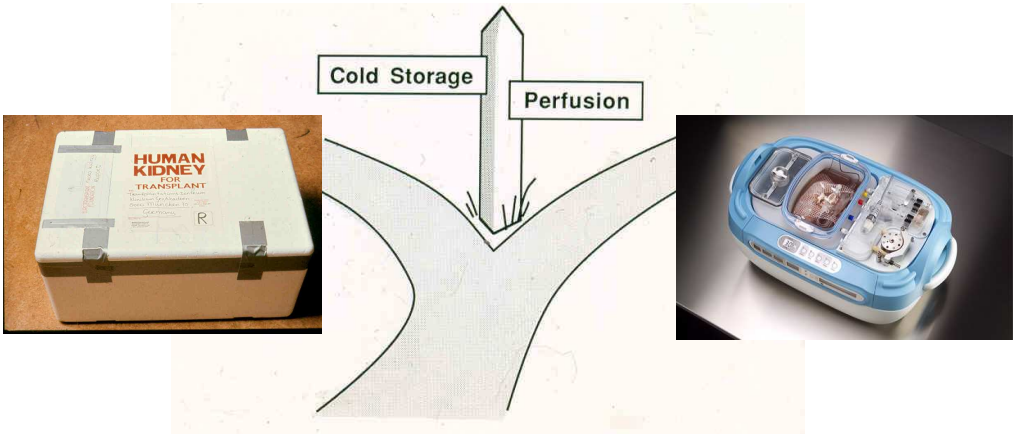
Protocol

Machine Preservation Trial

MP vs. CS in Kidney Transplantation in collaboration with Eurotransplant



A Multi-Center Randomized Controlled Trial

Groningen, 25 October 2005

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Sponsor:

Organ Recovery Systems, Inc.

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I. Background & Rationale

Simple cold storage (CS) has been the preferred method of organ preservation for most transplant centers in Europe. Major transplant centers in the US have indicated that continuous hypothermic machine perfusion (MP) has definite advantages over CS with reduced percentages of delayed graft function (DGF) after kidney transplantation. Nevertheless, in most european centers, predominantly due to logistics and the perception of increased costs, MP has not been utilized or properly evaluated. Therefore no decision has been made as to the standard of care for organ preservation in particular how the preservation method (CS or MP) will affect outcome after transplantation. This Study proposes a prospective randomized trial within an international organ sharing system to evaluate early graft function after MP preservation versus CS preservation.

Within the Eurotransplant (ET) region results after kidney transplantation have improved due to better immunosuppression and standardized techniques. However, in part due to older and more 'marginal/extended' donors DGF rate after kidney transplantation has risen to as high as 35%; despite the 21% reduction when the University of Wisconsin Cold Storage preservation solution (UW-CS) was introduced as the standard in the late nineteen eighties. In the past, in animal experiments as well as in historical controlled clinical studies MP has been shown to provide better early graft function than when kidneys were cold stored. In addition, when kidneys from extended donors, with long preservation times, and from non-heart beating (NHB) donors were used, MP has shown to be beneficial. A review of current literature concerning data on MP vs. CS, as the method of organ preservation, revealed a 20% reduction in DGF when MP was the preservation modality. Historical data also showed that DGF in combination with acute rejection was found to be significantly associated with a 10-15% decrease in graft survival, thus requiring restart of dialysis and retransplantation in a large number of recipients. Lastly, DGF inevitably leads to dialysis, prolonged hospital stay, and increased cost in the short and long term, especially when the graft fails and costs of dialysis while on the waiting list for a second transplant is included.

As stated above, for reasons of practicality, MP was abandoned or not even introduced by many programs. It needs equipment and consumables, can be labor intensive and carries the risk of equipment failure. Therefore, its usage seemed not justified versus the simplicity and low cost of CS. However, the question of superior early graft function of donor kidneys preserved by MP vs. CS remains unresolved and the added benefit of MP use for the more difficult donor kidneys needs to be quantified. While data point at potential benefits of MP that would imply not only less DGF, but also less acute rejection, and a better short- and long-term function at reduced cost, no real comparative data of these modalities under strict conditions has been done.

In this study, we attempt to resolve the controversy and will answer the question whether or not MP is superior in preservation of cadaveric kidney grafts and logistically feasible within an international organ sharing system.

II. Trial Design

A prospective randomized controlled multi center trial of paired kidneys from cadaveric donors (the "study").

III. Objectives/Outline of the Study

Main aim of the study:

Does MP with UW-MP (Kidney Preservation Solution: KPS-1) improve early graft function in cadaveric renal transplantation in comparison to UW-CS (Viaspan®)? Assuming the 0-hypothesis that MP and CS give equal early graft function, the alternative hypothesis is that early graft function improves with MP.

Primary endpoint:

DGF, defined as any dialysis requirement within 7 days post transplant.

Secondary endpoints:

Duration of DGF, renal function (serum creatinine; 1/creatinine; creatinine clearance; decrease of serum creatinine > 10% per day for at least 3 consecutive days for more than one week after tx; length of hospital stay; acute graft rejection, hyperkaliemia, calcineurin inhibitor toxicity), graft and patient survival at 1-year.

Additional points for evaluation (amendments):

Participating regions have the opportunity to suggest amendments to this basic study protocol. Proposed amendments will be discussed by the Steering Committee and adopted for either all regions, regionally, or rejected. Costs of accomplishing these amendments will be considered outside of the basic financial support structure of the study and are the responsibility of the proposing group.

