

MyTEMP: Statistical Analysis Plan of a Registry-Based, Cluster-Randomized Clinical Trial

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Abstract

Background: Major Outcomes with Personalized Dialysate TEMPerature (MyTEMP) is a 4-year cluster-randomized clinical trial comparing the effect of using a personalized, temperature-reduced dialysate protocol versus a dialysate temperature of 36.5°C on cardiovascular-related death and hospitalization. Randomization was performed at the level of the dialysis center (“the cluster”).

Objective: The objective is to outline the statistical analysis plan for the MyTEMP trial.

Design: MyTEMP is a pragmatic, 2-arm, parallel-group, registry-based, open-label, cluster-randomized trial.

Setting: A total of 84 dialysis centers in Ontario, Canada.

Patients: Approximately 13 500 patients will have received in-center hemodialysis at the 84 participating dialysis centers during the trial period (April 3, 2017, to March 1, 2021, with a maximum follow-up to March 31, 2021).

Methods: Patient identification, baseline characteristics, and study outcomes will be obtained primarily through Ontario administrative health care databases held at ICES. Covariate-constrained randomization was used to allocate the 84 dialysis centers (1:1) to the intervention group or the control group. Centers in the intervention group used a personalized, temperature-reduced dialysate protocol, and centers in the control group used a fixed dialysate temperature of 36.5°C.

Outcomes: The primary outcome is a composite of cardiovascular-related death or major cardiovascular-related hospitalization (defined as a hospital admission with myocardial infarction, congestive heart failure, or ischemic stroke) recorded in administrative health care databases. The key secondary outcome is the mean drop in intradialytic systolic blood pressure, defined as the patients’ predialysis systolic blood pressure minus their nadir systolic blood pressure during the dialysis treatment. Anonymized data on patients’ predialysis and intradialytic systolic blood pressure were collected at monthly intervals from each dialysis center.

Analysis plan: The primary analysis will follow an intent-to-treat approach. The primary outcome will be analyzed at the patient level as the hazard ratio of time-to-first event, estimated from a subdistribution hazards model. Within-center correlation will be accounted for using a robust sandwich estimator. In the primary analysis, patients’ observation time will end if they experience the primary outcome, emigrate from Ontario, or die of a noncardiovascular cause (which will be treated as a competing risk event). The between-group difference in the mean drop in intradialytic systolic blood pressure obtained during the dialysis sessions throughout the trial period will be analyzed at the center level using an unadjusted random-effects linear mixed model.

Trial status: The MyTEMP trial period is April 3, 2017, to March 31, 2021. We expect to analyze and report results by 2023 once the updated data are available at ICES.

Trial registration: MyTEMP is registered with the US National Institutes of Health at clinicaltrials.gov (NCT02628366).

Statistical analytic plan: Version 1.1 June 15, 2021.



Abrégé

Contexte: L'essai MyTEMP (*Major Outcomes with Personalized Dialysate Temperature*) est un essai clinique randomisé en grappes d'une durée de 4 ans comparant l'effet d'un protocole de dialysat personnalisé à température réduite par rapport au dialysat à 36,5 °C sur les hospitalisations et les décès dus à des problèmes cardiovasculaires. La répartition aléatoire des sujets a été effectuée au niveau du centre de dialyse (ci-après appelé «groupe»).

Objectifs: Exposer les grandes lignes du plan d'analyse statistique de l'essai MyTEMP.

Type d'étude: MyTEMP est un essai clinique pragmatique ouvert, à deux bras, en groupes parallèles, basé sur un registre, et randomisé en grappes.

Cadre: L'essai est mené dans 84 centres de dialyse en Ontario (Canada).

Sujets: On estime qu'environ 13 500 patients auront reçu des soins d'hémodialyse dans les 84 centres de dialyse participants au cours de la période de l'essai (3 avril 2017 au 1er mars 2021; suivi maximal jusqu'au 31 mars 2021).

Méthodologie: Les résultats et les données concernant l'identification des patients et leurs caractéristiques initiales seront principalement tirés des bases de données administratives du système de santé ontarien tenues par l'ICES. Une répartition aléatoire restreinte par les covariables a été employée pour classer les 84 centres de dialyse (1:1) dans le groupe d'intervention ou le groupe témoin. Le groupe d'intervention a utilisé un protocole personnalisé de dialysat à température réduite et le groupe témoin un dialysat à température fixe (36,5 °C).

