Study Protocol PDF Trial

Study working title:

The PDF Trial: Preventing Delayed Graft Function in Kidney Transplant Patients: A single-centre, randomised, feasibility trial

Version 1.0 / March 27, 2024

Principle Investigator

PI	Stuart A McCluskey
Email	stuart.mccluskey@uhn.ca
Phone	14-8561 Mobile 416 988 6233
Location	TGH, Eaton Building, 200 Elizabeth St, 3rd Floor, Room 3EN-405, Toronto, Ontario, Canada, M5G 2C4

Protocol authors	Marc Sicova, Anesthesiology Ryan McGinn, Anesthesiology Wilton van Klei, Anesthesiology Joseph Kim, Nephrology Stuart A. McCluskey, Anesthesiology
Principal investigator	Stuart A. McCluskey, MD, PhD, FRCPC
Co-investigators	Ryan McGinn, MD MSc FRCPC Wilton van Klei, MD, Anand Ghanekar, PhD, MD, FRCSC Matthanja Bieze, MD PhD Joseph Kim, MD FRCPC Sonia Rodriguez-Ramirez, MD FRCPC Yanhong Li, Statistician Anna Santiago, Statistician Segun Famure, Research Manager Jo Carroll, Study Coordinator
Document type	Study protocol
Document status	Version 1.0
Date	March 27, 2024

1. PROTOCOL SYNOPSIS

TITLE	The PDF Trial: Preventing Delayed Graft Function in Kidney Transplant Patients: A single-centre, randomised, feasibility trial
OBJECTIVES	**Primary Objectives** To determine the feasibility of recruiting and randomizing kidney transplant recipients to an RCT evaluating the administration of a perioperative bundle of care. The bundle of care is based on the best available evidence and includes the use of plasmalyte for fluid management, maintaining mean arterial pressure > 75 mmHg, identify and treat blood glucose > 9 mmol/L, and a restrictive RBC transfusion trigger (i.e. hemoglobin (Hb) < 70 g/L). **Secondary Objectives** To determine protocol adherence and follow-up rates.
DESIGN / PHASE	Randomized controlled feasibility trial.
STUDY DURATION	September 1, 2024 – October 1, 2025
CENTRE	Toronto General Hospital, Department of Anesthesia and Pain Management and Department of Nephrology, Ajmera Transplant Centre, Toronto General Hospital, University Health Network, Toronto, ON, Canada
PATIENTS / GROUPS	• Patients undergoing a kidney transplantation
INCLUSION CRITERIA	• ≥ 18 years of age undergoing kidney transplantation surgery • Recipients of living or deceased kidney donors Note: If a patient has one or more kidney transplant surgeries in the study period, each transplant surgery will be considered separately.
EXCLUSION CRITERIA	• Multi-organ transplant • Pre-emptive kidney transplantation (transplant prior to initiation of dialysis) • Functional arterial line not available
STUDY PERIODS	TBD
ENDPOINTS	**Primary endpoints – Feasibility Outcomes** • Recruitment rate **Secondary endpoints – 3 months following kidney transplant** • >90% success in implementing the full bundle of care and each item individually within the bundle • Follow-up rate

	Covariates: • Demographic factors (age, sex, height, weight) • Elixhauser comorbidities • Pre-operative hemoglobin and other laboratory values (INR, hematocrit, platelet, albumin, serum creatinine) • Pre-operative erythroid stimulating agents during the 30 days prior to kidney transplantation • Pre-operative iron supplementation (iv and oral) • Living or deceased donor kidney
STATISTICAL METHODOLOGY	Categorical variables will be summarized as frequencies and percentages; continuous variables as means with standard deviation. The unadjusted association of potential predictors of the secondary outcomes will be evaluated for both continuous (t test, Wilcoxon rank sum test) and categorical ($\chi 2$ test, Fisher's exact test, Mantel-Haenszel $\chi 2$ test) variables. Independent predictors of the secondary outcomes will be identified by multivariable logistic regression analysis.

