Patient Preference and Adherence

Dovepress

open access to scientific and medical research

Open Access Full Text Article

CLINICAL TRIAL REPORT

Video Education and Behavior Contract to Improve Outcomes After Renal Transplantation (VECTOR): A Randomized Controlled Trial

Holly Mansell[1], Nicola Rosaasen[2], Jenny Wichart[3], Patricia West-Thielke[4], David Blackburn[1], Juxin Liu[5], Rahul Mainra[6], Ahmed Shoker[6], Brianna Groot[7], Kevin Wen[8], Anita Wong[9], Bita Bateni[10], Cindy Luo[11], Paraag Trivedi[12]

[1]College of Pharmacy and Nutrition, University of Saskatchewan, Saskatoon, SK, Canada; [2]Saskatchewan Transplant Program, Saskatchewan Health Authority, Saskatoon, SK, Canada; [3]Department of Pharmacy, Alberta Health Services, Calgary, AB, Canada; [4]University of Illinois Health Sciences System, Chicago, IL, USA; [5]Department of Mathematics and Statistics, College of Arts and Science, University of Saskatchewan, Saskatoon, SK, Canada; [6]Saskatchewan Transplant Program; Department of Medicine, University of Saskatchewan, Saskatoon, SK, Canada; [7]Canadian Hub for Applied and Social Research, University of Saskatchewan, Saskatoon, SK, Canada; [8]Division of Nephrology and Transplant Immunology, Department of Medicine University of Alberta, Edmonton, AB, Canada; [9]Department of Pharmacy, University of Alberta Hospital, Edmonton, AB, Canada; [10]St. Paul's Hospital, and University of British Columbia, Vancouver, BC, Canada; [11]Vancouver General Hospital; Faculty of Pharmaceutical Sciences, the University of British Columbia, Vancouver, BC, Canada; [12]Transplant Recipient/Patient Advisor, Regina, SK, Canada

Correspondence: Holly Mansell, College of Pharmacy and Nutrition, Health Sciences Building (E3208), 107 Wiggins Road, Saskatoon, SK, S7N 5E5, Canada, Email holly.mansell@usask.ca

Abstract: Sub-optimal adherence to immunosuppressant medications reduces graft survival for kidney transplant recipients and adherence-enhancing interventions are resource and time intensive. We performed a multi-center randomized controlled trial to investigate the impact of an electronically delivered intervention on adherence. Of 203 adult kidney transplant recipients who received a de novo kidney transplant n = 173 agreed to participate (intent-to-treat population) and were randomized to the intervention (video education plus behavior contract n = 91) or the control (standard education, n = 82). No significant differences were found between the groups for medication adherence measured by the Basel Assessment of Adherence to Immunosuppressive Medications Scale, intrapatient variability in tacrolimus levels, time in therapeutic range for any immunosuppressant, knowledge, self-efficacy, QOL, or hospitalizations. Among a subgroup of 64 participants randomized to the intervention group who completed a post-intervention questionnaire, two-thirds (67%, n = 43) reported watching at least 80% of the videos and 58% (n = 37) completed the electronic goal setting exercise and adherence contract. An autonomous goal setting exercise and electronic behavioural contract added to standard of care did not improve any outcomes. Our findings reiterate that nonadherence in transplantation is a difficult multifactorial problem that simple solutions will not solve. Trial registration number NCT03540121.

Keywords: kidney transplant, solid organ transplant, medication adherence, immunosuppression

Introduction

Transplantation, the preferred treatment for improving health outcomes for those with end-stage kidney disease,[1] is demanding. Kidney recipients must manage lifestyle modifications and maintain strict adherence to immunosuppressant medications despite frequent adverse effects. An inability to adapt to these changes may result in an increased risk of transplant rejection and graft loss.[2,3] Routine monitoring of medication adherence is recommended as a "fifth vital sign" in all transplant recipients[3] as even a 5% deviation from the prescribed immunosuppressant regimen can have negative consequences.[2]

Adherence-enhancing interventions have been generating recent attention, with multi-dimensional behavioural strategies showing efficacy in randomized controlled trials (RCT).[4] In the MAESTRO-Tx trial (n = 205; heart, liver, and lung recipients), a tailored intervention involving electronic monitoring feedback and motivational interviewing contributed to 16% higher dosing adherence compared to the control.[5] Likewise, an electronic medication tray and a smartphone app

Received: 24 April 2024
Accepted: 24 June 2024
Published: 31 July 2024

with monitoring and reinforcement messages significantly reduced tacrolimus intrapatient variability (IPV) in non-adherent kidney recipients (n = 80).[6] Multicomponent interventions such as these seem promising, but they can be expensive, time consuming and difficult to implement widely.[7] Given that nearly a quarter of kidney transplant patients are estimated to struggle with medication adherence,[2] sustainable solutions should be explored.

The Video Education and behavior Contract to improve Outcomes after Renal transplantation (VECTOR) RCT evaluated whether a low-cost, simple intervention improves adherence, compared to usual care. VECTOR combined an educational component (three-part video series) with a behavioural component (goal setting exercise and adherence contract) delivered electronically to kidney recipients after their transplant.[8] The evidence-based patient-centered videos[9] were shown to improve knowledge and satisfaction when administered before kidney transplantation in a previous RCT.[10] The behavioral component was inspired by a study showing education provided by a pharmacist combined with a behavioral contract post-transplant improved immunosuppressant adherence and decreased hospitalizations.[11,12] The intervention, however, involved intensive collaboration between patients and a study pharmacist, and to our knowledge has not been widely implemented. Therefore, we sought to determine whether a streamlined simpler approach could improve adherence.

Materials and Methods

Trial Design

A prospective, multicenter, parallel design randomized-controlled trial was conducted in de novo kidney transplant recipients, in 6 centers in North America. Methods have been described elsewhere,[8] clinicaltrials.gov (NCT03540121). The study timeline is presented in SDC Figure 1.

Study Population and Recruitment

Study participants were 18 years or older and received their first kidney transplant at one of the participating centers. They were enrolled within 2 weeks of hospital discharge. Patients were excluded if they had previously participated in an educational study, were not fluent in English and did not have a support person to assist them with participation.