IV. Study Population

Identification of donors

All potential consecutive cadaveric kidney donors >16 years from the collaborating donor regions (Belgium, The Netherlands and Nordrhein-Westfalen in Germany) reported to the ET desk are eligible for randomization.
This includes all heart beating organ donors and, in The Netherlands an Belgium, NHB donors (including Maastricht categories 3 and 4, excluding categories 1 and 2). No NHB donor kidneys will be procured or transplanted in Germany. Donors will meet the general and organ specific criteria for kidney donation. Donors will be managed by the local coordinator according to loco-regional and ET directions.

Randomization of donor kidneys

After accepting the potential organ donor for actual donation, one of the kidneys is randomized to preservation by MP with the contralateral organ serving as a control being preserved by CS (ET desk has randomization scheme).

In case, due to circumstances, only one kidney is eligible for procurement, preservation and transplantation, while the contralateral kidney is discarded, the eligible kidney will be cold stored.

In case of a recipient with a multi organ transplantation (pancreas, lung, liver, heart, or small intestine plus kidney), this kidney and the contralateral kidney will be excluded from the study. When technical

problems with MP are expected and the perfusionist, according to training, cannot fix the problem, preservation methods may be switched, thus frustrating initial randomization.

To guarantee a balanced design, block randomization may be applied (at the discretion of the Central Trial Assistance (CTA) that will assure that there are 300 paired sets at the end of the study). The first 24 left kidneys will be assigned to the treatment arms according to the scheme: AABB BBAA ABAB BABA ABBA and BAAB, with A=MP and B=CS. Obviously, the right kidneys will be assigned to the other treatment arm. The sequence for the following 24 kidneys will be determined at random.

Kidneys are offered for transplantation following the ET allocation rules. Whenever one of two kidneys is not transplanted (for whatever reason) or both kidneys are preserved in the same way (i.e. CS for double multi organ transplants) transplants are excluded from analysis for this study.

V. Preservation Techniques

Following the donor operation wash-out and preservation is performed preferably using UW-CS. In case of kidney donors only, usage of histidine-tryptophane-ketoglutarate (HTK: Custodiol®) in the donor operation and CS preservation is acceptable, but UW is preferred. On the back-table, kidneys will be flushed with 250 ml UW or HTK, respectively. The kidney assigned to MP is then prepared for perfusion using a cannula most suitable for attachment to the perfusion device ("bull-dog patch clamp" or suitable ORS cannulae for the aortic patch). If no aortic patch is present, renal arteries may be cannulated using a straight-end cannula. When perfusion is impossible due to vascular anomaly, preservation methods may be altered and the contralateral kidney is preserved by MP. After cannulation, the assigned kidney will be placed in the prepared perfusion machine, primed with approximately 1000 ml UW-MP. All kidneys assigned to MP will be placed on the device at the donor hospital. The kidney assigned to CS will be preserved in UW-CS or HTK on melting ice.

After adequate packaging, kidneys will be transported to the accepting transplant centers as assigned by ET. Organs will be preserved by either method from donor operation until transplantation.

VI. Machine Perfusion

Prior to the study three Regional Perfusion Centers (RPC) (Groningen, Essen and Leuven) will be established as separate entities that are responsible for the logistics that will allow a safe and high quality procedure using machine preservation according to the state of the art and ruling quality standards. For a good conduct of this study three teams of perfusionists will be trained by professionals from ORS to take care of preservation machines, handle donor kidneys in collaboration with the donor surgeon and accompany the transport of the preservation devices as well as accumulate data for the study. Details concerning the training, responsibilities and standard operation procedures are defined in a separate logistics support protocol (see addendum 4). Each RPC will have a Regional Supervisor who is not the Principle Investigator for that region.

During the study, after reporting a donor for kidney donation, randomization by the ET desk is performed and the transplant coordinator on duty is informed which kidney should be machine perfused and which kidney cold stored. Next the Regional Perfusion Center (RPC) is notified by the transplant coordinator on duty concerning the expected donor operation and told at what point in time a MP-unit ought to be present in the OR at the donor hospital.

At the time the donor operation begins, the RPC will have arranged logistics concerning MP, e.g. the perfusion machine including cannulae, preservation solutions, questionnaires, etc. All details will be available and ready for use in the operating room at the donating center. The RPC, in close collaboration with the responsible transplant coordinator and ET will coordinate and take care of the logistics

concerning transportation of the preservation device. The RPC is responsible for preparing preservation, guiding and instructing surgeons on the spot in the use of common preservation protocol and process. The perfusionist on call is a member of the RPC and is responsible for the individual case. The perfusionist will collect data for the study during the donor procedure, during the first hour of machine preservation and at time of transplantation. Also, he or she will collect data to assess user-friendliness and feasibility of MP. Once kidneys are placed on a MP device they will remain in that preservation mode until delivered to the transplant center OR. The kidney will travel stand-alone from donor hospital to recipient center via the standard transportation method. Perfusate of the MP kidneys will be sampled periodically using the standard machine-ports and aliquots of collected effluent appropriately stored by the perfusionist for quality control and organ viability assessment at a later date. At no time point during preservation any lab results or vascular resistance results may lead to a change of policy or decision to transplant that particular kidney, as the donor kidney pair has been previously accepted for allocation and transplantation on viable grounds according to standard ET regulations.

VII. Organ Allocation Logistics

Organ allocation logistics, including transportation logistics to the assigned transplant center, will be, as usual, the responsibility of ET in close collaboration with the transplant coordinator. In defiance to standard procedures: to prevent possible bias during the study period, ET will at time of offering of the donor kidneys included in the study reveal all pertinent information to the recipient centers but not the preservation method before the individual center has made its appropriate choice for a left or right kidney on recipient or center related grounds. Otherwise, logistics will follow standard policies and the study should not change any procedure or the timing of transplantation in individual recipient centers.