Résultats: Le principal critère d'évaluation est la combinaison d'un décès d'origine cardiovasculaire ou d'une hospitalisation majeure liée à la santé cardiovasculaire (définie comme une hospitalisation pour un infarctus du myocarde, une insuffisance cardiaque congestive ou un AVC ischémique) enregistrée dans les bases de données administratives du système de santé. Le principal critère d'évaluation secondaire est la baisse moyenne de la tension artérielle systolique intradialytique, laquelle est définie comme la tension artérielle systolique du patient avant la dialyse moins la tension artérielle systolique minimale pendant la dialyse. Les données anonymisées sur la tension artérielle systolique initiale et la tension artérielle systolique intradialytique des patients ont été colligées à intervalles mensuels dans chaque centre de dialyse.

Plan d'analyse: L'analyse primaire adoptera une approche fondée sur l'intention de traiter. Le principal critère d'évaluation sera analysé au niveau du patient comme le risque relatif de survenue d'un premier événement, estimé à partir d'un modèle de risques de sous-distribution. La corrélation intracentre sera prise en compte à l'aide d'un robuste estimateur sandwich. Dans l'analyse primaire, le temps d'observation des patients prendra fin s'ils présentent le principal critère d'évaluation, s'ils déménagent hors de l'Ontario ou s'ils décèdent d'une cause non cardiovasculaire (qui sera traitée comme un événement à risque concurrentiel). La différence entre les groupes quant à la baisse moyenne de la tension artérielle systolique intradialytique, obtenue pendant les séances de dialyse tout au long de l'essai, sera analysée au niveau du centre avec un modèle linéaire mixte à effets aléatoires non corrigé.

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Statut de l'essai: L'essai MyTEMP couvre la période du 3 avril 2017 au 31 mars 2021. Nous comptons analyser et rendre compte des résultats d'ici 2023, dès que les données mises à jour seront disponibles à l'ICES.

Enregistrement de l'essai: MyTEMP est enregistré auprès du National Institute of Health des États-Unis sur clinicaltrials.gov (NCT02628366).

Keywords

cluster-randomized control trial, pragmatic trial, personalized dialysate temperature, cardiovascular events, hemodialysis

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Introduction

This article details the statistical analysis plan for the *Major outcomes with personalized dialysate TEMPerature (MyTEMP)* trial. Details on the background, rationale, and design of MyTEMP are provided elsewhere.¹ Briefly, the trial was undertaken to test the effect of randomizing outpatient hemodialysis centers to provide (1) a personalized, temperature-reduced dialysate protocol (intervention) or (2) a dialysate temperature of 36.5°C (control) on cardiovascular-related death and hospitalization. Centers in the intervention arm were asked to set the dialysate temperature to between 0.5°C and 0.9°C below the patient's predialysis body temperature for each dialysis session, to a minimum dialysate temperature of 35.5°C. Centers in the control arm were asked to use a dialysate temperature of 36.5°C for all patients.

This province-wide trial is embedded into routine care with the intervention delivered by dialysis unit personnel. We expect approximately 13 500 patients will have received in-center hemodialysis at the 84 participating dialysis centers during the 4-year trial period (April 3, 2017, to March 31, 2021). Patient characteristics and outcomes will primarily be obtained from routinely collected data captured in Ontario provincial administrative health care databases held at ICES. The pragmatic design of MyTEMP allows broad inclusion of dialysis centers and a large representative sample of patients that should yield highly generalizable findings.

Trial Objectives and Hypotheses

The *primary objective* of MyTEMP is to examine the effect of the intervention on a composite outcome of cardiovascular-related death or major cardiovascular-related hospitalization (a hospital admission with myocardial infarction, congestive heart failure, or ischemic stroke). We hypothesize that this composite outcome will be lower in patients in the intervention arm than in the control arm. Patient-level data for this outcome will be obtained from administrative health care databases.

