*Clinical Research Protocol*

# Enhance Access to Kidney Transplantation and Living Kidney Donation (EnAKT LKD): Statistical Analysis Plan of a Registry-Based, Cluster-Randomized Clinical Trial

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## Abstract

**Background:** Enhance Access to Kidney Transplantation and Living Kidney Donation (EnAKT LKD) is a quality improvement intervention designed to enhance access to kidney transplantation and living kidney donation. We conducted a cluster-randomized clinical trial to evaluate the effect of the intervention versus usual care on completing key steps toward receiving a kidney transplant.

**Objective:** To prespecify the statistical analysis plan for the EnAKT LKD trial.

**Design:** The EnAKT LKD trial is a pragmatic, 2-arm, parallel-group, registry-based, open-label, cluster-randomized, superiority, clinical trial. Randomization was performed at the level of the chronic kidney disease (CKD) programs (the "clusters").

**Setting:** Twenty-six CKD programs in Ontario, Canada.

**Participants:** More than 10 000 patients with advanced CKD (ie, patients approaching the need for dialysis or receiving maintenance dialysis) with no recorded contraindication to receiving a kidney transplant.

**Methods:** The trial data (including patient characteristics and outcomes) will be obtained from linked administrative health care databases (the "registry"). Stratified covariate-constrained randomization was used to allocate the 26 CKD programs (1:1) to provide the intervention or usual care from November 1, 2017, to December 31, 2021 (4.17 years). CKD programs in the intervention arm received the following: (1) support for local quality improvement teams and administrative needs; (2) tailored education and resources for staff, patients, and living kidney donor candidates; (3) support from kidney transplant recipients and living kidney donors; and (4) program-level performance reports and oversight by program leaders.

**Outcomes:** The primary outcome is completing key steps toward receiving a kidney transplant, where up to 4 unique steps per patient will be considered: (1) patient referred to a transplant center for evaluation, (2) a potential living kidney donor begins their evaluation at a transplant center to donate a kidney to the patient, (3) patient added to the deceased donor transplant waitlist, and (4) patient receives a kidney transplant from a living or deceased donor.

**Analysis plan:** Using an intent-to-treat approach, the primary outcome will be analyzed using a patient-level constrained multistate model adjusting for the clustering in CKD programs.

**Trial Status:** The EnAKT LKD trial period is November 1, 2017, to December 31, 2021. We expect to analyze and report the results once the data for the trial period is available in linked administrative health care databases.

**Trial Registration:** The EnAKT LKD trial is registered with the U.S. National Institute of Health at clincaltrials.gov (NCT03329521 available at https://clinicaltrials.gov/ct2/show/NCT03329521).

**Statistical Analytic Plan:** Version 1.0 August 26, 2022.

## Abrégé

**Contexte:** EnAKT LKD est une intervention d'amélioration de la qualité visant à améliorer l'accès à la transplantation rénale et au don vivant de rein. Nous avons mené un essai clinique randomisé par grappes afin d'évaluer l'effet de

l'intervention, par rapport aux soins habituels, sur le taux d'étapes clés réalisées dans le processus de réception d'une greffe de rein.

**Objectif:** Exposer les grandes lignes du plan d'analyse statistique de l'essai EAKT LKD.

**Conception:** EAKT LKD est un essai clinique pragmatique ouvert, à deux bras, en groupes parallèles, basé sur un registre, et randomisé en grappes. La randomisation a été réalisée au niveau des programmes d'insuffisance rénale chronique (IRC) (les «grappes»).

**Cadre:** 26 programmes d'IRC en Ontario (Canada).

**Sujets:** Plus de 10 000 patients atteints d'IRC de stade avancé (des patients approchant le besoin de dialyse ou recevant une hémodialyse d'entretien) sans contre-indication documentée à la greffe rénale.

**Méthodologie:** Les données de l'essai (y compris les caractéristiques et les résultats des patients) seront obtenues à partir de bases de données administratives en santé (le «registre»). La randomisation stratifiée avec contraintes de covariables a servi à répartir les 26 programmes d'IRC (1:1) selon qu'ils allaient fournir l'intervention ou les soins habituels entre le 1er novembre 2017 et le 31 décembre 2021 (4,17 ans). Les programmes d'IRC du bras d'intervention ont eu droit au soutien suivant: (1) des équipes locales d'amélioration de la qualité et du soutien administratif; (2) de l'information et des ressources sur mesure pour le personnel, les patients et les donneurs vivants; (3) du soutien de la part de receveurs et de donneurs vivants; et (4) des rapports sur le rendement au niveau du programme et une surveillance assurée par les chefs de programme.