2. LIST OF ABBREVATIONS

CBC	Complete blood count
DD-KT	Deceased donor kidney transplant recipient
DGF	Delayed graft function
DGF-CRR	DGF based on serum creatinine reduction ratio
DGF-D	DGF based on the need for dialysis within the first week of transplantation
ESA	Erythroid stimulating agents
INR	International normalized ratio
IV	Intra-venous
Kidney Donor Prediction Index	KDPI
LD-KT	Living donor kidney transplant recipient
RBC	Red blood cell
TGH	Toronto General Hospital

3. TABLE OF CONTENTS

4. BACKGROUND INFORMATION

4.1 Background/Introduction

Kidney transplantation (KT) is the treatment of choice for patients with end-stage kidney disease, improving survival, and quality of life.[1] Unfortunately, delayed graft function (DGF) occurs in 20-30% of deceased donor kidney transplant (DD-KT) recipients and often requires dialysis.[2-5] DGF-D refers to the requirement for at least one session of dialysis within the first week after transplantation, and is associated with worse graft and patient survival making efforts to avoid this complication important.[6,7] Dialysis is required much less often after living donor kidney transplantation (LD-KT) (1-3%).[8] In order to assess graft function after LD-KT, a delay in kidney graft function is better identified by a suboptimal (i.e., < 30%) reduction in serum creatinine between postoperative days 1 and 2 (DGF-CRR).[8-12] DGF after LD-KT is also associated with long-term complications.[13]

Optimizing perioperative care to support graft kidney function in order to decrease the incidence of DGF may improve outcomes, reduce hospital length of stay and mitigate morbidity.[14-16] In other surgery, postoperative acute kidney injury (AKI) has many similarities to DGF and measures to prevent AKI may be used to guide perioperative care in KT. For example, in cardiac surgery The Kidney Disease: Improving Global Outcomes (KDIGO) guidelines have been shown to reduce the incidence and severity of AKI.[17] A single centre, randomized controlled trial determined that the use of the KDIGO guidelines resulted in a 16% absolute risk reduction of AKI following cardiac surgery, compared to routine perioperative care.[18] In addition, several Enhanced Recovery After Surgery (ERAS) protocols developed for the non-cardiac surgery population have been proposed for KT. Similar to the KDIGO Guidelines, avoiding nephrotoxins, maintaining normothermia and euglycemia, and early ambulation are proposed.[19-21]

Still, these suggestions do not consider the most recent evidence and do not include other perioperative factors that impact graft function after KT, such as hypotension,[22] type of intravenous fluid used,[23] red blood cell transfusions[24-28] and glycemic control[29]. For example, we recently found that intraoperative hypotension was associated with DGF-CRR following KT, with a threshold mean arterial blood pressure of 65 mmHg (manuscript submitted). Furthermore, the odds of DGF-CRR increased when the MAP was < 75 mmHg. A method to manage blood pressure during KT is administering intravenous fluids, either with crystalloids or blood. A recent multicenter, randomized controlled trial showed that plasmalyte, a balanced crystalloid fluid, reduces the incidence of DGF-D after DD-KT by 25% (i.e. 40% to 30%) compared to normal saline.[30] In the KT population, blood transfusion was reported to be associated with reduced graft function, early graft loss, and reduced patient survival.[24-28] As the vast majority of patients receiving blood transfusion receive only 1-2 units, many transfusion events likely could be avoided with better adherence to appropriate triggers, potentially leading to improved outcomes following KT. Finally, irrespective of a pre-transplant diabetes diagnosis, hyperglycemia (blood sugar > 9.0 mmol/L) in the post-anesthesia care unit is associated with an increased odds of DGF-D following KT. Therefore, glucose control (i.e. blood sugar < 9 mmol/L) may improve immediate graft function in this patient population.

4.2 Study Rationale

Preserving graft function following kidney transplant is critical to ensuring favourable outcomes. We propose to study the application of a modified version of the KDIGO guidelines for kidney transplant patients. This perioperative bundle of care includes maintenance of MAP >75 mmHg after kidney reperfusion, use of plasmalyte for fluid administration, reducing red blood cell transfusion and identifying and treating a blood sugar > 9 mmol/L. Although this care bundle shows promise for reducing the risk of DGF following transplant, this should first be investigated in a pilot, feasibility trial to ensure successful patient recruitment and adherence to the study protocol, prior to undergoing a full RCT.