VIII. Data Collection

Donor, preservation and recipient data

Pertinent data (see addendum 1-3) for the study will be registered in a specially designed web-based database by the perfusionist during the donor, preservation and transplant procedure. Follow-up data (day 0-14, 1, 3 and 12 months) will be filed in the same secure online database by a member of the recipient team in the recipient center. Normal documentation for ET purposes will be carried out in the standard fashion. Recipient centers will be financially compensated for providing follow-up data to be used for the analysis of the study. ET (J. Smits) in close collaboration with the coordinating principal investigator (RJ Ploeg) will monitor accrual and quality of data throughout the study. However all PI's share responsibility in encouraging data submission from their transplantation centers.

IX. Safety Related Issues

Organs will be handled according to professional standards within current ET-approved sharing agreements.

The solutions used are the Belzer's Solution for MP (KPS-1) and the University of Wisconsin solution (UW-CS, Viaspan®) for CS. Although UW-CS is preferred, HTK (Custodiol®) is also acceptable for CS preservation.

Adverse effects attributed to the use of either preservation method will be recorded at every donor and recipient operation by the local transplant coordinator, RPC/CTA and transplant recipient center.

Volumes and type of solutions used for in-situ flush will all be documented for each study organ. All solutions and devices used will be CE marked.

If any adjustment to a kidney is required after being placed on a perfusion pump, such adjustment shall only be made while under a biologic hood or in a clean room/operating room environment in order to maintain sterile integrity.

X. Operations

Ethics Committee Approval / Local Contacts

The ET Ethics Committee has ruled that no informed consent will be needed for this study. Each PI will seek approval by his center's local Ethics Committee (Groningen, Essen, Leuven).

XI. Regional Perfusion Center Operations

Equipment, Supplies, Upkeep and Maintenance

At the sole expense of ORS, initial stocking of each participating Perfusion Center shall include:

4 LifePort™ kidney transporters
20 cassettes
20 liters of (KPS-1) machine perfusion solution
Cannulae, tubing, solutions, gowns, gloves and drapes to supply 20 cases
Other analytical devices as may be required
LifePort™ custom transit carts

Thereafter, once inventory of supplies is reduced to 10 cases the Regional Perfusion Center supervisor will submit a formal requisition order to ORS Europe (Brussels) to replenish inventory. Supplies for no less than 5 donor cases shall be maintained in inventory at all times during the study.
Throughout the study, all RPC equipment and supplies will remain the property of ORS.

Staffing and Coverage

All three RPCs will maintain a 24/7 staff schedule for their respective area. Backing up participant centers in emergency cases shall be determined on a case by case basis.

Belgium Perfusion Center Management

ORS will manage the Belgium RPC for 24/7 operations.

The Netherlands and Nordrhein-Westfalen Regional Perfusion Centers

ORS will provide at its sole expense the initial training and set-up for the participating Perfusion Centers in Groningen, The Netherlands, and in Essen, Nordrhein-Westfalen, Germany. Ongoing RPC operating costs will be reimbursed by ORS up to a level sufficient to provide 24/7 coverage of each respective region for the duration of the required perfusions in Phase II of the study.

Upon completion of the study, each participating RPC may acquire from ORS any or all perfusion related facilities, equipment or supplies for fair its then market value.

XII. Epidemiology

DGF is reported to be 25-35% after CS preservation. MP is expected to reduce this rate by 10% (RR 0.9). DGF rates for extended criteria donors and NHB kidney donors are higher, and results will be included in the overall analysis with the possibility of stratification.

XIII. Statistics

Power analysis is done on the assumption that DGF will be reduced at least by 10% using MP vs. CS. For a power of 0.80 with $p<0.05$, the expected sample size (N) is 300 donors with 300 donor kidneys in either MP or CS, respectively.

Statistical analysis of demographic donor and recipient characteristics will be carried out to check adequate randomization and find relevant differences. To account for the within-donor dependence structure of the data, a multivariate model will be built with a normal gamma frailty term for the donor.

A paired study design leads to a situation in which each donor is the perfect match to himself. On average both treatment arms will have an equal distribution of known and unknown prognostic factors. However, there is no assurance that all prognostic factors are evenly distributed. Therefore, an a posteriori stratification will be performed, implying a modeling of the data using the appropriate multivariate analysis technique. The following preservation and recipient factors are associated with early renal graft dysfunction and thus will be included in the stratification: preservation time (cold ischemic time = CIT), number of HLA mismatches, recent PRA level, recipient age, 1st/retransplant, length of time on dialysis, donor source (e.g. traditional, expanded, non-heart beating) and donor age. Correlation of perfusate organ function testing information to post-transplant graft function and survival will also be done. Lastly, a cost-benefit analysis of the two modalities as regards to graft outcome and survival will be performed.