**Résultats:** Le principal critère d'évaluation est le taux d'étapes clés accomplies vers la réception d'une greffe de rein, où jusqu'à quatre étapes uniques par patient seront comptabilisées: (1) le patient est aiguillé vers un centre de transplantation pour évaluation; (2) un possible donneur vivant de rein contacte un centre de transplantation pour un receveur en particulier et amorce son évaluation; (3) le patient est ajouté à la liste d'attente pour une transplantation d'un donneur décédé, et (4) le patient reçoit une greffe de rein d'un donneur vivant ou décédé.

**Plan d'analyse:** Selon une approche fondée sur l'intention de traiter, le critère d'évaluation principal sera analysé au niveau du patient en utilisant un modèle multiétats contraint, corrigé dans les programmes d'IRC en fonction du regroupement.

**Statut de l'essai:** L'essai EnAKT LKD s'est tenu du 1er novembre 2017 au 31 décembre 2021. Nous analyserons les résultats et en rendrons compte dès que les données seront disponibles dans les bases de données administratives couplées du système de santé.

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# Introduction

Kidney transplantation is the preferred treatment option for many patients with kidney failure.[1,2] However, there are multiple barriers to receiving a transplant.[3-7] In an effort to improve access to kidney transplant in Ontario, Canada, a quality improvement intervention was developed by 2 government-funded agencies: the Ontario Renal Network (https://www.ontariorenalnetwork.ca/) and the Trillium Gift of Life Network (https://www.giftoflife.on.ca/). Both agencies are part of Ontario Health, the government agency responsible for connecting and coordinating the province's health care system. This intervention, Enhance Access to Kidney Transplantation and Living Kidney Donation (EnAKT LKD), was designed in consultation with multiple stakeholders, including patients and health care providers. The intervention has 4 main components: (1) support for local quality improvement teams and administrative needs; (2) tailored education and resources for staff, patients, and living kidney donor candidates; (3) support from kidney transplant recipients and living kidney donors; and (4) program-level performance reports and oversight by program leaders.[8]

We conducted a cluster-randomized clinical trial to evaluate the effect of the EnAKT LKD intervention on completing key steps toward receiving a kidney transplant. Details on the background, rationale, and design of the trial are described elsewhere.[8] Briefly, we randomly allocated 26 chronic kidney disease (CKD) programs in Ontario to provide the EnAKT LKD intervention or usual care from November 1, 2017, to December 31, 2021. The intervention was embedded and delivered in routine care. The data needed for the main analysis of this trial, including patient characteristics and outcomes, will be obtained from linked administrative health care databases held at ICES (https://ices.on.ca). Here, we provide the prespecified statistical analysis plan for the trial. As a recommended research practice, we are publishing this statistical analysis plan before analyzing the trial outcomes.[9]

## Trial Objectives and Hypotheses

The *primary objective* is to estimate the effect of the EnAKT LKD quality improvement intervention versus usual care on completing key steps toward receiving a kidney transplant. Up to 4 unique steps per patient will be considered: (1) referral to a transplant center for evaluation for either a living or deceased donor transplant; (2) a potential living kidney donor begins their evaluation at a transplant center to donate a kidney to the patient; (3) patient added to the deceased donor transplant waitlist; and (4) patient receives a kidney transplant from a living or deceased donor. We hypothesize that the rate of completed steps will be higher among patients in programs allocated to the intervention group versus usual-care group.

# Study Methods

We will analyze and report the trial according to the Consolidated Standards of Reporting Trials (CONSORT) statement extended to cluster-randomized trials[10] and will follow the extension of the CONSORT statement for routinely collected data and pragmatic trials.[11] Our statistical analysis plan follows the Guidelines for the Content of Statistical Analysis Plans in Clinical Trials (Table S1).[9] Administrative information for the EnAKT LKD Statistical Analysis Plan (including the revision history) is detailed in Appendix 1 with the Statistical Analysis Plan checklist in Table S1 of the Supplement.

