Transplant Social Worker Support for Live Kidney Donation in African Americans

Statistical Analysis Plan
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1 Study Overview

"The Talking about Living Kidney Donation Support (TALKS) study is a randomized controlled trial designed to test the incremental effectiveness of (1) a culturally sensitive educational and behavioral social worker intervention and (2) a live donor financial assistance intervention to improve potential kidney recipient activation (i.e., discussions with physicians and family about live donor kidney transplant [LDKT]) and live kidney donation among African American patients on the deceased donor kidney transplant waiting list at Duke University Medical Center."

1.1 Study Aims

1.1.1 Primary and Secondary Aim

To assess the effects of behavioral and financial interventions compared to usual care on 1) LDKT activation (primary) and 2) scenario movement (secondary). ("Table 2" in Appendix)

1.1.2 Tertiary Aims

1. Describe characteristics and correlates of pursuit of LDKT ("Table 3" in Appendix)
2. Summarize use of TALKS materials, attendance of TALK SWI sessions, and satisfaction with sessions. (Section 3 of Appendix)
3. Summarize use of financial assistance program
4. Summarize outcomes of donor inquiries (e.g., did it lead to evaluation, were they eligible, ineligible, etc.)

1.2 Study Hypotheses

1.2.1 Primary Hypothesis

Those in the two intervention groups will have higher levels of activation and scenario movement compared to those in usual care.

1.2.2 Secondary Hypotheses

These aims are descriptive and no formal hypotheses will be tested.

2 Study Population

2.1 Inclusion/Exclusion Criteria

The target population, and inclusion/exclusion criteria have been previously published (Protocol Paper, 2015). Briefly, participants were African-American adults (18+ years old) with ESRD on the transplant waiting list at Duke. They had no prior LDKT. Family members and friends were also recruited into the study to attend the SWI meetings.

The data consist of a baseline visit, a 4-month visit, and a follow-up visit. EHR data were also collected up to 12 months' post randomization.

2.2 Data Acquisition

Data were obtained via primary data collection through telephone surveys administered by study personnel. Study personnel entered the data into a REDCap database and the study statistician downloads the raw data directly from REDCap using the SAS export tool. EHR data are obtained from data

pulls from the Duke Kidney and Pancreas Transplant Program by Tara Strigo. The statistician converted these pulls to SAS datasets and the original pulls were archived. The data are stored on the GIM server under BoulwarePrivate/TALKS.

3 Outcomes, Exposures, and Variables of Interest

3.1 Primary and Secondary Outcomes

1. Live kidney donor activation (primary): per the protocol, "defined as the composite rate of live kidney donor inquiries on behalf of patient participants, completed live kidney donor transplant evaluations, and live kidney donor transplants in each arm, ascertained via medical records maintained by the Duke Kidney and Pancreas Transplant Program."
   In other words: For each participant, the total number of donor inquires, evaluations, and LDKT over a 12-month period will be summed and defined as the live donor activation score. For example, if a participant had 5 inquiries, 2 evaluations, and an LDKT, then this person's score would be 8.
   In sensitivity analyses, we will look at these individually, and the composite at 24 months.
2. Pursuit of LDKT (secondary) (scenario): Assessed by two questions, Q1: "Has a family member or friend told you that they would give you a kidney?" And Q2: "Have you talked with family and/or friends about the possibility of someone giving you a kidney?". Participants will be categorized into 3 groups: 3=identified a donor (answered "yes" to Q1); 2=talked with family members/friends but did not identify a donor ("no" to Q1 and "yes" to Q2); 1=did not talk to family members/friends ("no" to Q1 and Q2). Note that once a person has reached a level, he cannot regress to a previous level, e.g., if at level 2 at randomization, the person cannot be at level 1 at month 4.