The *key secondary objective* is to examine the effect of the intervention on the mean drop in intradialytic systolic blood pressure, defined as the patients' predialysis systolic blood pressure minus their intradialytic nadir systolic blood pressure. We hypothesize that the average drop in intradialytic

systolic blood pressure obtained during the dialysis sessions throughout the trial period will be smaller in centers in the intervention arm than in the control arm. Anonymized, center-level data on intradialytic systolic blood pressure were obtained at monthly intervals from each dialysis center.

Study Methods

The trial will be analyzed and reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) statement extended to cluster-randomized trials.² We will also adhere to the extension of the CONSORT statement for routinely collected data and pragmatic trials.³ The statistical analysis plan was developed in accordance with the Guidelines for the Content of Statistical Analysis Plans in Clinical Trials.⁴ A table showing the revision history of this plan is provided in Appendix 1 in the Supplemental Material.

Trial Design

MyTEMP is a pragmatic, 2-arm, parallel-group, registry-based, open-label, cluster-randomized trial. The trial started on April 3, 2017, and enrolled 84 of Ontario's 97 hemodialysis centers (Canada). This province-wide trial was embedded into routine care with center-wide implementation of the intervention by dialysis unit personnel. Patients in the trial's analysis population will be identified from the Ontario Renal Reporting System (ORRS), an administrative health care registry managed by the Ontario Renal Network, the provincial organization that manages the delivery of chronic kidney disease services in Ontario, Canada.⁵ Baseline characteristics and trial outcomes will be primarily obtained through routinely collected data captured in administrative health care databases held at ICES. The data sets will be linked using unique encoded identifiers and analyzed at ICES. More information about the ICES databases are provided in the trial protocol.¹

Randomization, Sample Size, Hypothesis Testing Framework, and Interim Analysis

The randomization procedures and sample size calculation are detailed in the study protocol.¹ Briefly, 84 centers were randomly allocated in a 1:1 ratio using covariate-constrained

randomization to balance key characteristics between the trial arms.⁶⁻⁸ We expect approximately 13 500 patients will have received in-center hemodialysis at the 84 participating dialysis centers during the trial period. The trial is powered to detect a hazard rate reduction in the primary composite outcome of at least 20% (corresponding to a hazard ratio of 0.80); described in more detail below (see sections “Statistical Principles”, “Confidence Intervals and *P* Values: Level of Statistical Significance”), a 2-sided α of 0.04 for a superiority hypothesis test was chosen for the primary outcome to control the error rate (total 2-sided α of 0.05) with a 2-sided α of .01 for the key secondary outcome (mean drop in intradialytic systolic blood pressure).

No interim analyses were planned or performed.

Timing of Final Analysis

All analyses described in this document will be conducted after the trial ends and when the data covering the trial period are available at ICES. We expect to complete the analysis when the data covering the trial period are released from the Office of the Registrar General Database (ORGD) (updated releases from this database occur every 2-3 years).

Timing of Outcome Assessments

Data on the primary outcome (cardiovascular-related death or major cardiovascular-related hospitalization) will be obtained from routinely collected data captured in administrative health care databases held at ICES. Data on the key secondary outcome (the mean drop in intradialytic systolic blood pressure) were obtained directly from hemodialysis run sheets; the predialysis systolic blood pressure is taken before each dialysis treatment and the nadir systolic blood pressure during the dialysis treatment, both typically measured while seated. The blood pressure data are recorded as part of routine care as part of the patients’ medical record. We collected anonymized blood pressure data from hemodialysis run sheets from each center weekly for the first month of the trial, biweekly for the second month, and monthly thereafter. Each collection consisted of data for hemodialysis sessions on the last Friday or Saturday of the period from 15 different patients, who were randomly selected from all patients receiving maintenance hemodialysis at the center at that time.

Statistical Principles

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

We planned the trial using a parallel gatekeeping procedure⁹ to control the overall error rate at 0.05 (to control for multiple testing).¹ The 2-sided significance level will be 0.04 for the primary hypothesis and 0.01 for the key secondary hypothesis.

The remaining secondary outcomes will be tested as follows: If the overall error rate for the primary hypothesis and key secondary hypothesis exceeds 0.05, the results of subsequent tests will be provided as point estimates with 95% confidence intervals (CIs; without *P* values), and we will indicate that the interval widths are not adjusted for multiple testing and that the inferences may not be reproducible.¹⁰

If there is a statistically significant improvement in the primary outcome or the key secondary outcome, the remaining secondary outcomes will be tested in the following order at a level of significance that maintains the overall error rate across all prior testing at 0.05 (example below): (1) A composite of all-cause mortality or cardiovascular-related hospitalization, (2) all-cause mortality, (3) hospital admission with myocardial infarction, (4) hospital admission with congestive heart failure, (5) hospital admission with ischemic stroke, and (6) cardiovascular death.