5. STUDY OBJECTIVES (HYPOTHESIS)

We hypothesize that the proposed perioperative bundle of care will be feasible to implement and improve postoperative outcomes for kidney transplant recipients.

5.1 Primary Objective

To determine the feasibility of recruiting and randomizing kidney transplant recipients to an RCT evaluating the administration of a perioperative bundle of care.

5.2 Secondary Objectives

To determine protocol adherence and follow-up rates.

6. STUDY DESIGN

6.1 Study type

Randomized controlled feasibility trial

6.2 Study population

Patients ≥18 years of age undergoing kidney transplantation at Toronto General Hospital (TGH).

6.2.1 Department

The study will be conducted by the Department of Anesthesia and Pain Management and the Department of Transplant Nephrology, Ajmera Transplant Centre at the Toronto General Hospital, University Health Network.

6.2.2 Subjects

Patients who are admitted to hospital to undergo KT at TGH. Patients will be screened for eligibility and included in the study if the criteria listed below are met:

6.2.3 Inclusion criteria

- ≥ 18 years
- Patients undergoing kidney transplantation
- Living and deceased donor recipients

6.2.4 Exclusion criteria

- Multi-organ transplant
- Pre-emptive KT
- Arterial line not planned for surgery

6.2.5 Study duration

We anticipate completing data collection, cleaning, and analysis by the end of December 2025.

6.3 Outcomes

6.3.1 Primary outcomes

Our primary outcome is the feasibility of implementing a perioperative bundle of care for KT patients. The specific outcome is:

- **Recruitment rate**, which will be the number of patients who are approached to participate in the study and who are randomized to either the treatment or routine clinical care group, as a percentage of the total number of eligible transplant patients. In order to complete a full multicenter trial in a reasonable time period (2-3 years), the number needed to recruit per week is at least 1 patient, but we will aim to recruit 2 patients per week.

6.3.2 Secondary outcomes

- **Protocol adherence.** The aim is for ≥90% compliance with at least 3 of the 4 components of the perioperative bundle of care i.e. use of Plasmalyte for fluid management, maintenance of MAP > 75 mmHg from time of cross-clamp removal to 4-hours post KT, the initiation of an insulin infusion to maintain a serum blood sugar < 9 mmol/L and avoidance of RBC transfusion unless the Hb < 70 g/L or symptoms of oxygen insufficiency and Hb < 80 g/L.
- **Patient follow-up.** For this trial, patient follow-up will end at 90-days after transplant and the target is to follow ≥90% of the patients until this time. DGF and acute rejection will not be assessed in the feasibility trial, and instead this data will be analyzed in the full trial. Patient follow-up of clinical outcomes will occur at 1-year following KT in the full trial.

6.3.3 Covariates

- Baseline patient factors: age, sex, height and weight
- Transplant details: graft type (deceased or living donor), kidney donor prediction index (KDPI)[31] etiology of kidney failure, transplant number, preoperative hemoglobin optimization strategies (iron, erythroid stimulating agents), previous blood transfusion, method and duration of pre-transplant dialysis.
- Comorbidities: previous abdominal surgery, coronary artery disease, heart failure, cardiomyopathy, hypertension, diabetes mellitus (diet, oral medications or insulin control), chronic obstructive pulmonary disease, smoking history, medications including anticoagulants and anti-platelets.
- Immediate preoperative laboratory values: hemoglobin, hematocrit, platelet count, INR, albumin, ferritin, iron saturation, glucose and creatinine.

7. METHODOLOGY

7.1 Screening and inclusion

Eligible patients will be identified by a member of the perioperative clinical transplant team. Surgical consent includes consent for research activities, which provides the transplant team member the opportunity to ask the patient if a member of the study team can discuss the study details and potential participation. Informed consent to participate in the study will be obtained from the patient by a study team member or member of the patient's circle of care after admission for KT. Patients are typically admitted 12-36 hours prior to KT, however we will ensure patients are consented at a minimum of 6 hours prior to KT for study participation. This provides the necessary time to allow the patient to consider participation, to randomize study participants, and communicate with the transplant team regarding the patient's group allocation.

