- **"A Randomized Trial of Mild Hypothermia and Machine Perfusion in Deceased Organ Donors for Protection against Delayed Graft Function in Kidney Transplant Recipients"**
- **The Regents of University of California, San Francisco, and Oregon Health & Science University**
- **Local PI:**
- **Local Study Coordinator :**
- **PI: Darren Malinoski, MD, FACS – malinosk@ohsu.edu, (503) 701-7628**
- **PI: Claus Niemann, MD – Claus.Niemann@ucsf.edu, (415) 502-2162**

BACKGROUND: In the initial Mild Hypothermia Randomized Control Trial (RCT), in collaboration with the UNOS Region 5 Donor Management Goals (DMG) Workgroup and Web Portal, the research team was able to conduct a multi-center RCT examining the benefits of mild hypothermia in donors after neurologic determination of death (DNDDs) on the outcomes of kidney transplantation. The trial was stopped early by the DSMB due to a significant positive benefit to kidney transplant recipients, including a 38% reduction in the odds of delayed graft function (DGF, the primary outcome measure of the trial). The results of this study have been published in the *New England Journal of Medicine* (July 2015). This research offers a zero-cost intervention that can substantially increase transplant success as well as the pool of potential donors.

To expand upon the success of the hypothermia study, the team is conducting a new RCT to test whether hypothermia is as effective as machine perfusion (MP) of kidneys from DNDDs. In an RCT conducted by the Eurotransplant International Foundation in 2009 (Moers et al. *NEJM*), the protective effect of MP (OR = 0.57) was similar to that found in our trial (OR = 0.62). However, the cost of MP can be very significant for organ procurement organizations (OPOs) and transplant centers.

MP of kidneys from deceased donors has been increasingly adopted by many centers even though clinical and cost effectiveness studies remain uncertain in the United States. Between 2012 and 2014, out of 31,798 kidneys available for transplant, 11,998 (38%) of them were machine perfused. Over the same three-year period, the number of kidneys pumped annually increased by over 20%.

This is an opportune time to investigate the effectiveness of MP compared to mild hypothermia, as there are enough OPOs currently using MP that if mild hypothermia was found to be a non-inferior intervention, there would be considerable cost savings. Similarly, over 60% of kidneys do not receive machine perfusion and a positive finding in favor of machine perfusion would likely lead to rapid increase in use. In addition, DGF still occurs in up to 56% of high-risk kidneys despite using one of these protective measures and their combined use may be the best approach moving forward. Either way, a new evidence-based standard will be created that will significantly affect the way kidney transplants are handled.

METHODS: This will be a pragmatic multi-site randomized controlled trial that bases enrollment on each OPO/Donation Service Area's current pumping criteria **(Figure 1**, page 2**).** There will be two main groups of DNDDs, (1) those that are "*pump eligible*" based on current practice (this group typically resembles traditional expanded criteria donors, but is increased in some areas) and (2) those that are lower risk and whose kidneys do not receive MP ("*not pump eligible*"). Kidneys from donors who are considered "pump eligible" currently receive MP based on their increased risk for failure. In this trial, "pump eligible" DNDDs will be randomized to one of three groups (**Figure 2**): (1) normothermia (36.5-37.5 C) plus MP of both kidneys (standard of practice control group), (2) mild hypothermia (34-35 C) plus MP of the left kidney only, and (3) mild hypothermia plus MP of the right kidney only. In this manner, the same number of kidneys will be randomized to each of the three treatment strategies (MP alone, mild hypothermia alone, or MP+hypothermia).

It is important to note that kidneys from "pump eligible"/higher risk DNDDs will still receive one form of protection and possibly two.

In contrast, "not pump eligible" DNDDs will only be randomized to one of two groups: (1) therapeutic mild hypothermia or (2) normothermia. Being that our first trial was stopped early for efficacy in the overall DNDD population, there was insufficient statistical power to confirm a benefit in standard criteria donors (p=0.1 at stoppage). The purpose of this arm of the trial is to validate the protective effect of hypothermia in a larger sample size of lower-risk / "not pump eligible" donors.

The following objectives will be addressed by the trial:

- Determine the non-inferiority of a hypothermia-only strategy to a standard pump-only strategy in high risk DNDDs
- Evaluate the superiority of a combined hypothermia+MP strategy to both hypothermia or MP alone in high risk DNDDs
- The superiority of mild hypothermia versus standard of care normothermia in lower risk, "not pump eligible" DNDDs
- The safety of the hypothermia strategy with respect to the function of "bystander" organs (e.g., heart, lung, liver, pancreas)

This protocol has been approved by the UNOS Region 5 Research Committee. The following additional steps will be taken:

- Only donors whose families and/or advanced directives (donor registry) have authorized research will be included.
- **The outcomes of all non-targeted, bystander organs (liver, lung, heart, pancreas), will be included in a safety analysis** and all organ offers from DNDDs enrolled in the study will include a message in the "Donor Highlights" section of DonorNet®, a copy of the study summary will be attached to the record, and allocation/transplantation will occur based on standard practice.
- There will not be any interaction between the study team and the transplant recipients and no additional data will be collected.
- Recipient graft function data will be derived from standard UNet forms and obtained from the OPTN in a de-identified format.
- Transplant centers receiving organs will not be engaged in research related to this study.