XIV. Study Schedule

Phase I – Pre-Study Preparation

	Estimated Time to Completion	Responsible Party
"All Hands" organizational meeting including PI's, RPC supervisors, key ORS, ET personnel. Purpose: 1. Introduce participants, define roles & responsibilities and trial branding 2. Provide study overview, outcomes 3. Define common outcomes terminology e.g. long and short term graft survival, graft function 4. Define scope, frequency and authorship of study reports 5. Establish RPC site development for The Netherlands, Belgium and Nordrhein Westfalen and training schedule NRW and The Netherlands	Within first 30 days of signing the definitive study sponsorship	ORS will host at its Zaventem (Brussels) facility
Forms/documentation development	Within first 60 days of study agreement signing	PI's & CTA
Further information of key persons (e.g. donor & tx surgeons, TC's, tx nephrologists) in respective regions for collaboration and relevant agreements signed by participant hospitals as necessary		PI's & CTA
Database development		PI's & CTA

Phase II – Transplantation

	Estimated Time to Completion	Responsible Party
Paired kidney procurement, preservation (static/perfusion), & transplantation	10–12 months	Participant hospitals & RPC's
Interim reports issued (Content to be determined in initial organizational meeting as described above)	Quarterly	PI's & CTA hosted by ORS

Phase III – Data Analysis and Final Report

	Estimated Time to Completion	Responsible Party
Final data analysis and draft final report generation	Within 14 months of last Study transplant procedure	PI's & stat
PI final meeting		PI's & CTA
Final report submission		PI's & CTA

CTA = Central Trial Assistance - Eurotranplant
ORS = Organ Recovery Systems
PI = Principal Investigator
RPC = Regional Perfusion Center

XV. Addendum 1: Donor Parameters

Donor identification

ET Donor number: |_|_|_|_|_|_|
Name donor center: _____
Date of admission (dd-mm-yy): __-__-__
Date of donor operation (dd-mm-yy): __-__-__
Kidney left donated: [ ] yes [ ] no
Kidney right donated: [ ] yes [ ] no
Liver donated: [ ] yes [ ] no
Lung donated: [ ] yes [ ] no
Heart donated: [ ] yes [ ] no
Pancreas donated: [ ] yes [ ] no
Other organ donated: _____
Donor date of birth (dd-mm-yy): __-__-__
Donor sex: [ ] male [ ] female
Donor weight: _____ kg
Donor blood group: [ ] O [ ] A [ ] B [ ] AB
HLA-typing: A _____ B _____ DR _____

Donor pre-operative clinical data

Diagnosis:
- [ ] multi trauma
- [ ] trauma capitis
- [ ] intra cranial bleeding
- [ ] primary brain tumor
- [ ] cardiomyopathy
- [ ] other

Diabetes Mellitus (IDDM): [ ] yes [ ] no
DM family history: [ ] yes [ ] no
Alcohol abuse: [ ] yes [ ] no
Cardiac arrest [ ] yes [ ] no
Systolic blood pressure (mean): _____ mmHg
Diastolic blood pressure (mean): _____ mmHg
Hypotensive period (syst. < 100 mmHg): [ ] yes [ ] no
- number of hypotensive periods: ___
- lowest systolic blood pressure: _____ mmHg
- lowest diastolic blood pressure: _____ mmHg
- duration lowest hypot. period: _____ minutes

Mean diuresis / hr. last 24 hrs.: _____ ml
Donor anuria / oliguria (< 500 ml/24h): [ ] yes [ ] no
- duration an-/oliguria: _____ hours

Vasopressors:
- Dopamine: [ ] yes [ ] no | Last dose: _____ mg
- Dobutamine: [ ] yes [ ] no | Last dose: _____ mg
- (Nor)adrenaline: [ ] yes [ ] no | Last dose: _____ mg
- Others: _____ | Last dose: _____ mg

Other relevant data: _____

Donor operation data

Donor heart beating: [ ] yes [ ] no
If NHBD:

Maastricht category: [ ] 1 [ ] 2 [ ] 3 [ ] 4
Time of detubation (hh:mm): ___:___
Time of cardiac arrest (hh:mm): ___:___
Time of start perfusion (hh:mm): ___:___
Hypotensive period (syst. < 100 mmHg): [ ] yes [ ] no
lowest systolic blood pressure: _____ mmHg
lowest diastolic blood pressure: _____ mmHg
duration hypotensive period: _____ minutes
Donor anuria / oliguria: [ ] yes [ ] no
Diuresis last hour: _____ ml
Phenoxybenzamin (Dibenzylin): [ ] yes [ ] no
Fentolamine (Regitin): [ ] yes [ ] no
Prostaglandins: [ ] yes [ ] no
Others: _____
Heparin: [ ] yes [ ] no

Donor operation left kidney

Preservation modality: [ ] CS [ ] MP
Preservation solution (if CS): [ ] UW [ ] HTK
Number of renal arteries left: _____
Arterial damage: [ ] yes [ ] no
Venous damage: [ ] yes [ ] no
Ureteral damage: [ ] yes [ ] no
Parenchymal damage: [ ] yes [ ] no
Washout perfusion left kidney: [ ] homogenous [ ] patchy [ ] blue
Washout parameters:
Volume of washout with UW/HTK: _____ ml
Cross clamping time + start washout (hh:mm): ___:___
Removal time left kidney (hh:mm): ___:___
Visible perfusion defects: [ ] yes [ ] no
Warm ischemia period: _____ minutes
Time points transport:
Leaving donor hospital (hh:mm): ___:___
Arrival at holding (if applicable) (hh:mm): ___:___
Departure of holding (if applicable) (hh:mm): ___:___
Arrival at recipient hospital (hh:mm): ___:___
Name recipient transplantation center: _____
Number of recipient: _____