## Trial Design

The EnAKT LKD trial is a pragmatic, 2-arm, parallel-group, registry-based, open-label, cluster-randomized, superiority, clinical trial. All 26 CKD programs in Ontario were randomized to provide the intervention or usual care from November 1, 2017, to December 31, 2021 (the intervention period). Provincial administrative health care data (the "registry") will be used to identify and follow patients who received advanced CKD care (those approaching the need for dialysis or receiving maintenance dialysis) (Table 1) at any of the 26 programs from November 1, 2017, to September 30, 2021 (the patient accrual period). Patient outcomes will be followed until December 31, 2021. Ending the accrual period on September 30, 2021, meant all patients could have at least 90 days of follow-up to assess outcomes. The data sets will be linked using unique encoded identifiers and analyzed at ICES. Additional information on the ICES databases is provided in the original trial protocol.[8]

## Randomization

The details on the randomization procedures are in the protocol.[8] In brief, covariate-constrained randomization, stratified by historic transplant center referral patterns, was used to allocate the 26 CKD programs (1:1) to the intervention arm or the usual-care arm.

## Sample Size

During the patient accrual period, the 26 CKD programs are expected to care for more than 10 000 patients with advanced CKD (ie, patients approaching the need for dialysis or receiving maintenance dialysis) with no recorded contraindication to receiving a kidney transplant. The trial was designed to have at least 80% power to detect a rate ratio of 1.5 (2-sided $\alpha = 0.05$). This effect size would translate to patients completing an average of 12 more steps toward receiving a transplant (per 100 person-years) in one arm versus the other.[8] Power calculations were completed using the sample size

**Table 1.** Patient Eligibility Criteria for Inclusion in the EnAKT LKD Trial Analysis.

| Criteria | | Data sources |
|---|---|---|
| 1 | Patients (aged 18-75 years) who were approaching the need for dialysis on November 1, 2017, or demonstrated they were approaching the need for dialysis between November 2, 2017, and September 30, 2021. "Approaching the need for dialysis" defined by evidence of a multi-care kidney clinic visit with (i) or (ii): (i) An eGFR <15 mL/min/1.73 m² [a] (ii) A 2-year predicted risk of kidney failure (calculated using the kidney failure risk equation [KFRE])[b] ≥ 25% To ensure stability of kidney function, at least 2 eGFR or 2 KFRE measures were required to enter the cohort, and these measures had to be separated by at least >90 days but within 365 days. or Patients (aged 18-75 years) who were receiving outpatient maintenance dialysis (in a dialysis center or at home) on November 1, 2017, or initiated maintenance dialysis between November 2, 2017, and September 30, 2021. | Ontario Renal Reporting System, Ontario Laboratories Information System, Registered Persons Database |
| 2 | Patient has no evidence of any of the following recorded contraindications to receiving a kidney transplant:[c] End-stage kidney disease (ESKD) Charlson comorbidity index score ≥7[12], home oxygen use, dementia, living in a long-term care facility, received ≥1 physician house call in past year, or any history of the following cancers: bladder, cervical, colorectal, liver, lung, lymphoma, active multiple myeloma.[13] Patients are not receiving conservative renal care; these patients have advanced CKD (ie, individuals with an eGFR <15 mL/min/1.73 m² excluding individuals on dialysis) and have decided not to pursue dialysis or kidney transplantation. | Canadian Institute for Health Information Discharge Abstract Database and Same Day Surgery, Assistive Devices Program, Ontario Dementia Database, Continuing Care Reporting System, Ontario Health Insurance Plan, Ontario Cancer Registry, Ontario Renal Reporting System |
| 3 | Data cleaning steps (ie, invalid individual identifiers which would prevent linkage across databases, missing age or sex, death on or before index, etc.). We expect very few patients (<0.5%) will be excluded for these reasons. | Registered Persons Database |

Abbreviations: eGFR = estimated glomerular filtration rate; KFRE = kidney failure risk equation.
[a]Using the 2021 Chronic Kidney Disease–Epidemiology Collaboration Equation, without race.[14]
[b]Estimated using the Kidney Failure Risk Equation (https://kidneyfailurerisk.com).
[c]These contraindications were defined based on analysis of 80+ characteristics in adult patients approaching the need for dialysis or receiving maintenance dialysis between 2013 and 2015; >97% of patients with ≥1 of these characteristics or with an age over 75 years did not receive a kidney transplant within a median follow-up of 3.2 years.[13]

equation for comparing rates (accounting for the coefficient of variation in CKD programs).[15]

### Hypothesis Testing Framework

Two-sided hypothesis testing will be used to examine the effect of the intervention on the trial outcomes. This will be done using a stepwise, fixed-sequence testing procedure to minimize type 1 error (see "Confidence Intervals and *P* Values: Level of Statistical Significance" and "Analysis Methods" sections below).