7.2 Sample size considerations

Based on our transplant activity over the last several years, we conduct an average of at least 5 KTs per week. We expect 40% of eligible patients to be recruited for the study, based on a similar trial and patient population.[23] A sample size of 25 patients per group will provide sufficient statistical power to be within the 95% confidence interval if we are able to recruit a total of 43-57 patients within 1-year (50 weeks). Furthermore, this sample size will provide a 95% confidence interval of ~70% to ~98% around the expected ≥90% compliance with the study protocol and ≥90% complete follow-up 90-days post KT.

7.3 Data sources

EPIC.

7.4 Study intervention

Patients will be randomized 1:1 to either routine care or to the treatment group. The treatment group will receive a perioperative bundle of care that will be a modified version of the KDIGO guidelines and will include: use of Plasmalyte for fluid management, maintenance of MAP >75 mmHg, identifying and treating blood sugar > 9 mmol/L, and avoidance of RBC transfusion unless the hemoglobin < 70 g/L or symptoms of oxygen insufficiency and hemoglobin < 80 g/L.

7.5 Statistical methods and endpoints analysis

Categorical variables will be summarized as frequencies and percentages; continuous variables as means with standard deviation. The unadjusted association of potential predictors of the secondary outcomes will be evaluated for both continuous (t test, Wilcoxon rank sum test) and categorical ($\chi 2$ test, Fisher's exact test, Mantel-Haenszel $\chi 2$ test) variables. Independent predictors of the secondary outcomes will be identified by multivariable logistic regression analysis.

7.6 Statistical software

SPSS, R studio, and SAS.

7.7 Data management

All study data will be kept on secure, password-protected storage media, and with restricted access at the Department of Anesthesiology and Pain Medicine and Transplant Nephrology, at TGH. Only research personnel involved in the study will have access to the study data. The files resulting from the data analysis will be password protected. A Participant Master Log will be maintained with the participant's MRNs to facilitate data collection. The Participant Master List will be kept securely on a password-protected storage platform, UHN One Drive. Apart from the participant Master List, all data will be pseudonymized using an independent study ID before analysis and de-identified before publishing. Study data and all files resulting from the analysis will be kept on UHN One Drive for 10 years after the conclusion of the study.

8. ETHICAL AND LEGAL ASPECTS

8.1 Informed consent

A transplant team member will identify eligible patients who present on admission for KT. If deemed eligible, the transplant team member will inform the patient of the study, and ask if a member of the study or transplant team can discuss the study details and potential participation. If the patient is willing to participate, the study or transplant team member will obtain informed consent from the patient.

8.2 Confidentiality

The information contained in this document, especially unpublished data, is the property of the Investigators. It is therefore provided to you in confidence as an Investigator, potential Investigator, or consultant for review by you, your staff, and an Ethics Committee or Institutional Review Board. It is understood that this information will not be disclosed to others without written authorization from an Investigator.

8.3 Ethics and Good Scientific Practice

The investigators will ensure that this study is conducted in full conformance with the principles of the "Declaration of Helsinki" (as amended at the 64th WMA General Assembly, Fortaleza, Brazil, 2013) and with the laws and regulations of the country in which the clinical research is conducted.

8.4 Benefit and risk assessment

This pilot study seeks to assess whether we can recruit kidney transplant patients for an RCT and assess compliance to a surgical care bundle aiming to reduce the incidence of delayed graft function. Preserving graft function after transplant is critical to ensuring favourable outcomes. The primary objectives of this study will assess protocol adherence and outcome collection rates. The results of this pilot trial will serve as the rationale to conduct a large, randomized controlled trial with the use of the surgical care bundle to enhance the recovery of kidney transplant patients.