Intervention (Video Education + Behavior Contract + Standard Education)

On demand video education was delivered immediately after enrolment along with standard education. Participants were provided access to password-protected videos, available for viewing on any electronic device. The three-part video series (Introduction; Medications; Your New Life) was adapted from an existing educational program.[9] These patient-centered videos incorporate principles from adult learning theory and were developed according to best-practices for education for patients awaiting transplantation.[13] Participants were asked to watch the videos (in hospital or at home) and replay as desired. Participants without electronic access were provided with a study device to view the videos in hospital.

Approximately 1-month post-enrolment an email link invited participants to work through an electronic self-directed goal setting exercise and sign an adherence contract pledging to take immunosuppressant medications as directed. This autonomous activity encouraged participants to reflect on their motivation for remaining adherent, potential barriers and consequences, and set an action plan for taking medications as directed.[11] A signature box enabled participants to commit to the contract. It was revisited during the 3-month and 12-month post-enrolment surveys and was not reviewed by the healthcare team.

Control Condition (Standard Education)

Participants in the control condition received the standard education only, including one-on-one medication teaching from a healthcare provider, medication teaching sheets and a personalized medication schedule. These participants received the same assessments throughout the study and were sent a control message at the 1-month period, in substitution for the behavior contract.

Study Overview

Ethics approval was obtained at each site from the local institutional review boards. A site lead oversaw activities at each center. During the study period, a front-line healthcare worker identified patients who received a transplant and used a standardized script to ask recipients whether they were interested in learning about an educational study. A research assistant contacted patients who expressed interest to provide details and take informed consent. This process was performed in-person, until the COVID-19 pandemic declaration (March 2020). The study was temporarily halted until a virtual enrolment process was approved by each regional ethics board (March–September 2020). The Canadian Hub for Applied and Social Research (CHASR) at the University of Saskatchewan oversaw the experimental research activities, achieving a standardized process across the sites. They disseminated surveys, videos, adherence contracts and reminders. All data from the surveys was immediately transmitted and managed in a central repository and deidentified prior to analysis by the research team. Gift cards in the amount of $20 and $25 were issued after completion of the 3-month and 12-month post-transplant questionnaires, respectively. The research activities were consistent with the principles outlined in the "Declaration of Istanbul on Organ Trafficking and Transplant Tourism" and the "Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects".

Randomization and Blinding

Randomization (1:1) was performed centrally in permuted blocks of six or eight and stratified according to site. Pre-generated codes were embedded into the participation links and numbered sequentially to conceal treatment. Groups received communications of similar content and frequency. Participants in the intervention group were given unique login credentials and passwords and were reminded not to discuss the nature of the intervention with anyone; the research team was blind to participant allocation.

Outcome Measures

The primary outcome was medication adherence measured by the differences between the two groups in percentage of patients self-reporting optimal adherence using the Basel Assessment of Adherence to Immunosuppressive Medications (BAASIS) Scale[14] sent electronically to each participant at 3 and 12 months post-enrolment. A patient was considered "non-adherent" if they answered "yes" to any of the questions (pertaining to missing doses/drug holidays, timing, and dose adjustment). Other adherence measures included the visual analogue scale (VAS) on the BAASIS as a continuous measure of adherence and tacrolimus blood levels (IPV and immunosuppressant time in therapeutic range (TTR)) at the end of the study. Immunosuppressant blood levels (tacrolimus, cyclosporine, sirolimus and everolimus) were collected according to routine practice. TTR was calculated using the Rosendaal method[15] where immunosuppressant blood levels were imputed for every day of the follow-up period based on linear extrapolation between dates of actual (ie, measured) results. Observed and imputed levels were then coded as either 1 (within target) or 0 (outside target) based on drug-specific targets for calculation of TTR. For IPV, tacrolimus trough variability was defined as the coefficient of variance ([CV]; calculated as [SD/Mean] × 100%). Only patients taking tacrolimus were included since validity studies indicate different immunosuppressants should not be combined within the same CV calculation.[16] Secondary outcome measures were collected with a self-reported survey administered 3 and 12 months post-enrolment. The survey contained several components; transplant knowledge was measured using the Kidney Transplant Understanding Tool (KTUT),[17] self-efficacy, quality of life and medication beliefs were measured by the generalized self-efficacy scale (GSE),[18] short form-12 version 2 (SF-12®),[19] and Beliefs about Medications Questionnaire (BMQ),[20] respectively. Satisfaction was measured using Likert scale questions where patients rated their confidence, understanding and satisfaction with education. Adherence to appointments or "no shows" (percentage of times a patient missed a scheduled transplant appointment or test without calling to cancel) and the number of days in hospital were collected retrospectively. Potential predictors or covariates collected at baseline included age, sex, marital status, race/ethnicity, education level, province, distance to transplant center, and health literacy.

Statistical Analysis

A sample of 100 patients in each group was estimated to detect a 15% absolute increase (from 75% to 90%) in percentage of adherent patients at an alpha of 0.05 and a beta of 0.20.

Randomized participants with at least one immunosuppressant blood level were included in the ITT analysis. A rolling monthly average compared immunosuppressant blood level measures (TTR and CV) between the intervention and the control. To account for the dependence of repeated measures from the same patient, generalized linear mixed models were used to compare groups during the 1-year follow-up period. For CV, individual-specific random intercepts were included in both mean and standard deviation models. For TTR, we used the zero-one-inflated beta regression model to accommodate the 0's and 1's. A Bayesian MCMC method, implemented by the R package brms, estimated model parameters. A square-root transformation was applied to rolling average CVs to adjust for the skewness in the original scale.

For the assessment of self-reported outcomes, we analyzed our results using the last observation carried forward when final assessments (ie, 12-month questionnaire) were missing. The percentage of patients indicating optimal adherence in each group by the BAASIS was compared using χ^2. The K-TUT, GSE, SF-12® and BMQ were scored according to standardized methods.[17–20] Independent *t*-tests compared the mean adherence calculated according to the VAS, and the secondary endpoints. A "per protocol" analysis was conducted after excluding intervention patients that did not have objective evidence (confirmed by time spent on each video webpage) of watching >80% of the videos and completing the adherence contract.