### Interim Analysis

Given that the trial intervention poses minimal risk, and the data are stored in provincial administrative health care databases, we did not plan or perform any interim analyses.

### Timing of Outcome Assessment and Analysis

The outcome analysis will begin once the data for the trial is available at ICES. Data on the primary outcome (steps

completed toward receiving a kidney transplant) will be obtained from the Trillium Gift of Life Network (part of Ontario Health) database available at ICES.

## Statistical Principles

### Confidence Intervals and P Values: Level of Statistical Significance

The level of statistical significance, confidence intervals, and *P* values are described in the protocol.[8] In brief, the primary outcome will be compared between the intervention and usual-care arms using a 2-sided hypothesis test ($\alpha = 0.05$). If the primary outcome is significantly different between arms, we will proceed with a fixed sequence of 2-sided tests ($\alpha = 0.05$) for the 5 prespecified secondary outcomes (as defined and ordered in Box 2 in the protocol[8] and available in Table S2 of Appendix 2). Formal statistical testing will stop if a non-significant test result is obtained. For all subsequent analyses, we will provide point estimates with 95% confidence intervals and acknowledge that interval widths are not adjusted for multiple testing.

Small sample corrections are required when the number of clusters is <40.[16] As such, our Wald-based statistical tests and confidence intervals will use a degree-of-freedom correction through the Student's *t* distribution, rather than using a normal approximation which relies on asymptotic theory (ie, large numbers). Additional details can be found in Appendix 3 of the Supplement.

### Adherence and Protocol Deviations

In Ontario, starting on March 16, 2020, the COVID-19 pandemic resulted in the suspension of nearly all kidney transplant activity, including donor and recipient evaluations.[17] The delivery of many components of the intervention also stopped. In June 2020, transplant activity started to ramp-up, and intervention delivery resumed in September 2020.[18] However, additional pandemic waves resulted in further reductions in transplant activity and intervention delivery until the end of the trial period (December 31, 2021). For example, non-emergent surgeries, including many kidney transplants, decreased between April 20, 2021, and May 19, 2021.[19] At the beginning of the pandemic, we decided to extend the period of intervention delivery and patient follow-up to December 31, 2021 (the previous end date was March 31, 2021). Our rationale was to allow more time for patients to complete key steps toward receiving a kidney transplant and more time for programs to deliver the intervention to make up for pandemic-related slowdowns and suspensions of transplant activity.

As specified in our protocol, the primary analysis for this trial will not account for pandemic-related changes in transplant activity.[8] However, we will conduct an additional analysis in which patients' follow-up times will be truncated on the date transplant activity was first suspended in Ontario as described below. We are also conducting a concurrent process evaluation using surveys and interviews to understand how the intervention was delivered in each CKD program, and we will ask respondents how the pandemic affected these activities.[20]

### Analysis Population

The analysis of the trial population will follow an intent-to-treat approach. All outcome events will be attributed to a patient's CKD program where the patient entered the trial.

## Trial Population

### Eligibility Criteria

The EnAKT LKD trial includes all 26 CKD programs in Ontario (no exclusion criteria were applied at the cluster level). The trial's analysis population will include adult patients with advanced CKD (ie, patients approaching the need for dialysis or receiving maintenance dialysis) who attended any of the 26 CKD programs from November 1, 2017, to September 30, 2021 (the patient accrual period), and

who had no recorded contraindication to receiving a kidney transplant as assessed in our data sources;[13] more details on the eligibility criteria and data sources are provided in Table 1. Briefly, the Ontario Renal Reporting System will be used to identify patients approaching the need for dialysis (in Ontario this care is provided at Multi-Care Kidney Clinics) or receiving outpatient maintenance dialysis (in a dialysis center or at home). We will use laboratory measures in the Ontario Laboratories Information System to define patients who are approaching the need for dialysis.[21] Specifically, these patients are required to have an estimated glomerular filtration rate (eGFR) <15 mL/min/1.73 m$^2$ or a ≥25% 2-year predicted chance of permanent kidney failure (as assessed with the Kidney Failure Risk Equation [KFRE]).[21,22]