Donor operation right kidney

Preservation modality: [ ] CS [ ] MP
Preservation solution (if CS): [ ] UW [ ] HTK
Number of renal arteries right: _____
Arterial damage: [ ] yes [ ] no
Venous damage: [ ] yes [ ] no
Ureteral damage: [ ] yes [ ] no
Parenchymal damage: [ ] yes [ ] no
Washout perfusion right kidney: [ ] homogenous [ ] patchy [ ] blue
Washout parameters:
Volume of washout with UW/HTK: _____ ml
Cross clamping time + start washout (hh:mm): ___:___
Removal time right kidney (hh:mm): ___:___
Visible perfusion defects: [ ] yes [ ] no
Warm ischemia period: _____ minutes

Time points transport:
Leaving donor hospital (hh:mm): ___:___
Arrival at holding (if applicable) (hh:mm): ___:___
Departure of holding (if applicable) (hh:mm): ___:___
Arrival at recipient hospital (hh:mm): ___:___
Name recipient transplantation center: _____
Number of recipient: _____

Donor laboratory values (last available values)

Hb: _____ mmol/l
Ht: _____
pH: _____
pCO_2: _____ Pa
pO_2: _____ Pa
Urea: _____ mmol/l
Mean creatinine: _____ umol/l
Max. creatinine: _____ umol/l

XVI. Addendum 2: Recipient ID and Operation Parameters

Recipient identification

Kidney received: [ ] left kidney [ ] right kidney
ET donor number: |_|_|_|_|_|_|
ET recipient number: |_|_|_|_|_|_|
Name recipient transplantation center: _____
Recipient date of birth (dd-mm-yy): __-__-__
Recipient sex: [ ] male [ ] female
Renal disease: _____
Number of previous transplants: _____
Pre-transplant diuresis: _____ ml/24h
Recipient blood group: [ ] O [ ] A [ ] B [ ] AB
Recipient HLA-typing: A _____ B _____ DR _____
ET-urgency: [ ] 0 [ ] 1 [ ] 2 [ ] 4
Number of HLA mismatches: A |__| B |__| DR |__|

Recipient operation – peri-operative data

Transplantation date (dd-mm-yy): __-__-__
Start time operation (induction of anesthesia) (hh:mm): ___:___
Mannitol: [ ] yes [ ] no
Diuretics: [ ] yes [ ] no
Dopamine: [ ] yes [ ] no
Hypotensive period (syst. < 100 mmHg): [ ] yes [ ] no
lowest systolic blood pressure: _____ mmHg
lowest diastolic blood pressure: _____ mmHg
duration hypotensive period: _____ minutes
CVP during anastomisis: [ ] deceased [ ] normal [ ] increased
Incision: [ ] med. laparotomy [ ] extraperitoneal
Transplant side: [ ] left [ ] right
Arterial problems:
[ ] no
[ ] ligated polar artery
[ ] reconstructed polar / hilar artery
[ ] repaired intima dissection
[ ] other
Venous problems: [ ] yes [ ] no
Start time anastomosis (hh:mm): ___:___
Total anastomosis time: _____ minutes
Reclamping time: _____ minutes
Time of reperfusion (hh:mm): ___:___
Cold ischemia period: _____ hours _____ minutes
Remarks: _____

Recipient operation – perfusion characteristics

Upper pole: [ ] smooth [ ] spotted [ ] infarction
Middle pole: [ ] smooth [ ] spotted [ ] infarction
Lower pole: [ ] smooth [ ] spotted [ ] infarction
Intra-operative diuresis: [ ] yes [ ] no [ ] unknown
Remarks: _____

XVII. Addendum 3: Recipient Follow Up Parameters

Kidney graft failure day 1 – 14

Graft failure: [ ] yes [ ] no
Date of graft failure (dd-mm-yy): __-__-__
Primary cause:
[ ] immunologic
[ ] preservation
[ ] technical - arterial
[ ] technical – venous
[ ] infection – bacterial
[ ] infection – viral
[ ] other
Graft removal: [ ] yes [ ] no
Death: [ ] yes [ ] no
Date of death (dd-mm-yy): __-__-__
Cause of death: [ ] Tx-related [ ] non-Tx-related

Hypotensive periods first 24 hours post-transplant

Hypotensive period I: [ ] yes [ ] no
duration: _____ minutes
lowest systolic blood pressure: _____ mmHg
lowest diastolic blood pressue: _____ mmHg
Hypotensive period II: [ ] yes [ ] no
duration: _____ minutes
lowest systolic blood pressure: _____ mmHg
lowest diastolic blood pressue: _____ mmHg

Serum creatinine and creatinine clearance day 1 - 14

Serum creatinine day 1: _____ umol/l
Serum creatinine day 2: _____ umol/l
Serum creatinine day 3: _____ umol/l
Serum creatinine day 4: _____ umol/l
Serum creatinine day 5: _____ umol/l
Serum creatinine day 6: _____ umol/l
Serum creatinine day 7: _____ umol/l
Creatinine clearance day 7: _____ ml/min.
Serum creatinine day 8: _____ umol/l
Serum creatinine day 9: _____ umol/l
Serum creatinine day 10: _____ umol/l
Serum creatinine day 11: _____ umol/l
Serum creatinine day 12: _____ umol/l
Serum creatinine day 13: _____ umol/l
Serum creatinine day 14: _____ umol/l
Creatinine clearance day 14: _____ ml/min.

