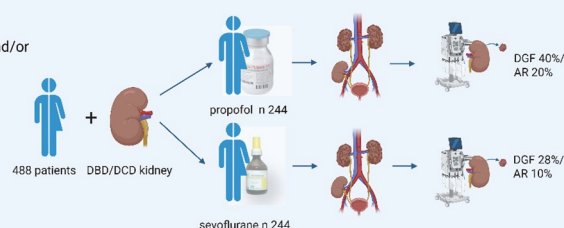
Exclusion criteria: Patients with a high immunological risk, ABO incompatible transplantation

Co-primary endpoints:

Incidence of delayed graft function (DGF) and/or
Incidence one-year acute rejection (AR)

Secondary endpoints:

Functional delayed graft function
Primary non function
Length of hospital stay
Postoperative complications of all kind
Graft function at 1 week, 3 and 12 months
Readmissions at 3 and 12 months
Graft survival at 12 months
Patient survival at 12 months



Trial registration number: NCT02727296, www.vapor-2.org, inclusion completed, results expected 2026

Figure 3 Overview of study. This infographic illustrates the key phases of the randomised controlled trial, including participant recruitment, intervention and follow-up.

preservation method. A sensitivity analysis using multivariate logistic regression will be performed to assess if those covariates confound or modify the treatment effect.^{38 39} Differences between groups with respect to categorical data will be tested by χ^2 or Fisher's exact tests (baseline characteristics, donor, transplantation and recipient data, DGF, fDGF, hyperacute rejection, PNF, readmissions at 3 and 12 months). Continuous data (baseline characteristics, donor, transplantation and recipient data, length of hospital stay) will be tested for normality with the use of Kolmogorov-Smirnov. In case of normality, t-tests will be used. If not, Mann-Whitney tests will be applied. Values are given as mean with SD and median with IQR. The Kaplan-Meier method will be used to analyse 1-year acute rejection episodes. Differences between the curves will be determined with the log-rank test. The repeated measurements on GFR at 1 week and 3 and 12 months analysis will be performed using a mixed effect model. The 12-month GFR in recipients will be analysed with t-test or Mann-Whitney. The Kaplan-Meier method will be used to analyse graft and patient survival. Differences between the curves will be determined with the log-rank test. Post hoc stratification will be done for type of donor; living, DCD, DBD. Tests will be two-tailed and $p < 0.05$ will be considered statistically significant.

An overview of the study is presented in [figure 3](#).

ETHICS AND DISSEMINATION

Ethical and safety considerations

The study protocol (V.2, 8 June 2016) is approved by national agencies in Denmark, Norway, Spain and the Netherlands including the local ethical committees and the data protection agencies (Netherlands: METc UMCG 2016/203, A-UMC METc 2021_220; Denmark: The

central Denmark Region Committee in Biomedical and Research Ethics 1-10-72-55-17; Norway: Regional komité for medisinsk og helsefaglig for skningsetikk 2018/2472; Spain: CEIm Fundacio Puigvert IUNA ORG-100038907). The study will be conducted according to the principles of the Declaration of Helsinki and Istanbul and in accordance with the Medical Research Involving Human Subjects Act (WMO).

Dissemination plan

The study is registered in a clinical trials database. The results of the study will be disclosed unreservedly and will be submitted to a peer-reviewed scientific journal. Results and knowledge obtained will be shared according to UNESCO Open Science principles. Results will be shared as (oral) presentations at (inter)national scientific meetings, patient meetings and (inter)national events. When the study follow-up and data processing is terminated, the anonymised data will be stored at a secured server at the University Medical Centre Groningen and biological samples will be stored at the Central Freezer Facility at the University Medical Centre Groningen, Groningen, the Netherlands.

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