We also further refined the eligibility criteria based on an analysis we conducted in patients approaching the need for dialysis or receiving dialysis, where we compared 80+ baseline characteristics between patients who did and did not receive a kidney transplant during follow-up.[13] We found that >97% of patients with one or more of the following characteristics did not receive a transplant in follow-up, and so patients with these characteristics will not enter the trial for analysis: an ESKD adapted Charlson comorbidity index score[12] ≥7 (a higher score represents greater comorbidity), age >75 years, home oxygen use, dementia, living in a long-term care facility, receiving ≥1 physician house call in the past year, or any of the following cancers: bladder, cervical, colorectal, liver, lung, lymphoma, or active multiple myeloma.[13] Of note, not all these comorbidities are listed in provincial referral and listing criteria for kidney transplant[23]; however, as described above, few patients with these characteristics receive a transplant in practice. We have also clarified that receiving conservative renal care will be considered a contraindication to transplant as these patients have decided not to purse dialysis or transplantation. See Table S3 in Appendix 4 for additional clarification and changes from the originally published protocol.

### Recruitment—Flow Diagram

All 26 CKD programs in Ontario were included in the trial. The number of CKD Programs and the number of patients included in the analyses will be presented by allocation arm in a flow diagram (an example figure is provided in Figure S1).

### Withdrawal and Loss to Follow-up

No programs withdrew from the trial. One program divided into 2 programs after the trial started; these 2 programs will be treated as a single cluster for the analysis. We will use administrative databases to follow all patients, with emigration from the province being the only reason for loss to follow-up (<0.5% of Ontarians emigrate each year).[24] Otherwise, a patient's observation time will only stop on the trial end date (December 31, 2021), death, receipt of a kidney transplant, evidence of recovered kidney function, or on the

date a recorded contraindication to transplant occurs (as defined in criteria 2 of Table 1, with the exception of age >75 years; we will keep patients aged >75 years in the trial during follow-up given they were not older than 75 years when they entered the trial). Given the trial period is less than 5 years, patients will only be able to enter the trial once.

### Baseline Characteristics

Baseline characteristics will be obtained through administrative health care data at ICES. We will present continuous variables as means (standard deviations) or medians (25th, 75th percentile), and categorical variables as counts (proportions). More information about the key ICES databases that we will use was previously provided in the Supplemental Appendix of the protocol.[8] A list of key baseline characteristics can be found in Table S4 of the supplement. Baseline characteristics will be defined using validated algorithms (used in prior studies) whenever possible.

## Analysis

### Outcome Definitions

The *primary outcome* is completed steps toward receiving a kidney transplant, where up to 4 unique steps per patient will be considered: (1) patient referred to a transplant center for evaluation, (2) a potential living kidney donor begins their evaluation at a transplant center to donate a kidney to the patient, (3) patient added to the deceased donor transplant wait list, and (4) patient receives a kidney transplant from a living or deceased donor.[8] Completion of any individual step will only be counted once. For example, if multiple potential living kidney donors begin their evaluation to donate to the same patient, only the date the first potential donor contacts the program will be considered. We can consider these steps as a patient transitioning between the different states on their way to a final state of receiving a kidney transplant. Figure S2 in Appendix 5 illustrates potential steps (pathways) toward kidney transplantation.

Patients with a history of a failed kidney transplant may be eligible for a new kidney transplant. For these patients, only steps completed toward receiving a new kidney transplant will be considered in our outcome. The *secondary outcome* details are available in Table S2 of Appendix 2 in the supplement, which we have previously reported.[8]

### Analysis Methods

The patients' observation time will begin on the date they meet the eligibility criteria (Table 1), termed the trial entry date or index date. The index date will be November 1, 2017, for patients who meet the eligibility criteria on, or prior to, this date; and for the others, it will be the date they meet the eligibility criteria during the accrual period. This ensures that patients who enter a CKD program during the trial are still

included in the analysis at the time they become eligible. All patients will be followed until December 31, 2021, death, receipt of a transplant, evidence of recovered kidney function, emigration, or an observed contraindication occurs as described in "Withdrawal and Loss to Follow-up" section. We will report descriptive statistics of the observation time: average time spent in each state (ie, mean sojourn time in each state), frequency of transitions between states, patient crossovers between CKD programs and/or trial arms, and reasons why the observation time ended for patients in the intervention and control arms.