Fluid intake and diuresis day 1 - 14

Day 1 diuresis: _____ ml
Day 2 diuresis: _____ ml
Day 3 diuresis: _____ ml
Day 4 diuresis: _____ ml
Day 5 diuresis: _____ ml
Day 6 diuresis: _____ ml

Day 7 diuresis: _____ ml
Day 8 diuresis: _____ ml
Day 9 diuresis: _____ ml
Day 10 diuresis: _____ ml
Day 11 diuresis: _____ ml
Day 12 diuresis: _____ ml
Day 13 diuresis: _____ ml
Day 14 diuresis: _____ ml

Immunosuppressive therapy and rejection

Prednisolon: [ ] yes [ ] no
Cyclosporin: [ ] yes [ ] no
Tacrolimus: [ ] yes [ ] no
Azathioprine: [ ] yes [ ] no
MMF: [ ] yes [ ] no
ATG: [ ] yes [ ] no
IL-2 receptor antagonists: [ ] yes [ ] no
Other immunosuppressive drugs: _____
Number of treatments for rejection day 1 - 14:
Prednisolon: ____
Other: ____
Rejection biopsy proven: [ ] yes [ ] no
Calcineurin inhibitor toxicity day 1 - 14 (based on levels): [ ] yes [ ] no
Remarks: _____

Dopamine and Lasix

Post-operative dopamine: [ ] yes [ ] no
Post-operative Lasix: [ ] yes [ ] no

Dialysis requirement day 1 - 14

Dialysis type: [ ] CAPD [ ] hemodialysis
Day 1 dialysis required: [ ] yes [ ] no
Day 2 dialysis required: [ ] yes [ ] no
Day 3 dialysis required: [ ] yes [ ] no
Day 4 dialysis required: [ ] yes [ ] no
Day 5 dialysis required: [ ] yes [ ] no
Day 6 dialysis required: [ ] yes [ ] no
Day 7 dialysis required: [ ] yes [ ] no
Day 8 dialysis required: [ ] yes [ ] no
Day 9 dialysis required: [ ] yes [ ] no
Day 10 dialysis required: [ ] yes [ ] no
Day 11 dialysis required: [ ] yes [ ] no
Day 12 dialysis required: [ ] yes [ ] no
Day 13 dialysis required: [ ] yes [ ] no
Day 14 dialysis required: [ ] yes [ ] no

Discharge / readmission

Date of primary post-Tx discharge (dd-mm-yy): __-__-__
Readmission within 3 months post-tx: [ ] yes [ ] no
Reason for readmission: _____
Nr. of in hospital days after readmission: _____

Follow up at 1 month post transplant

Graft failure: [ ] yes [ ] no
Date of graft failure (dd-mm-yy): __-__-__
Primary cause:
[ ] immunologic
[ ] preservation
[ ] technical - arterial
[ ] technical – venous
[ ] infection – bacterial
[ ] infection – viral
[ ] other
Graft removal: [ ] yes [ ] no
Death: [ ] yes [ ] no
Date of death (dd-mm-yy): __-__-__
Cause of death: [ ] Tx-related [ ] non-Tx-related
Serum creatinine at 1 month: _____ umol/l
Creatinine clearance at 1 month: _____ ml/min.
Total nr. of dialysis treatments post-Tx: _____
Currently on dialysis: [ ] yes [ ] no
dialysis type: [ ] CAPD [ ] hemodialysis
Date of last dialysis (dd-mm-yy): __-__-__
Nr. of rejection periods (day 15 – 1 month): _____
Complications interferring with graft function not mentioned above: _____

Follow up at 3 months post transplant

Graft failure: [ ] yes [ ] no
Date of graft failure (dd-mm-yy): __-__-__
Primary cause:
[ ] immunologic
[ ] preservation
[ ] technical - arterial
[ ] technical – venous
[ ] infection – bacterial
[ ] infection – viral
[ ] other
Graft removal: [ ] yes [ ] no
Death: [ ] yes [ ] no
Date of death (dd-mm-yy): __-__-__
Cause of death: [ ] Tx-related [ ] non-Tx-related
Serum creatinine at 3 months: _____ umol/l
Creatinine clearance at 3 months: _____ ml/min.
Total nr. of dialysis treatments post-Tx: _____
Currently on dialysis: [ ] yes [ ] no
dialysis type: [ ] CAPD [ ] hemodialysis
Date of last dialysis (dd-mm-yy): __-__-__
Nr. of rejection periods (1 – 3 months): _____
Complications interferring with graft function not mentioned above: _____

Follow up at 1 year post transplant

Graft failure: [ ] yes [ ] no
Date of graft failure (dd-mm-yy): __-__-__
Primary cause:
[ ] immunologic
[ ] preservation

[ ] technical - arterial
[ ] technical – venous
[ ] infection – bacterial
[ ] infection – viral
[ ] other

Graft removal: [ ] yes [ ] no
Death: [ ] yes [ ] no
Date of death (dd-mm-yy): __-__-__
Cause of death: [ ] Tx-related [ ] non-Tx-related
Serum creatinine at 1 year: _____ umol/l
Creatinine clearance at 1 year: _____ ml/min.
Total nr. of dialysis treatments post-Tx: _____
Currently on dialysis: [ ] yes [ ] no
dialysis type: [ ] CAPD [ ] hemodialysis
Date of last dialysis (dd-mm-yy): __-__-__
Nr. of rejection periods (3 – 12 months): _____
Complications interferring with graft function not mentioned above: _____

XVIII. Addendum 4: Procedure Overview Machine Preservation

Schematic map of the Netherlands, Belgium and Nordrhein Westfalen. Dots represent regional perfusion centers.

Goal

To describe the subsequent events from donor to recipient concerning the Machine Preservation Trial.

Rules of engagement

There are three Regional Perfusion Centers (RPCs): Leuven in Belgium, Groningen in the Netherlands and Essen in Nordrhein-Westfalen. Each RPC takes care of the LifePort logistics in its own country.