3.2 Tertiary Outcomes

1. Interest in LDKT (lkt_interest): assessed by the question "On a scale of 0-10, with 0 being not at all interested and 10 being extremely interested, how interested do you think you would be in getting a kidney from your family member?"
2. Factual knowledge of LDKT (lktknow1- lktknow10): assessed by 10 factual true/false questions, with a score ranging from 0 (none answered correctly) to 10 (all answered correctly).
3. Perceived knowledge of LDKT (ldt_info11): assess by the question "How much knowledge do you feel you have now about live donor kidney transplant?" (0=none to 2=a great deal)
4. Knowledge of financial assistance programs: assessed by three questions:
   a. ldt_info13: Are you aware of any programs that cover the costs of medical evaluations or medical treatment for people who are thinking about donating a kidney or for people who have already donated a kidney?
   b. ldt_assist1: One program that is available to help people cover the costs of kidney donation is the National Living Donor Assistance Center. There are also state and privately funded programs that can

help. Have you heard of any programs like these before?

c. ldt_financial2: Is someone you know receiving financial help for donating a kidney on your behalf from a program like this?

5. Concerns about LDKT (lkt_concern1- concern9): participants were asked to rate their level of concern in 9 areas of the LDKT process, such as having help after surgery, financial concerns, and guilt and family relationship after donation. Ranges from 0=not at all concerned to 10=extremely concerned.
6. Personal financial well-being (pfwbs1- pfwbs8): 8 questions from the Personal Financial Well- Being Scale (PFWBS) were collected. An average score is calculated across all 8 questions (each ranges from 1 to 10), for a final score ranging from 1 to 10. A score of 1 represents "overwhelming financial distress/lowest financial well-being" and 10 represents "no financial distress/highest financial well-being".

3.3 Primary Exposure

The primary exposure is the study arm. Usual Care (arm 1) consists of the care participants would normally receive through the Duke Kidney and Pancreas Transplant Program. TALK SWI (arm 2) is a previously developed and validated intervention consisting of "an educational booklet and video coupled with a social worker-led brief behavioral support intervention to help patients and their families overcome barriers to considering and pursuing LDKT." TALK SWI + FI (arm 3) includes TALK SWI plus a financial assistance intervention "to provide financial support for potential live kidney donors in circumstances where existing federal programs do not provide support."

4 Statistical Analysis Plan

Exploratory analyses will be performed on the outcomes of interest and distributional assumptions will be checked via histograms, boxplots, and crosstabs. We will also look at the distributions of the outcomes stratified by arm and explore the relationship between the study groups and the outcomes via boxplots and crosstabs. A consort diagram of the flow of participants over the course of the study will be created.

Baseline demographic and clinical characteristics will be presented stratified by study group. No baseline comparisons across study groups will be made. (Table 1 in appendix)

4.1 Analysis Plan for Primary Aim: Live Donor Kidney Activation

Continuous living donor activation at 12 months will be compared across study arms using Kruskal- Wallis test and categorically (if appropriate) using Fisher's exact test. Similarly, donor inquiries, evaluations, and LDKT will also be compared.

4.1.1 Poisson / ZIP Regression

Note that this section is no longer the main approach and is omitted from the final manuscript.

4.1.1.1 12-month composite activation

The live kidney donor activation score will be compared across study groups using an ANOVA or Kruskal-Wallis test as appropriate. We will then use Poisson regression to determine if the mean rate of activation over 12 months differs by intervention arms. Specifically, we will fit a model of the form

$$g(\mu) = \beta_0 + \beta_1(\text{Arm2}) + \beta_2(\text{Arm3}).$$

Arm2 and Arm3 are indicators of study arm. A Vuong test for comparing non-nested models will be used to test the null that the Poisson and zero-inflated Poisson (ZIP) models are equally close to the true model. If the test rejects in favor of the alternative that the ZIP model is closer, a ZIP will be presented.