- **"A Randomized Trial of Mild Hypothermia and Machine Perfusion in Deceased Organ Donors for Protection against Delayed Graft Function in Kidney Transplant Recipients"**
- **The Regents of University of California, San Francisco, and Oregon Health & Science University**
- **Local PI:**
- **Local Study Coordinator :**
- **PI: Darren Malinoski, MD, FACS – malinosk@ohsu.edu, (503) 701-7628**
- **PI: Claus Niemann, MD – Claus.Niemann@ucsf.edu, (415) 502-2162**

Figure 1 – Participating OPO "Pump Eligible" Criteria

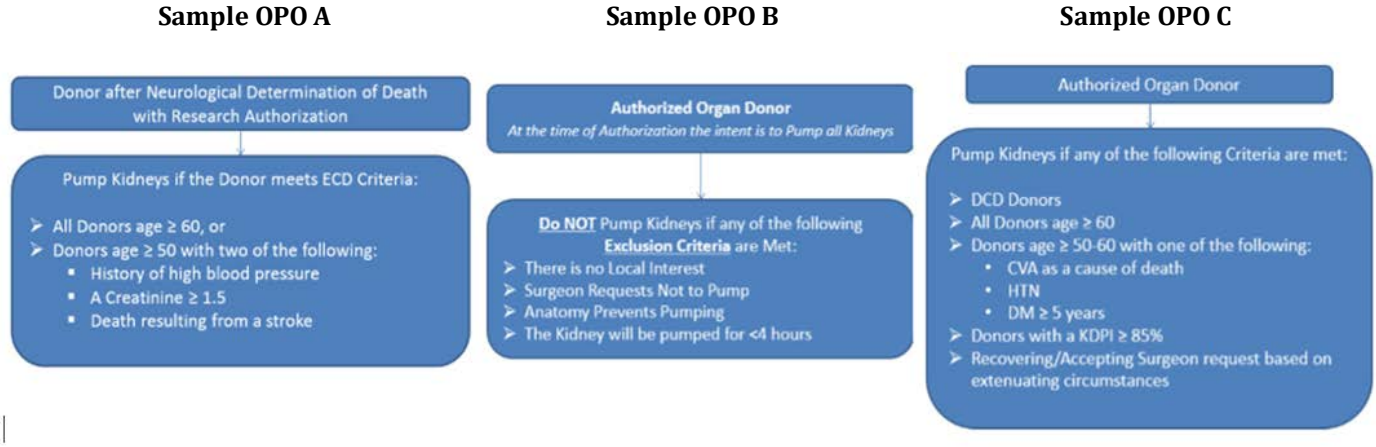
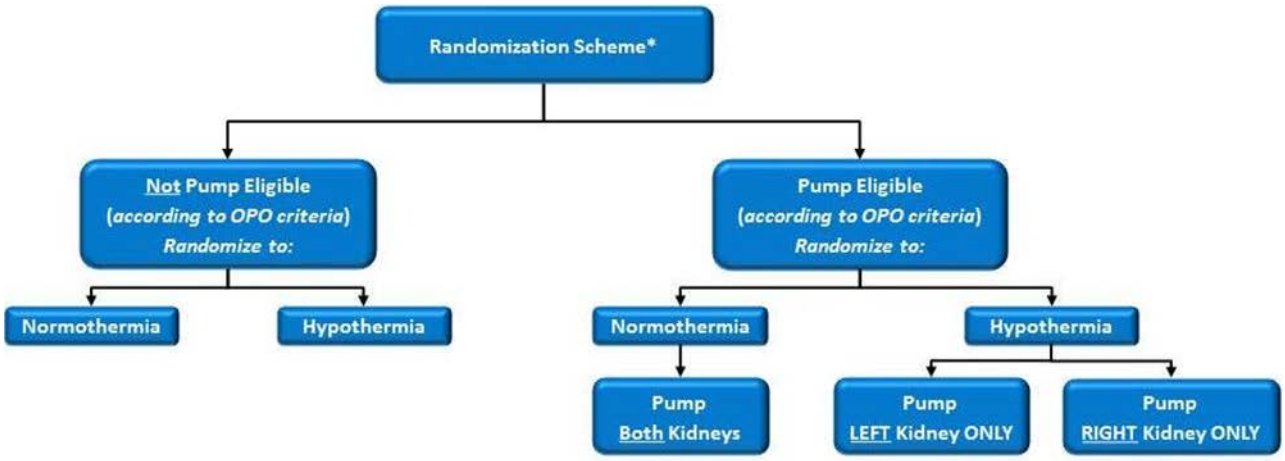


Figure 2 – Randomization Scheme



***Note:** Once pump eligibility is determined, the assigned OPO Study Coordinator will enter the donor into www.randomize.net which will automatically randomize the donor into a **Treatment Group Assignment**.*