Working hours for team members

Every RPC has a regional supervisor and a team of perfusionists. Working hours for the perfusionist start when ET announces a potential donor and stop when the perfusionist travels home. As the average procedure of traveling to the donor center, to the transplant center and going home amounts to approximately 30 h, two perfusionists are involved in one procedure. One perfusionist will cover the donor logistics and one perfusionist the recipient logistics. The goal is to limit the maximum hours of work and split at a convenient moment.

LifePort travels alone

In order to limit the working hours for team members the LifePort may travel standalone from donor to recipient hospital. This implies that no solution aliquots can be taken in this period.

Scenario 1: Donor and recipient within the same trial region

Transplant coordinator

- Notifies ET desk about possible donor

ET desk

- Uses randomization scheme to determine which kidney is cold stored and which is machine perfused
- Calls perfusionist 1 on call in respective RPC: (= pre-warning ASAP, immediately after donor announcement to ET) B- Leuven; NL-Groningen; NRW-Essen
- Faxes ET donor form (4 pages) to RPC

Perfusionist 1

- Calls transplant coordinator
- Informs about time of procurement; hospital of procurement
- Records telephone numbers of coordinator and hospital in file
- Goes to RPC
- Prepares LifePort ice container
- Checks LifePort Batteries
- Collects one LifePort, Perfusion Circuit and spare disposables
  - cannulae
  - couplers
  - drapes
  - extra circuit
  - spare batteries
  - 2 liters of cold (!) KPS-1
- Takes necessary sampling materials
  - blood sampling
    - pre-tagged tubes (EDTA, blank)
    - dewer with ice
  - biopsy
    - Acecut Biopsy Gun 16G
    - small and large forceps

        - scalpelblade 15
        - pre-tagged 1,5 ml microcentrifuge tubes filled with 200 µl RNALater
        - pre-tagged 1,5 ml microcentrifuge tubes filled with formalin (blue)
    - perfusate sampling
        - alcohol swabs
        - syringes 10 ml
        - tagged tubes

- Prepares perfusion file
- Reports call in perfusion logbook
- Drives to donor hospital before the time of procurement
- Collects additional donor & procurement data in perfusion file
- Collects 2 tubes blood + spleen for x-matching (only in Belgium)
- Collects 2 x 10 ml (EDTA, no additives) of donor blood for Amendment 4 (donor markers) and stores it at room temperature (tagged as ET number + EDTA= e1 / blank = s(erum)-1) Example: 123456-e1 / 123456-s1
- Completes LifePort set-up

[Organ procurement: UW for flush out preferred, in case only kidneys: HTK may be used]

Procurement surgeon

- Splits kidneys
- Takes cortical biopsy just prior to MP

Perfusionist 1

- Splits and stores biopsy
- Submerges one half of biopsy in formalin in 1,5 ml microcentrifuge tube (blue) tagged as ET number + b(iopsy)1
- Submerges other half of biopsy in 200µl of RNALater in 1.5 ml microcentrifuge tube tagged as ET number + b(iopsy)1
- Scrubs in (if requested by surgeon), advises, helps cannulate kidney and helps connect kidney to perfusion circuit

- Sets initial Systolic Pressure on LifePort (35 mmHg)
- Starts MP
- Evaluates initial perfusion, corrects and adjusts (+ surgeon) if necessary
- Records initial MP parameters in perfusion file
- After 10 minutes takes 10ml (2 x 10 if donor > 55 yr.) perfusate samples (viability markers) tagged as ET-number + p0
- After 1 hour takes two 10 ml (three if donor > 55yr.) perfusate samples tagged as ET-number + p1 (store on ice)
    - one sample for chemistry analysis perfusate
    - one sample for viability markers
    - one sample for Amendment 5 (older donor)

Transplant coordinator

- Sends necro report to ET

ET desk

- Prepares allocation list
- Makes organ offer without revealing preservation method
- Informs transplant coordinator donor center about recipient location
- Arranges transport logistics (courier / plane)

Transplant coordinator

- (In Belgium) Sends blood / spleen to recipient center for crossmatching

Perfusionist 1

- Completes procurement data in perfusion file
- Completes Transportation Form (Checks organ type, blood group, ice, batteries, perfusion file, blood & spleen (in Belgium), and sterile drapes.)
- Attaches transportation form to LifePort exterior

- Checks batteries and replenishes ice before sending kidney on LifePort unattended to recipient center
- Drives back to RPC
- Centrifuges and stores samples at – 80°c
- Checks completeness of perfusion file (donor data, procurement data, LifePort perfusion data)
- Replenishes transportation cart for next case

Transplant coordinator / nephrologist of recipient center

- Receives kidney offer without knowing preservation method (preservation method revealed after offer has been accepted)

[NL & NRW: kidney on Lifeport + blood & spleen sent directly from donor hospital to transplant site]
[B: blood & spleen for crossmatching sent directly from donor hospital to transplant site by coordinator donor site; LifePort + extra blood & spleen will be kept at Belgian perfusion lab]

ET desk

- Calls perfusionist 2 on call, notifies location of transplant procedure

[In case of positive crossmatch for NL & NRW, transplant coordinator recipient center forwards LifePort & crossmatch specimen to next center on allocation list. For B: only forwards crossmatch specimen + informs RPC Leuven about new transplant location
ET notifies perfusionist 2 about new location]

Perfusionist 2

- Calls OR supervisor in recipient center and informs about scheduled start time of transplant procedure
- Goes to RPC
- Takes necessary sampling materials
    - biopsy
        - Acecut Biopsy Gun 16G
        - small and large forceps
        - scalpelblade 15