Changes to the Study Protocol

Saskatoon, Calgary, Chicago, and Halifax were the planned study sites. The site lead in Halifax was unable to initiate the study. Enrolment rates were lower than anticipated necessitating the addition of Edmonton and two Vancouver transplant centres, but we could not obtain missed appointments and hospitalizations from Vancouver. During the pandemic, the study was amended to allow a central research coordinator in Saskatchewan to obtain consent remotely (phone or virtual meeting) rather than face-to-face by a research assistant. This study did not have a Data Safety Monitoring Board due to the low-risk nature of the intervention; however, the research team (clinicians, statisticians, patients) decided to halt enrollment due to futility after an interim analysis of the first 126 patients to complete the trial. The original protocol specified that self-reported adherence would be collected at baseline (in addition to 3 and 12 months) but since sites varied on their in-hospital medication administration protocols (eg, nursing administration versus self-administration) this baseline timepoint was removed. A cost-utility analysis was not completed due to the lack of difference between the groups.

Results

Of 203 patients approached by a research assistant, 175 met inclusion criteria and agreed to randomization. Two patients passed away immediately post-transplant leaving 173 (91 intervention, 82 control) for the ITT analysis. One hundred and twenty participants (69%) completed a post-intervention questionnaire and were analyzed as the complete case population. Video viewing statistics revealed that 43 participants randomized to the intervention group (67% of the complete case group) had objective evidence of watching at least 80% of the videos and 37 participants (58%) also completed the electronic goal setting exercise and adherence contract (per protocol analysis). Fifty-seven participants were enrolled after the onset of the pandemic using the virtual process. Comments from those who viewed the videos were generally positive (SDC Table 1). The study participation flow chart is presented in Figure 1.

Participant Characteristics

Participants had a mean age of 51.0 (12.3) and 86% spoke English as a first language. Baseline characteristics were similar between both groups (Table 1). Significantly more participants who completed a post-baseline questionnaire were white and from a Canadian center ($p < 0.001$). Over three-quarters (85%, 45/53) of the participants who did not finish the study were enrolled in Illinois, and nearly half (42%, 22/53) were Black or African American (Table 2).

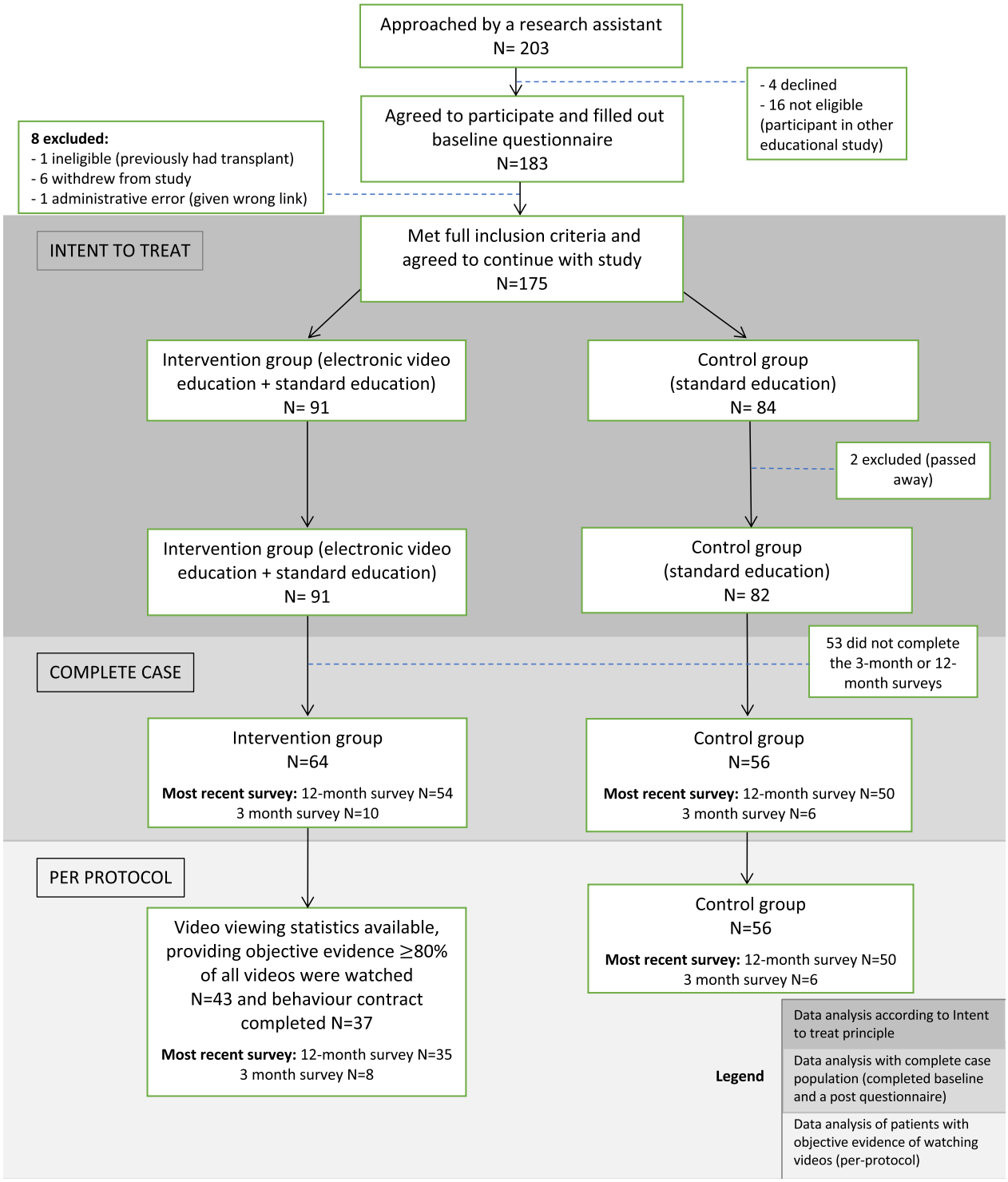

Figure 1 Study participant flow chart.