This study poses a potential risk to study participants, as it will impact their care. Firstly, MAP will be maintained >75 mmHg, which is a ~10 mmHg difference above the current MAP standard of care (i.e., 65 mmHg). For the second component, normal saline is a routinely used fluid for kidney transplants, but instead patients will receive plasmalyte. For the third component, the patient’s clinical care team will avoid hyperglycemia in the

72h post-transplant. Although this should be completed in routine clinical care, we are directly specifying the patient's blood glucose will be maintained <9 mmol/L. For the final component of the care bundle, we would ask the surgical care team to avoid RBC transfusions, and to only transfuse if the hemoglobin falls below 70 g/L or a symptom that indicates inadequate oxygen delivery is present. Although kidney transplants are associated with a relatively low amount of blood loss, and 30-50% of patients receive 1-2 units of RBCs, we are asking the surgical care team to follow a restrictive protocol with the administration of RBC transfusions.

Patients will be informed that the control group will consist of routine clinical care, (i.e., what is routine KT surgery) while the treatment arm will receive a bundle of care which may potentially support the health of their new kidney.

All data will be de-identified before analysis and publishing, and all precautions will be taken to ensure data security, privacy, and confidentiality.

9. FINANCIAL ASPECTS

The Funds for the Fraser Elliot Chain in Cardiac Anesthesia and Department of Anesthesia and Pain Management is the sponsor of this study. Internal funding set aside. A detailed budget can be found below.

Category	**Detailed Breakdown**	**Anticipated Funding Need**
Personnel	Research Coordinator - $81,250 per annum inclusive of benefits, at 0.5 full-time equivalent	$40,625
Database	REDCAP build	$2,000
Statistical analysis	35 hours x $100	$3,500
Research Publication	Open Access Publication Costs, Conference Registration, and Knowledge Dissemination	$3,800
Other Costs	Stationary, paper for CRFs	$ 400
Total Anticipated Costs		$49,929

10. REFERENCES

1. Abecassis M, Bartlett ST, Collins AJ, et al. Kidney transplantation as primary therapy for end-stage renal disease: a National Kidney Foundation/Kidney Disease Outcomes Quality Initiative (NKF/KDOQI™) conference. Clinical Journal of the American Society of Nephrology 2008;3:471-80.
2. Cecka JM. The UNOS renal transplant registry. Clinical transplants 2002:1-20.
3. Shoskes D, Cecka J. Effect of delayed graft function on short-and long-term kidney graft survival. Clinical transplants 1997:297-303.
4. Mannon RB. Delayed Graft Function: The AKI of Kidney Transplantation. Nephron 2018;140:94-8.
5. Mendez NV, Raveh Y, Livingstone JJ, et al. Perioperative risk factors associated with delayed graft function following deceased donor kidney transplantation: A retrospective, single center study. World journal of transplantation 2021;11:114.
6. Grosso G, Corona D, Mistretta A, et al. Delayed graft function and long-term outcome in kidney transplantation. Transplant Proc 2012;44:1879-83.
7. Wu WK, Famure O, Li Y, Kim SJ. Delayed graft function and the risk of acute rejection in the modern era of kidney transplantation. Kidney Int 2015;88:851-8.
8. Damodaran S, Bullock B, Ekwenna O, et al. Risk factors for delayed graft function and their impact on graft outcomes in live donor kidney transplantation. International urology and nephrology 2021;53:439-46.
9. Kinoshita Y, Katano S, Nishida S, et al. Creatinine reduction ratio on postoperative day 2 predicts long-term outcomes after living donor kidney transplantation. International Journal of Urology 2022;29:114-20.
10. Rodrigo E, Ruiz JC, Piñera C, et al. Creatinine reduction ratio on post-transplant day two as criterion in defining delayed graft function. American Journal of Transplantation 2004;4:1163-9.
11. Vilar E, Varagunam M, Yaqoob MM, Raftery M, Thuraisingham R. Creatinine reduction ratio: a useful marker to identify medium and high-risk renal transplants. Transplantation 2010;89:97-103.
12. Govani MV, Kwon O, Batiuk TD, Milgrom ML, Filo RS. Creatinine reduction ratio and 24-hour creatinine excretion on posttransplant day two: simple and objective tools to define graft function. J Am Soc Nephrol 2002;13:1645-9.
13. Li MT, Ramakrishnan A, Yu M, et al. Effects of Delayed Graft Function on Transplant Outcomes: A Meta-analysis. Transplantation Direct 2023;9:e1433.
14. Gaston RS, Danovitch GM, Adams PL, et al. The report of a national conference on the wait list for kidney transplantation. American Journal of Transplantation 2003;3:775-85.
15. Clayton LM, Rizzolo D, Nair V. Kidney transplant wait list: review and current trends. JAAPA 2018;31:1-5.
16. Kinoshita Y, Katano S, Nishida S, et al. Creatinine reduction ratio on postoperative day 2 predicts long-term outcomes after living donor kidney transplantation. Int J Urol 2022;29:114-20.
17. Meersch M, Schmidt C, Hoffmeier A, et al. Prevention of cardiac surgery-associated AKI by implementing the KDIGO guidelines in high risk patients identified by biomarkers: the PrevAKI randomized controlled trial. Intensive care medicine 2017;43:1551-61.
18. Zarbock A, Küllmar M, Ostermann M, et al. Prevention of cardiac surgery–associated acute kidney injury by implementing the KDIGO guidelines in high-risk patients identified by biomarkers: The PrevAKI-multicenter randomized controlled trial. Anesthesia & Analgesia 2021;133:292-302.
19. Tan JHS, Bhatia K, Sharma V, et al. Enhanced recovery after surgery recommendations for renal transplantation: guidelines. Br J Surg 2022;110:57-9.
20. Kruszyna T, Niekowal B, Krasnicka M, Sadowski J. Enhanced Recovery After Kidney Transplantation Surgery. Transplant Proc 2016;48:1461-5.