  - pre-tagged 1,5 ml microcentrifuge tubes filled with 200 µl RNALater
  - pre-tagged 1,5 ml microcentrifuge tubes filled with formalin (blue)
- o perfusate sampling
  - alcohol swabs
  - syringes 10 ml
  - tagged tubes

- Travels to transplant center before scheduled transplant time

- Upon arrival checks and records MP parameters without revealing these to transplant surgeon

- Collects recipient data

- Scrubs in, disconnects kidney and hands it to transplant surgeon (if requested by surgeon)

- Takes one 10 ml (two if donor > 55 Yr) perfusate samples (viability markers) and one 50 ml sample for chemistry analysis both tagged as ET-number + p3

Transplant surgeon

- Takes cortical biopsy 60' after reperfusion or just prior to closing

Perfusionist 2

- Notes time of reperfusion of the kidney (clamps open)

- Notes time biopsy was taken

- Splits and stores biopsy

- Submerges one half of biopsy in formalin in 1,5 ml microcentrifuge tube (blue) tagged as ET number + b(iopsy)2

- Submerges other half of biosy in 200 µl of RNALater in 1.5 ml microcentrifuge tube tagged as ET number + b(iopsy)2

- Collects transplant procedure data in file

- Drives back to RPC

- Spins and stores samples

- Cleans LifePort

- Downloads MP data from LifePort
- Checks completeness of file (recipient data, transplant procedure data, LifePort perfusion data)

RPC supervisor or delegate

- Files donor, recipient, procurement and transplant data into online ET database

ET desk

- Coordinates recipient follow–up data completion with recipient transplant center

[Amendment data filled out by amending RPC after analyzing bulk shipped samples: donor markers, biopsies, viability markers by RPC's Groningen & Essen; perfusate chemistry by RPC Leuven]

Scenario 2: Donor and recipient in different trial regions

Donor and recipient procedure: identical to Scenario 1, with the following remarks

ET desk

- Arranges that kidney on LifePort + blood and spleen will be send directly from donor hospital in one region to transplant hospital in the other region (by courier / plane)
- Calls perfusionist 2 on call of recipient region RPC, notifies location of transplant procedure

Perfusionist 1 (from donor RPC)

- Requests, in case of low LifePort stock due to high case volume, perfusionist 2 from recipient center to send empty LifePort ASAP

Perfusionist 2 (from recipient RPC)

- Calls OR coordinator of recipient hospital and informs about scheduled start time of transplant procedure
- Will perform perfusionist 2 duties as outlined in Scenario 1

Scenario 3: Recipient outside trial region

Donor procedure identical to Scenario 1; thereafter

ET desk

- Informs recipient hospital about preservation method after kidney has been accepted
- Arranges transport of kidney in LifePort via the usual route (courier / plane)

[No perfusionist will be present at the recipient site]

[No sampling will be done at recipient site]

Transplant surgeon (at recipient hospital outside trial region)

- Removes kidney from LifePort per instruction sheet
- Seals cassette with dual lids (perfusate remains inside)

ET desk

- Arranges transport for LifePort back to RPC of origin
- Requests recipient and transplant data (identical to kidneys stored on ice) from transplant center

RPC supervisor or delegate

[When LifePort (+ final perfusate still sitting within the circuit) has arrived in RPC of origin]

- Takes one 10 ml perfusate samples for viability markers
- Takes one 50ml perfusate sample for chemistry analysis
- Takes one 10 ml sample if donor > 55 yr
- Spins and stores samples
- Cleans LifePort
- Downloads MP data

ET desk

- Coordinates recipient follow–up data completion with recipient transplant center

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LifePort™
Kidney Transporter

User Training and Development Program

Level	Curriculum	Duration	Location	Price
1	LifePort™ General orientation and introduction to your new device and our people.	4 hours Day One	Onsite Start right and get comfortable in your own practice setting.	
	Perfusion Required course on basic techniques and protocols.	1-3 days Day Two and following	Onsite Learn by hands-on repetition	
	Ongoing Technical and professional support.	24/7/365	Worldwide Reach our technicians and perfusionists online or via telephone.	
Additional Staff Training				TBD

LifePort™
Kidney Transporter

Level 1 Training
Day 1 Agenda

I. Quick demonstration

II. Introduction and objectives

III. Technical presentation:

- Getting to know LifePort™
  - Transporter
  - Perfusion Circuit
  - Cannulae
- Perfusion mode operation
- Operation
- Cleaning
- Maintenance

IV. Detailed demonstration

V. Q & A, Feedback

VI. Day 2 preview

LifePort™
Kidney Transporter

Level 1 Training
Day 2 Agenda

I. Day 1 refresher: LifePort™ setup and operation
(Coordinators, students, surgeons)
Overview of study purpose and endpoints

II. Day 2 introduction:
- Expanding horizons: perfusion in motion
- Expanding criteria: the marginal/expanded or high risk kidney
- Non-heart beating donor kidney

III. Quick review and discussion:
- Scrubbing, gowning, and gloving
- Physiology and anatomy
- Tying knots
- Performing and closing biopsies
- Culturing
- Weighing and measuring of organ

IV. Wet lab (x 5–25 cases) 5-15 participants
- Equipment setup
- Isolation of vascular structure
- Cannulation
- Equipment operation

V. Perfusion monitoring and troubleshooting

VI. Data downloading, distribution & specimen collection and distribution

VII. Data submission and forms

VIII. Presentation of Level 1 certificates

IX. Overview of comparison study

X. Filing donor and recipient data and time frame

XI. Study outcomes