Medication Adherence

No significant differences were found between the groups in any measure of adherence for the ITT, complete case or per protocol analysis. According to the self-reported scales, the percentage of participants reporting optimal adherence was 55% in the intervention group and 64% in the control, while the mean score on the VAS was 98.4% (3.1) and 98.5% (4.5)

Table 1 Characteristics of the Intention to Treat (ITT) Study Population Stratified According to Arm

Characteristics	Total		Control		Intervention		p-value
	Count 173	% 100	Count 82	% 100	Count 91	% 100	
Age, mean (SD)	51.0 (12.3)		49.4 (13.3)		52.6 (11.2)		0.98
Gender							
Male	110	63.6	48	58.5	62	68.1	
Female	61	35.3	33	40.2	28	30.8	0.42
Other or Prefer not to say	2	1.2	1	1.2	1	1.1	
First Language							
English	148	85.5	73	89.0	75	82.4	0.22
Other	25	14.5	9	11.0	16	17.6	
Ethnicity*							
White	76	43.9	40	48.8	36	39.6	0.22
Hispanic/Latin	22	12.7	10	12.2	12	13.2	0.85
Black/African American	40	23.1	24	29.3	16	17.6	0.07
First Nation/Metis/Inuit	9	5.2	4	4.9	5	5.5	0.86
Indigenous	5	2.9	1	1.2	4	4.4	0.21
Native American/American Indian	2	1.2	0	0.0	2	2.2	0.18
Asian/Pacific Islander	1	0.6	2	2.4	2	2.2	0.92
Other/Prefer not to say	25	14.5	5	6.1	16	17.6	0.03
Work Status							
Unemployed/Temporarily cannot work/	102	59.0	45	54.9	57	62.6	
Disability income	65	37.6	28	34.1	37	40.7	
Working	35	20.2	17	20.7	18	19.8	0.66
Retired	28	16.2	15	18.3	13	14.3	
Other/Prefer not to say	8	4.6	5	6.1	3	3.3	
Highest level of Education							
Less than high school	14	8.1	9	11.0	5	5.5	
High school	51	29.5	24	29.3	27	29.7	
University/Graduate studies	71	41.0	30	36.6	41	45.1	0.43
Trade/Technical training	33	19.1	18	22.0	15	16.5	
Prefer not to say	4	2.3	1	1.2	3	3.3	
Marital Status							
Unmarried	44	25.4	23	28.0	21	23.1	
Married/Common law	102	59.0	49	59.8	53	58.2	0.59
Divorced/Widowed/Separated	23	13.3	8	9.8	15	16.5	
Prefer not to say	4	2.3	2	2.4	2	2.2	
Support Person							
Yes	168	97.1	79	96.3	89	97.8	0.57
No	5	2.9	3	3.7	2	2.2	
Driving Distance to tx center							
Within 1 hour	132	76.3	67	81.7	65	71.4	
>1 but < 5 hours	33	19.1	12	14.6	21	23.1	0.37
> 5 hours	7	4.0	3	3.7	4	4.4	
Other/Prefer not to say	1	0.5	0	0.0	1	1.1	
Live kidney donor							
Yes	73	42.2	30	36.6	43	47.3	0.16
No	100	57.8	52	63.4	48	52.7	
On dialysis before transplant							
No	20	11.6	9	11.0	11	12.1	0.82
Yes	153	88.4	73	89.0	80	87.9	

(*Continued*)

Table 1 (Continued).

Characteristics	Total		Control		Intervention		p-value
	Count 173	% 100	Count 82	% 100	Count 91	% 100	
Time on dialysis[+]							
Less than 1 year	22	14.4	5	6.8	17	21.3	
1–5 years	87	56.9	45	61.6	42	52.5	
5–10 years	36	23.5	18	24.7	18	22.5	0.08
> 10 years	8	5.2	5	6.8	3	3.8	
Type of dialysis[+]							
Hemodialysis	94	61.4	43	58.9	51	63.7	
Peritoneal dialysis	49	32.0	25	34.2	24	30.0	0.83
Do not know/Mixed	10	6.5	5	6.8	5	6.3	
How often requires help reading hospital materials							
Never	62	35.8	28	34.1	34	37.4	0.66
Anytime	111	64.2	54	65.9	57	62.6	
Confidence filling out forms without assistance							
Extremely	98	56.6	42	51.2	56	61.5	
Quite a bit/somewhat	70	40.5	35	42.7	35	38.5	**0.04**
A little bit/Not at all	5	2.9	5	6.1	0	0.0	
Read brochures about tx	121	69.9	55	67.1	66	72.5	0.44
Previously watched videos about tx	57	32.9	30	36.6	27	29.7	0.33
Browsed internet about tx	103	59.5	47	57.3	56	61.5	0.57
Talked medical staff about tx	146	84.4	69	84.1	77	84.6	0.93
Province/State of study enrolment							
Alberta	32	18.5	15	18.3	17	18.7	
British Columbia	21	12.1	9	11.0	12	13.2	0.94
Saskatchewan	37	21.4	19	23.2	18	19.8	
Illinois	83	48.0	39	47.6	44	48.4	

Notes: *Results may not add up to 100% because participants could chose more than one response; [+]total equals the number of people on dialysis.
Abbreviation: Tx, transplant.

Table 2 Characteristics for Those Who Did and Did Not Complete the Study

Characteristics	Total		Completed (3-Month or 12-Month)		Not Completed		p-value
	Count 173	% 100	Count 120	% 100	Count 53	% 100	
Age, mean (SD)	51.0 (12.3)		51.1 (12.4)		50.9 (12.3)		0.92
Gender							
Male	110	63.6	78	65.0	32	60.4	
Female	61	35.3	40	33.3	21	39.6	0.49
Other or prefer not to say	2	1.2	2	1.7	0	0.0	
First Language							
English	148	85.5	102	85.0	46	86.8	0.76
Others	25	14.5	18	15.0	7	13.2	
Ethnicity*							
White	76	43.9	64	53.3	12	22.6	<0.001
Hispanic/Latin	22	12.7	12	10.0	10	18.9	0.11
Black/African American	40	23.1	18	15.0	22	41.5	<0.001

(*Continued*)

Table 2 (Continued).