21. Elsabbagh AM, Ghoneim I, Moiz A, Welch K, Brown JS. Enhanced Recovery After Surgery Pathway in Kidney Transplantation: The Road Less Traveled. Transplant Direct 2022;8:e1333.
22. Sandid MS, Assi MA, Hall S. Intraoperative hypotension and prolonged operative time as risk factors for slow graft function in kidney transplant recipients. Clinical transplantation 2006;20:762-8.
23. Collins MG, Fahim MA, Pascoe EM, et al. Balanced crystalloid solution versus saline in deceased donor kidney transplantation (BEST-Fluids): a pragmatic, double-blind, randomised, controlled trial. The Lancet 2023;402:105-17.
24. Rodriguez-Espinosa D, Broseta JJ, Rosario A, et al. Challenges in perioperative blood transfusions in kidney transplantation and the need for Patient Blood Management. Blood Transfus 2023.
25. Kang ZY, Liu C, Liu W, Li D. Association between blood transfusion after kidney transplantation and risk for the development of de novo HLA donor-specific antibodies and poor clinical outcomes: A single-center retrospective study. Transpl Immunol 2023;81:101930.
26. O'Brien FJ, Lineen J, Kennedy CM, et al. Effect of perioperative blood transfusions on long term graft outcomes in renal transplant patients
1. ClinNephrol 2012;77:432-7.
27. Hassan S, Mumford L, Robinson S, et al. Blood transfusions post kidney transplantation are associated with inferior allograft and patient survival-it is time for rigorous patient blood management. Front Nephrol 2023;3:1236520.
28. Hassan S, Mumford L, Robinson S, et al. Blood transfusions post kidney transplantation are associated with inferior allograft and patient survival—it is time for rigorous patient blood management. Frontiers in Nephrology 2023;3.
29. Parekh J, Roll GR, Feng S, Niemann CU, Hirose R. Peri-operative hyperglycemia is associated with delayed graft function in deceased donor renal transplantation. Clinical transplantation 2013;27:E424-E30.
30. Collins MG, Fahim MA, Pascoe EM, et al. Balanced crystalloid solution versus saline in deceased donor kidney transplantation (BEST-Fluids): a pragmatic, double-blind, randomised, controlled trial. Lancet 2023;402:105-17.
31. Rao PS, Schaubel DE, Guidinger MK, et al. A comprehensive risk quantification score for deceased donor kidneys: the kidney donor risk index. Transplantation 2009;88:231-6.