The primary outcome will be analyzed using a patient-level constrained multistate model adjusting for the clustering within CKD programs. Bootstrapping at the cluster level will be used to maintain valid inference in the presence of correlated outcomes within CKD programs. We are interested in the global intervention effect for all completed steps toward transplantation. That is, we will be constraining the intervention effect to be the same for each state transition in our primary analysis. This approach will provide a single estimate of the relative rate (i.e., hazard ratio) of steps completed toward receiving a transplant among patients in CKD programs in the intervention group versus the usual-care group.[25,26]

*Changes to the analysis of the primary outcome from the published protocol.* We initially proposed to analyze the primary outcome using a cluster-level analysis with a 2-staged approach defined by Hayes and Moulton in our protocol.[8,15] For several reasons, we changed to a patient-level analysis with a multistate statistical model. First, a patient-level analysis will likely provide more statistical precision, and it will naturally accommodate the variable cluster sizes. In contrast, a 2-staged, cluster-level analysis should be weighted using the estimated theoretical variance of cluster means (between- and within-cluster variances).[16] However, the weight may reduce statistical precision because estimated theoretical variance can be unstable with a small number of clusters (ie, < 30). Second, the primary outcome is a composite of 4 steps completed toward receiving a kidney transplant; however, these steps will not have a count distribution since a patient can only experience a maximum of 4 steps. Instead, these steps can be considered to create the different *states* on the path toward transplantation. As such, a multistate statistical model is better suited to handle this type of data.[27] A summary of changes and clarifications from our published protocol is available in Table S3 of Appendix 4.

We will adjust the primary analysis for baseline characteristics used in the trial design (ie, the covariates constrained in randomization) and other key characteristics. Adjusted baseline characteristics will be age, sex, ESKD Charlson comorbidity index, historic transplant rate, and whether the primary location of the CKD program has a transplant center (present in 6 of the 26 CKD programs). We will also include the CKD treatment modality at time of trial entry (ie, in-center hemodialysis, other form of dialysis, or approaching

the need for dialysis), ≥1 intensive care unit admission in the prior year, and the frequency of hospital admissions in the prior year. We will incorporate historic transplant center referral patterns in the analysis as these patterns were used as a stratification factor in the randomization.

We will evaluate model assumptions, report the results, and apply appropriate techniques if assumptions are violated. Specifically, integral to multistate models is the Markov assumption, where the transition between states (ie, the transition between steps as defined in the primary outcome) at a particular time is independent of the time spent in prior states (ie, the history process before that time).[27] For example, the probability of completing any of the steps defined in the primary outcome should not substantially depend on time since completing any previous step. We acknowledge that the Markov assumption may not hold. To test this assumption, we will include in the model covariates based on the history of prior steps and will determine whether this addition improves the model fit.[27-29] We will leave the covariates in the model when there is evidence that the history in prior states is relevant. Furthermore, by using a constrained model, we assume an overall effect of the intervention across all states (rather than the specific effect from transitioning between states). We will also assess for linearity of the continuous covariates. We will use rules of parsimony to identify our final model and will report all explorations.

## Analysis of the Secondary Outcomes

As described in the protocol, each of the 5 secondary outcomes is restricted to the completion of specific steps described for the primary outcome.[8] The multistate model framework is versatile in that it can be applied to a variety of simpler models, including a standard time-to-event model with a single event of interest.[27] As such, the same multistate model framework described in our primary outcome will be applied to all secondary outcomes. When exploring the secondary outcomes, we will incorporate prior states as time-varying covariates as appropriate. For example, referrals for transplant evaluation and the start of potential donor evaluations will be included in the model when estimating the intervention effect for living kidney transplantation as these states are important on the path toward living kidney transplantation. We will restrict the analysis to a cohort of patients *at risk* for the outcome. That is, we will exclude patients from the analysis of each secondary outcome if they had already completed that step before their index date. Additional details on secondary outcomes can be found in Appendix 2.

## Additional Analyses

Our primary analysis constrains on the intervention effect under the assumption of no substantial difference in the intervention effect across the transitions between states. By constraining, we will obtain a single overall rate ratio, akin to effect estimates for any composite outcome. Composite

outcomes are challenging to interpret when the intervention effect of the different components differs in direction or magnitude.[30] For example, the intervention may have less of an effect on deceased kidney transplantation, as many patients can wait 4 or more years on a list for an offer. To assess whether there is heterogeneity of the intervention effect across the components, we will conduct an additional analysis using an unconstrained multistate model to provide the estimated intervention effect of transitions for all states (ie, the arrows in Figure S2 of the Appendix 5). We will also examine all components of our primary composite outcome that are unspecified in our secondary outcomes (ie, deceased organ transplant waitlist).