Characteristics	Total		Completed (3-Month or 12-Month)		Not Completed		p-value
	Count 173	% 100	Count 120	% 100	Count 53	% 100	
First Nation/Metis/Inuit	9	5.2	7	5.8	2	3.8	0.57
Indigenous	5	2.9	2	1.7	3	5.7	0.15
Native American/American Indian	2	1.2	0	0.0	2	3.8	0.03
Asian/Pacific Islander	1	0.6	4	3.3	0	0.0	0.18
Other/Prefer not to say	25	14.5	16	13.3	5	9.4	0.47
Work Status							
Unemployed/Cannot work/Disability	102	59.0	72	60.0	30	56.6	
Working (part time/full time)	35	20.2	23	19.2	12	22.6	0.16
Retired	28	16.2	22	18.3	6	11.3	
Other/Prefer not to say	8	4.6	3	2.5	5	9.4	
Highest level of Education							
Less than high school	14	8.1	11	9.2	3	5.7	
High school	51	29.5	32	26.7	19	35.8	
University/Graduate studies	71	41.0	50	41.7	21	39.6	0.16
Trade/Technical/Vocational training	33	19.1	26	21.7	7	13.2	
Prefer not to say	4	2.3	1	0.8	3	5.7	
Marital Status							
Unmarried	44	25.4	25	20.8	19	35.8	
Married/Common law	102	59.0	76	63.3	26	49.1	0.20
Divorced/Widowed/Separated	23	13.3	16	13.3	7	13.2	
Prefer not to say	4	2.3	3	2.5	1	1.9	
Province/State of study enrolment							
Alberta	32	18.5	29	24.2	3	5.7	
British Columbia	21	12.1	20	16.7	1	1.9	<0.001
Saskatchewan	37	21.4	33	27.6	4	7.5	
Illinois	83	48.0	38	31.7	45	84.9	

Note: *Results may not add up to 100% because participants could chose more than one response.

for the intervention and control groups, respectively (Table 3). There were no significant differences for patient's self-reported adherence between the 3-month and 12-month data collection points.

No significant differences were found between the groups for IPV or TTR (Table 4 and Figure 2). For the ITT CV (transformed), the 95% credible interval for the slope difference between the two groups was (−0.018, 0.071), while for the TTR it was (−0.005, 0.044). Since 0 is covered within these intervals, there is no statistically significant difference in

Table 3 Adherence Measured the BAASIS Self-Report Questionnaire Stratified by Condition

Characteristics	Total		Control		Intervention		p-value
	Count 120	% 100	Count 56	% 100	Count 64	% 100	
Adherence (binary)*							
Adherent	71	59.2	36	64.3	35	54.7	0.286
Adherence (≥VAS 80%)**							
Adherent	119	99.2	55	98.2	64	100.0	0.283

Notes: *Adherence (binary): An answer of "yes" to any of the BAASIS questions pertaining to missing doses/drug holidays, timing, and dose reduction categorized the participant as "non-adherent"; **Adherence (VAS ≥80%): A Visual Analogue Scale (VAS) was used to assess overall medication adherence over the last 4 weeks (ranging from 0–100%). This represents the proportion of patients that responded with a number of 80% or higher).

Table 4 The Rolling Monthly Average IPV and TTR for the Intervention and Control Groups

Month	Intrapatient Variability (IPV) of Participants Taking Tacrolimus				Time in Therapeutic Range (TTR) of All Patients with Immunosuppressant Drug Levels			
	Intervention		Control		Intervention		Control	
	Mean IPV (%)	Number of Patients	Mean IPV (%)	Number of Patients	Mean TTR (%)	Number of Patients	Mean TTR (%)	Number of Patients
1	30.6	68	33.7	69	32	80	34.2	73
2	30.5	68	36.3	68	35	80	35.8	73
3	26.2	72	32.2	68	40.8	78	37.9	70
4	24.8	72	31.4	65	40.3	77	34.4	67
5	24.2	69	27.8	59	37.9	77	32.4	65
6	24	64	26.2	56	37.4	78	34.9	67
7	22.3	62	27	59	34.3	74	39	66
8	23.2	60	24.2	54	37.2	71	38.7	66
9	23.7	55	27.9	51	37.3	70	37.2	65
10	21	49	25.7	43	38.8	67	47.5	63
11	22.4	46	23.7	45	44	67	40.7	61
12	23.6	46	25.5	47	47.1	67	36.9	61

Note: The number of patients included in each time period is shown, since immunosuppressant regimens can vary over time.

the groups (instead of Bayesian p-values, we reported interval estimates because of their transparent calculation and interpretation).

Secondary Outcomes

Knowledge, self-efficacy, beliefs of medicine, quality of life and educational satisfaction assessments are reported in Tables 5 and 6. The mean number of days spent in the hospital was 9.9 (16.5) and 9.7 (15.2) and missed appointment rates were 0.03% and 0.02% for the intervention and control, respectively. No significant differences were found in any measure.

Discussion

We evaluated whether a low-cost, simple intervention can improve adherence compared to usual care in kidney transplant recipients and found no impact on any outcome. Chisholm-Burns et al conducted an RCT using an educational intervention and behaviour contract delivered from a clinical pharmacist.[12] Renal transplant recipients were enrolled into the study at least one year post-transplant. Participants in the intervention group met with the study pharmacist to negotiate and sign the behaviour contract, which was revisited three times during the study period, using in person or phone interviews. Participants in the adherence group experienced significantly higher adherence rates along with decreased hospitalizations at 12 months. Our autonomous goal setting exercise and behavior contract, in contrast, was not successful at improving adherence, indicating that a simplified approach does not work. These findings are in line with others that suggest that in a post-transplant population, a one-size fits all approach is likely insufficient[4] and support a case for investing in tailored adherence-enhancing interventions with evidence to support their efficacy.[5,6]

The ability to justify the expenses of more complex adherence solutions and to implement them into real-world settings remains a challenge. Specifically focusing these efforts on patients who are identified as struggling with nonadherence may be one way to offset the potential costs. Since our intent was to investigate an inexpensive