In ZIP models, individuals are separated into two groups: those not at risk of an activation (i.e. the excess zeros) with probability ψ, and those who are with probability $1 = \psi$. Then, among those at risk, the activation counts are assumed to be generated from a Poisson process with mean μ. The overall (marginal) distribution of activation score is then

$$Y = \begin{cases} 0 & \text{with probability } \psi \text{ if not at risk} \\ e^{-\mu}\mu^y/y! & \text{with probability } 1-\psi \text{ if at risk} \end{cases}$$

And the marginal probability function for $P(Y = y)$ is

$$P(Y = 0) = \psi + (1-\psi)e^{-\mu}$$

$$P(Y = y) = (1-\psi)\frac{e^{-\mu}\mu^y}{y!}, \quad y > 0.$$

Denote the prevalence of activation as $\pi = P(Y > 0) = 1 - P(Y = 0) = (1 - \psi)(1 - e^{-\mu})$. Note that the overall mean activation count is $\nu = E(Y) = \mu(1 - \psi)$, and $\text{Var}(Y) = E(Y)(1 + \psi\mu)$, which shows that the variance exceeds the mean when $\psi > 0$. Of primary interest is comparison of the prevalence (π) and overall mean (ν) activation.

The parameter ψ will be modeled by the following logit:

$$\text{logit}(\psi) = \gamma_0 + \gamma_1(\text{Arm2}) + \gamma_2(\text{Arm3}) + \gamma_3(\text{blACT}).$$

blACT is the activation score at randomization (inquiries + evaluations before randomization).

The corresponding Poisson part will be modeled as

$$\log(\mu) = \beta_0 + \beta_1(\text{Arm2}) + \beta_2(\text{Arm3}) + \beta_3(\text{blACT})$$

This models the mean activation counts among those at risk using log-linear models.

4.1.1.2 12-month donor inquiry alone

Similar to activation, donor inquiry will be modeled using Poisson or ZIP as appropriate.

4.1.1.3 12-month donor evaluation alone

Similar to activation, donor evaluation will be modeled using Poisson or ZIP as appropriate.

4.1.1.4 12-month LDKT

Similar to activation, donor inquiry will be modeled using Poisson or ZIP as appropriate.

4.1.2 Primary Approach: Time to First Event Survival Analyses

Note that this section is the PRIMARY approach in the manuscript.

4.1.2.1 12-month composite activation

Outcome: We will use survival analysis techniques to model time to first activation event (inquiry, evaluation, or LDKT) in the presence of two competing risks: deceased donor transplant (DDKT) and death.

Censoring: Participants will be censored if they did not have an activation event during the observation period. Participants with no event before withdrawing from the study will be censored at their withdrawal date; all others with no event will be administratively censored at 12 months after randomization.

Standard survival methods do not work in the presence of competing risks because the assumption that censoring is independent is violated. Independent censoring means that individuals who are censored have similar risk of the event of interest as those still in the study, but this is not the case for competing risk – if a person dies, that person no longer is at risk of having a donor inquiry or transplant, for example. Standard survival analyses will often overestimate the probability of the event of interest.

The competing risk framework can also be used in our case with nonfatal, semi-competing risks, if interest lies in which event type occurred first. We will use this logic for the analyses of our outcome.

We will use the cumulative incidence function (CIF) to estimate incidence of

occurrence of an activation event in the presence of competing risks. We will also fit subdistribution and cause- specific Cox proportional hazard models. Let $k = 3$ be the number of competing risks: activation event, DDKT, and death. The CIF for the kth event is defined as $\text{CIF}_k(t) = P(T \leq t, K = k)$, the probability of experiencing the kth event before time t and before the occurrence of one of the other events. This will be plotted both overall and by arm.

We will then investigate the subdistribution hazard function, defined as

$$\lambda_k(t) = \lim_{\Delta t \to 0} \frac{P(t < T \leq t + \Delta t,\ K = k | T > t \cup (T < t \cap K \neq K))}{\Delta t}$$

This is the "instantaneous *risk of failure* from the kth event in subjects who have not yet experienced an event of type k." This risk set include those who are event free and *those who have experienced a competing event*.

In contrast, the cause-specific hazard functions for each event is defined as

$$\lambda_k(t) = \lim_{\Delta t \to 0} \frac{P(t \leq T < t + \Delta t, K = k | T \geq t)}{\Delta t}$$

This is the instantaneous *rate of* event k at time t, in subjects *who have experienced none of the events* (of any type) before time t.