Due to the small number of clusters available in Ontario, imbalances in baseline characteristics may occur between the intervention groups. If we observe imbalances on clinically relevant characteristics, we will perform the additional analyses adjusting for these characteristics.

*Subgroup analyses.* In our protocol, we have 10 prespecified subgroup analyses listed as exploratory analyses for the EnAKT LKD trial.[8] After consultation with our project partners, we no longer plan to perform 2 of these subgroup analyses of the intervention effect; specifically, we will not report results by race (white vs. other) (as we do not have access to self-reported race which is considered the gold standard for determining individuals' race and ethnicity, specifically ethnicity information in the Ontario Renal Reporting System was collected by data leads in each CKD program at the time of patient registration, based on charting by clinical staff who could ask patients to self-identify ethnicity but who were not mandated to do so)[31,32] or immigration status. In addition to the subgroup analyses described in our protocol, we will also conduct subgroup analyses based on how the patient entered the trial (whether patients were approaching the need for dialysis or receiving maintenance dialysis, as well as if patients entered on November 1, 2017, or during the accrual period).

*Restricting the trial to the Pre-COVID period.* Given the challenges of delivering the intervention during the pandemic, we will perform a prespecified analysis of our primary and secondary outcomes restricting the trial period to November 1, 2017, to December 20, 2019, with follow-up to March 16, 2020. March 16, 2020, aligns with the suspension of transplant activity in Ontario.[17] It is possible any beneficial effect of the intervention will be more pronounced in the prepandemic period.

## Missing Data and Other Considerations

Transplant activity is recorded in a data set from the Trillium Gift of Life Network (TGLN). We are linking these TGLN data to the other Ontario health care administrative databases to perform the outcome analysis. We expect TGLN data will be robust. However, before performing any outcome analyses, we will review, document, and reconcile any

data discrepancies should they exist. For example, if someone received a deceased donor kidney transplant during the trial period with no evidence they had ever been referred or waitlisted, this could suggest missing data on the transplant steps completed. We will quantify any such missing data and define rules for imputation if needed before performing any outcome analyses. Based on our previous work, we recognize a selection of baseline characteristics may have a small amount of missing data. For example, there may be some missing in the neighborhood income quintile and rurality (<1%).

### Harms and Data Monitoring

Our trial poses minimal risk, as such there were no interim analyses and no Data Safety and Monitoring Board. In additional analyses, we are assessing for potential unintended consequences of the trial through a set of balancing measures.[8] No interim analyses were conducted beyond providing transplant activity reports to the programs in the intervention group (a component of the intervention). Further details are contained in the published protocol.[8]

### Statistical Software

We will use SAS software version 9.4 (Cary, NC) to perform data linkage for our cohort, baseline, and outcomes. We will use R statistical software for the multistate modeling.

## Discussion

We provide a detailed statistical analysis plan for the EnAKT LKD trial, discussing the methods used for our prespecified analyses. We have undertaken this level of rigor to reduce the risk of producing biased estimates of the true effect, thereby generating trusted evidence that can be used to improve patient care.

## Dissemination Policy

We plan to disseminate the results of the EnAKT LKD trial through a peer-reviewed publication.

## Ethics Approval

The Health Sciences Research Ethics Board at Western University centrally approved the research ethics for this multi-center study (Application Number: #108408). The Research Ethics Board approved our application with alteration to the informed consent process described in the study protocol. The use of the data for the ICES portion of the project is authorized under section 45 of Ontario's Personal Health Information Protection Act.

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## Availability of Data and Materials

The data set from this study is held securely in coded form at ICES. While legal data sharing agreements between ICES and data providers (eg, health care organizations and government) prohibit ICES from making the data set publicly available, access may be granted to those who meet prespecified criteria for confidential access, available at www.ices.on.ca/DAS (email: das@ices.on.ca). The full data set creation plan and underlying analytic code may be available from the authors upon request, understanding that the computer programs may rely upon coding templates or macros unique to ICES and are therefore either inaccessible or may require modification.

## Supplemental Material

Supplemental material for this article is available online.

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