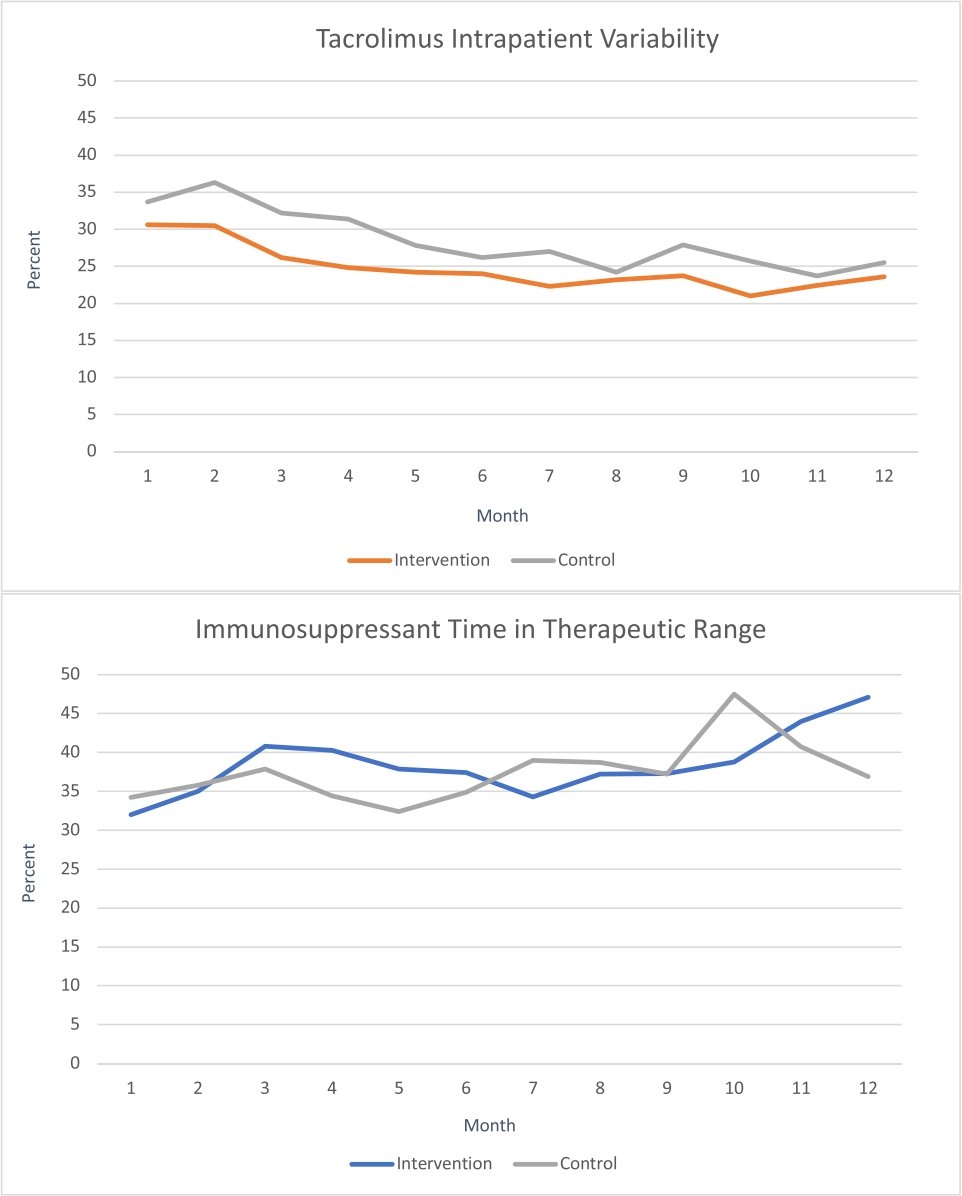

Figure 2 The mean tacrolimus intrapatient variability and time in therapeutic range for the immunosuppressants from baseline to 12 months post-randomization in the treatment and control arms.

intervention that could be easily put into practice, we employed convenience sampling enrolling all patients who met the inclusion criteria. Future studies should aim to enroll nonadherent patients[21] and specifically target this population. Interventions, however, must be engaging enough to encourage participation by nonadherent patients,[21] and investigators should strive to show how study-related interventions are incorporated in real-world settings.[22] Currently, even high-quality adherence RCTs lack implementation-relevant information.[22]

Although our findings are not entirely new, well-designed, robust trials conducted with educational interventions are exceedingly rare and are difficult to draw conclusions. In a systematic review of educational interventions for renal transplant recipients, most interventions and assessments were inadequately described and had a high risk of bias.[23] In the present trial, all efforts were made to minimize bias and the research team was blind to participant allocation. The development of the intervention has been meticulously documented using a theory-informed and evidence-based process which was guided by patient stakeholders. Nevertheless, the ability to recruit and retain all participants remains a major challenge with educational and adherence studies. For example, in an RCT of 245 kidney recipients, only 58% uptake

Table 5 Comparisons for the Intervention and Control Group for Mean Scores for Knowledge Self-Efficacy, Beliefs of Medicine, Quality of Life and Adherence

Outcome Measure	Control Group (n=56)		Intervention Group (n=64)		p-value
	Mean	SD	Mean	SD	
Baseline knowledge score	54.8	6.6	55.3	6.7	0.68
Follow up knowledge score	57.6	6.2	57.4	5.9	0.86
Improvement in knowledge score	2.8	6.0	2.1	5.2	0.49
Self-efficacy	31.0	5.8	30.8	4.3	0.82
Beliefs of medicine (necessity)	20.8	3.6	21.8	2.5	0.09
Beliefs of medicine (concern)	11.6	3.3	12.5	3.1	0.14
Beliefs of medicine (overuse)	9.0	3.2	9.4	3.1	0.50
Beliefs of medicine (harm)	7.3	2.4	6.8	2.2	0.32
Beliefs of medicine (differential)	9.2	5.4	9.3	3.9	0.88
Quality of Life (Mental)	50.1	9.1	49.2	9.1	0.60
Quality of Life (Physical)	46.9	9.8	45.8	9.7	0.57

Table 6 The Mean Scores on the Satisfaction Questions for the Intervention and Control Groups

Satisfaction Question	Control Group (n=56) Mean (SD)	Intervention Group (n=64) Mean (SD)	p-value
I am satisfied with my transplant education.	4.3 (0.9)	4.5 (0.8)	0.20
I am happy with the education provided to me about transplant medications.	4.5 (0.6)	4.5 (0.8)	0.80
I understand why I must take anti-rejection pills after my transplant.	4.8 (0.4)	4.9 (0.3)	0.13
I feel confident that I will be able to take my transplant medications as prescribed.	4.8 (0.5)	4.8 (0.4)	0.43
I am happy with the education provided to me about other transplant expectations (clinic appointments, bloodwork, life after transplant)	4.3 (0.9)	4.3 (0.8)	0.89