Both subdistribution and cause-specific hazard models will be fit, having the form

$$\lambda_k(t) = \log\{\lambda_{k0}(t)\} + \beta_1(\text{arm2}) + \beta_2(\text{arm3}).$$

Here, $\lambda_{k0}(t)$ denotes the hazard function for participants in arm 1, and "arm2" and "arm3" are indicator variables. Interest lies in β_1 and β_2, the increased hazard of each event being in the intervention arms compared to the control arm.

4.1.2.2 12-month donor inquiry alone

A similar survival approach described above will be used to model time to first inquiry (ignoring evaluations and LDKTs) in the presence of the competing risks DDKT and death.

4.1.2.3 12-month donor evaluation alone

A similar survival approach described above will be used to model time to first evaluation (ignoring inquiries and LDKTs) in the presence of the competing risks DDKT and death.

4.1.2.4 12-month LDKT

Though it is likely not possible or even meaningful with only 4 events, a similar survival approach will be used to model time to LDKT (ignoring inquiries and evaluations) in the presence of the competing risks DDKT and death.

4.2 Analysis Plan for Secondary Aim: Potential Recipient Activation

We will explore the crosstab of scenario by study arm cross-sectionally at each time and comparisons will be made via a chi-squared or Fisher's exact test as appropriate.

4.2.1 Continuous Formulation of Scenario

We will model scenario as a continuous variable and use longitudinal GEEs (normal outcome) with an unstructured correlation matrix to determine if the total scenario changes over time for each arm. Specifically, we will fit a model of the form

$$\begin{aligned} g(\mu) = \beta_0 &+ \beta_1(\text{Arm2}) + \beta_2(\text{Arm3}) + \beta_3(4\text{mo}) + \beta_4(12\text{mo}) \\ &+ \beta_5(\text{Arm2} \times 4\text{mo}) \\ &+ \beta_6(\text{Arm3} \times 4\text{mo}) + \beta_7(\text{Arm2} \times 12\text{mo}) + \beta_8(\text{Arm3} \times 12\text{mo}). \end{aligned}$$

Because all the variables are indicator functions, the right hand side reduces to

	Arm 1	Arm 2	Arm 3
Baseline	β_0	$\beta_0 + \beta_1$	$\beta_0 + \beta_2$
4 months	$\beta_0 + \beta_3$	$\beta_0 + \beta_1 + \beta_3 + \beta_5$	$\beta_0 + \beta_2 + \beta_3 + \beta_6$
12 months	$\beta_0 + \beta_4$	$\beta_0 + \beta_1 + \beta_4 + \beta_7$	$\beta_0 + \beta_2 + \beta_4 + \beta_8$

We will assess the changes in scenario within each arm, and then determine if there is a difference across arms at 12 months. Note that the difference from baseline to 12 months within each arm is given by

	Arm 1	Arm 2	Arm 3
4 months – Baseline	β_3	$\beta_3 + \beta_5$	$\beta_3 + \beta_6$
12 months – Baseline	β_4	$\beta_4 + \beta_7$	$\beta_4 + \beta_8$

If β_7 is non-zero, the change from baseline in Arm 2 is significantly different than the change from baseline in Arm 1. Similarly, if β_8 is non-zero, the change from baseline in Arm 3 is significantly different than the change from baseline in Arm 1.

4.2.2 Dichotomous Formulation of Scenario

We will also dichotomize the scenario into maximum activation (talked with family/friends and identified a donor) vs less activation (talked with family/friends but did not identify a donor, or did not talk to family/friends). We will use a similar GEE (binomial outcome) to determine if the probability of having maximum activation over time is different between arms.

4.2.3 Number of Steps Forward

The number of steps the participant moved forward at each follow-up visit will also be modeled with a GEE. Of interest is the number of steps moved from baseline to month 4, and from month 4 to month 12. All participants had baseline data. If participant was missing a M4 or M12 value, then 0 steps taken was imputed as the most conservative estimate. If participant was missing a value due to receipt of transplant, then the person was dropped from the analyses at the time of transplant reporting and thereafter.

Participants are not able to go back in scenario, thus if M4 scenario is less than baseline, or if M12 scenario is less than M4 (or baseline) then 0 steps will be imputed.

We will also fit a linear model looking at the total number of steps across the whole study, and a logistic regression model looking at any steps forward across the whole study as an outcome.