Note: Participants were asked to rate each statement on a scale of 1–5, with 1=strongly disagree, and 5=strongly agree.

occurred when patients worked through self-directed computer-based medication modules.[24] In the present study, of 203 patients screened, 173 patients participated, with only 69% following through to completion. It is unlikely that participants forgot about the study because the central research coordinator provided up to 3 email and phone reminders. The videos were co-developed with patients and feedback indicated that the videos were appealing and understandable[9,10] and attrition was similar in both groups suggesting the acceptability of the video intervention was not a factor. Notably, more participants who completed the study were white and from a Canadian center ($p < 0.001$). Over three-quarters of the participants who did not finish the study (85%, 45/53) were enrolled in Illinois, and nearly half (42%, 22/53) were Black or African American. In a pre-transplant RCT in Missouri, transplant education presented to Black and White low-income patients receiving dialysis was more effective when presented directly compared to video and print modules.[25] Black patients are more likely to experience inequalities in access to technology[26] and exhibit mistrust of the medical system.[27] Familiarity with central study site and location of data storage may have also facilitated trust with the patients at Canadian centers and contributed to higher completion rates.

Slow recruitment was a limitation with this study. Research assistants relied on ward staff to identify and triage patients. Efforts were made to improve engagement, but this remained a challenge that worsened during the pandemic. After reviewing the evidence from an interim analysis, we decided to halt VECTOR enrolment at the end of 2021. Premature discontinuation is acceptable when the study hypothesis is unexpectedly unprovable based on an interim analysis[28] and a signal towards improvement in the outcome measures would have been expected at the interim analysis enrolment of 126 participants. We offered an honorarium for participation to maximize recruitment and the study's potential for success. However, in a real-world setting, an honorarium would not be offered and recruitment for this type of intervention could be potentially lower without. A combination of methods is recommended for measuring adherence[3] and we used self-report and immunosuppressant blood levels. While there is an increasing amount of psychometric data on the BAASIS,[29] electronic monitoring may have provided a more sensitive method for detecting the specific phases of adherence. Unfortunately, the cost of this type of monitoring could not be supported under the current funding allotment. This study was limited to one year and declines in medication adherence may not be apparent until later. Behavioral studies by nature have some intrinsic limitations, including the inability to truly blind participants. Efforts were made to minimize bias and the research team was blind to participant allocation. Development of the intervention has been meticulously documented.[9,10]

Conclusion

We tested whether a feasible adherence intervention could be of benefit in de novo kidney transplant recipients. An autonomous goal setting exercise and electronic behavioural contract added to standard of care did not improve any outcome. The negative results and recruitment challenges highlight the challenge of fidelity with adherence interventions in the real-world setting and reiterate that nonadherence in transplantation is a difficult multifactorial problem.

Abbreviations

BAASIS, Basel Assessment of Adherence to Immunosuppressive medications; BMQ, Beliefs about Medications Questionnaire; CHASR, Canadian Hub for Applied and Social Research; CI, confidence interval; CV, coefficient of variation; K-TUT, Kidney Transplant Understanding Tool; GSE, generalized self-efficacy scale; IPV, interpatient variability; ITT, intent-to-treat analysis; RCT, Randomized controlled trial; SF-12, short form-12 version 2; TTR, time in therapeutic range; VAS, visual analogue scale; VECTOR, Video Education and behavior Contract to improve Outcomes after Renal transplantation.

Data Sharing Statement

The participants of this study did not give written consent for their data to be shared publicly, so due to the sensitive nature of the research supporting data is not available.

Acknowledgments

The authors wish to thank Terry Steeves-Gurnsey, Maithiri Amararajan, Benjamin Midgley, Wei Chen, Kelly Bruno and Scott Benken for their assistance with enrolment and data collection; Errin Willenborg, Patrick Head and Gerald Chartier for their assistance during the study design; Elijah Shurmer and Jessica McCutcheon for helping with the statistical analysis; all of the patients and healthcare providers who shared their time and expertise during the video development; and the support of the Transplant Pharmacy Adherence Consortium (TPAC).

Funding

The funding for the clinical trial was provided by an American Society of Transplantation (AST) Research Network Clinical Science Faculty Development Research Grant, the Saskatchewan Health Research Foundation (SHRF) and the Saskatchewan Center for Patient Oriented Research (SCPOR).

Disclosure

HM, NR, RM, and AS developed the video intervention used in this project. HM reports grants from the American Society of Transplantation (AST) Research Network, Saskatchewan Health Research Foundation (SHRF), Saskatchewan Center for

Patient Oriented Research (SCPOR), during the conduct of the study. The other authors declare no conflicts of interest in this work.

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/KDOQITM) conference. *Clin J Am Soc Nephrol*. 2008;3(2):471–480. doi:10.2215/CJN.05021107
2. Butler JA, Roderick P, Mullee M, Mason JC, Peveler RC. Frequency and impact of nonadherence to immunosuppressants after renal transplantation: a systematic review. *Transplantation*. 2004;77(5):769–776. doi:10.1097/01.TP.0000110408.83054.88
3. Neuberger JM, Bechstein WO, Kuypers DRJ, et al. Practical recommendations for long-term management of modifiable risks in kidney and liver transplant recipients: a guidance report and clinical checklist by the Consensus on Managing Modifiable Risk in Transplantation (COMMIT) Group. *Transplantation*. 2017;101(4S Suppl 2):S1.
4. Kuypers DRJ. From Nonadherence to Adherence. *Transplantation*. 2020;104(7):1330–1340. doi:10.1097/TP.0000000000003112
5. Dobbels F, De Bleser L, Berben L, et al. Efficacy of a medication adherence enhancing intervention in transplantation: the MAESTRO-Tx trial. *J Heart Lung Transplant*. 2017;36(5):499–508. doi:10.1016/j.healun.2017.01.007
6. McGillicuddy JW, Chandler JL, Sox LR, Taber DJ. Exploratory analysis of the impact of an mHealth medication adherence intervention on tacrolimus trough concentration variability: post hoc results of a randomized controlled trial. *Ann Pharmacother*. 2020;54(12):1185–1193.
7. Oberlin SR, Parente ST, Pruett TL. Improving medication adherence among kidney transplant recipients: findings from other industries, patient engagement, and behavioral economics-A scoping review. *SAGE Open Med*. 2016;4:2050312115625026. doi:10.1177/2050312115625026
8. Mansell H, Rosaasen N, West-Thielke P, et al. Randomised controlled trial of a video intervention and behaviour contract to improve medication adherence after renal transplantation: the VECTOR study protocol. *BMJ Open*. 2019;9(3):e025495. doi:10.1136/bmjopen-2018-025495
9. Rosaasen N, Mainra R, Kukha-Bryson A, et al. Development of a patient-centered video series to improve education before kidney transplantation. *Patient Educ Couns*. 2018;101:1624–1629.
10. Mansell H, Rosaasen N, Wichart J, et al. A randomized controlled trial of a pretransplant educational intervention in kidney patients. *Transplant Direct*. 2021;7(10):e753. doi:10.1097/TXD.0000000000001202
11. Chisholm-Burns MA, Spivey CA, Sredzinski E, et al. Intervention toolbox to promote immunosuppressant therapy adherence in adult renal transplant recipients. *J Am Pharm Assoc*. 2012;52(6):816–822. doi:10.1331/JAPhA.2012.11083
12. Chisholm-Burns MA, Spivey CA, Graff Zivin J, et al. Improving outcomes of renal transplant recipients with behavioral adherence contracts: a randomized controlled trial. *Am J Transplant*. 2013;13(9):2364–2373. doi:10.1111/ajt.12341
13. Skelton SL, Waterman AD, Davis LA, et al. Applying best practices to designing patient education for patients with end-stage renal disease pursuing kidney transplant. *Prog Transpl*. 2015;25(1):77–90. doi:10.7182/pit2015415
14. Dobbels F, Berben L, De Geest S, Drent G, Lennerling A, Whittaker C; Kugler C and the Transplant360 Task Force. The psychometric properties and practicability of self-report instruments to identify medication non-adherence in adult transplant patients to date: a systematic review. *Transplantation*. 2010;90(2):205-219. doi:10.1097/TP.0b013e3181e346cd
15. Rosendaal FR, Cannegieter SC, van der Meer FJ, Briët E. A method to determine the optimal intensity of oral anticoagulant therapy. *Thromb Haemost*. 1993;69(03):236–239. doi:10.1055/s-0038-1651587
16. Pizzo HP, Ettenger RB, Gjertson DW, et al. Sirolimus and tacrolimus coefficient of variation is associated with rejection, donor-specific antibodies, and nonadherence. *Pediatr Nephrol*. 2016;31(12):2345–2352. doi:10.1007/s00467-016-3422-5
17. Rosaasen N, Taylor J, Blackburn D, et al. Development and validation of the Kidney Transplant Understanding Tool (K-TUT). *Transplant Direct*. 2017;3:e132.
18. Schwarzer R, Jerusalem M. Generalized Self-Efficacy scale. In: Weinman I, Wright S, Johnston M, editors. *Measures in Health Psychology: A User's Portfolio. Causal and Control Beliefs*. Windsor: NEFR Nelson; 1995.
19. Ware J, Kosinski M, Keller SD. A 12-item short-form health survey: construction of scales and preliminary tests of reliability and validity. *Med Care*. 1996;34:220–233.
20. Horne R, Weinman J, Hankins M. The beliefs about medicines questionnaire: the development and evaluation of a new method for assessing the cognitive representation of medication. *Psychol Health*. 1999;14:1–24.
21. Duncan S, Annunziato RA, Dunphy C, LaPointe Rudow D, Shneider BL, Shemesh E. A systematic review of immunosuppressant adherence interventions in transplant recipients: decoding the streetlight effect. *Pediatr Transplant*. 2018;22(1). PMID: 29218760; PMCID: PMC5811374. doi:10.1111/petr.13086
22. Kostalova B, Ribaut J, Dobbels F, et al. Medication adherence interventions in transplantation lack information on how to implement findings from randomized controlled trials in real-world settings: a systematic review. *Transplant Rev*. 2022;36(1):100671. doi:10.1016/j.trre.2021.100671
23. Urstad KH, Wahl AK, Andersen MH, Øyen O, Hagen KB. Limited evidence for the effectiveness of educational interventions for renal transplant recipients. Results from a systematic review of controlled clinical trials. *Patient Educ Couns*. 2013;90(2):147–154. doi:10.1016/j.pec.2012.10.020
24. Harrison JJ, Badr S, Hamandi B, Kim SJ. Randomized controlled trial of a computer-based education program in the home for solid organ transplant recipients: impact on medication knowledge, satisfaction, and adherence. *Transplantation*. 2017;101(6):1336–1343. doi:10.1097/TP.0000000000001279
25. Waterman AD, Peipert JD, McSorley AM, Goalby CJ, Beaumont JL, Peace L. Direct delivery of kidney transplant education to black and low-income patients receiving dialysis: a randomized controlled trial. *Am J Kidney Dis*. 2019;74(5):640–649. doi:10.1053/j.ajkd.2019.03.430
26. Lockwood MB, Saunders MR, Lee CS, Becker YT, Josephson MA, Chon WJ. Kidney transplant and the digital divide: is information and communication technology a barrier or a bridge to transplant for African Americans? *Prog Transpl*. 2013;23(4):302–309. doi:10.7182/pit2013869
27. Wachterman MW, McCarthy EP, Marcantonio ER, Ersek M. Mistrust, misperceptions, and miscommunication: a qualitative study of preferences about kidney transplantation among African Americans. *Transplant Proc*. 2015;47(2):240–246.
28. Deichmann RE, Krousel-Wood M, Breault J. Bioethics in practice: considerations for stopping a clinical trial early. *Ochsner J*. 2016;16(3):197–198.
29. Denhaerynck K, Dobbels F, Košťálová B, De Geest S; BAASIS consortium. Psychometric properties of the BAASIS: a meta-analysis of individual participant data [published online ahead of print, 2023 Mar 23]. *Transplantation*. 2023. doi:10.1097/TP.0000000000004574