For example, if the primary outcome is nonsignificant ($P \geq .04$) and the key secondary outcome is nonsignificant ($P \geq .01$), no further hypothesis testing will be performed. If the primary outcome is significant and the key secondary outcome is nonsignificant, then the remaining secondary outcomes will be tested at a significance level of 0.04 until a *P* value is $\geq .04$. If the primary outcome is nonsignificant and the key secondary outcome is significant, then the remaining secondary outcomes will be tested at a significance level of 0.01 until a *P* value is $\geq .01$. Once one of these tests exceeds an overall error rate across all prior testing at 0.05, as described above, the results of subsequent analyses will be limited to point estimates with 95% CIs (without *P* values), and we will indicate that the interval widths are not adjusted for multiple testing and that the inferences may not be reproducible.¹⁰

Adherence and Protocol Deviations

We obtained anonymized data on the programmed dialysate temperature from hemodialysis run sheets in the same manner and following the same schedule as for the collection of blood pressure data (described in section “Timing of Outcome assessments,” above). We used these temperature data to assess adherence to the intervention. During the trial period, we identified and worked with centers if they demonstrated <80% adherence (ie, if the dialysate temperature was routinely being set outside the specified range in the protocol; strategies used to address non-adherence are provided in Al-Jaishi et al).¹ In the final report, we will display the distribution of dialysate temperatures used in the intervention and control groups over the trial period, and the difference between patients’ mean predialysis temperature and the programmed dialysate temperature. Summary measures for each group and between-group differences will be presented with 95% CIs.

The allocated dialysate temperature protocol was implemented by hemodialysis centers and did not follow patients who transferred to centers using a different temperature

protocol (ie, patients received the protocol used at the center they transferred to [also referred to as patient crossovers]). As well, patients no longer received the allocated protocol if they switched to peritoneal dialysis, home hemodialysis, or nocturnal hemodialysis, or if they transferred to a center not participating in the trial in Ontario or a center outside Ontario.

For both the intervention and control groups, we will report the proportion of patients' observation time spent receiving (1) in-center hemodialysis at the index center (or a center providing the same allocated temperature protocol as the index center), (2) in-center hemodialysis at a study center providing the other allocated temperature protocol ("patient crossovers"), (3) dialysis at a nonstudy center in Ontario, (4) other types of dialysis (ie, home hemodialysis, peritoneal dialysis, in-center nocturnal hemodialysis, or in-center self-care hemodialysis), (5) no dialysis due to receipt of a kidney transplant, and (6) no dialysis due to receiving palliative care or due to recovered kidney function. The aggregate proportions will be weighted by the patient's observation time. Based on our analysis of historical records, we expect $\geq 85\%$ of the patients' observation time will be spent receiving in-center hemodialysis with the originally allocated temperature protocol.

Analysis Populations

The trial's analysis population will include adult outpatients who received maintenance hemodialysis at a study center for at least 90 days between April 3, 2017, and March 1, 2021, and who met the trial's eligibility criteria (defined in section "Eligibility Criteria," below). Patients' observation time in the trial will begin on their index date: Patients already receiving maintenance hemodialysis at the beginning of the trial will have an index date of April 3, 2017; the index date of other patients will be when they initiate maintenance hemodialysis for at least 90 days during the trial period (where the index date is the 90-day date; described in more detail in the "Trial Population", "Eligibility Criteria" section below).

Intent-to-treat population. The primary analysis will use an intent-to-treat approach, which consists of all eligible patients from the 84 study centers who entered the trial regardless of what kidney replacement treatments they received in follow-up. All outcome events will be attributed to the center that patients received hemodialysis at on their index date.

As-treated population. As an additional analysis, we will analyze the data using an as-treated approach, which will account for patient crossovers to centers in the other trial arm and patient transfers to different treatment modalities. Given the potential biases of an as-treated analysis, we will give precedence to the results of the intent-to-treat analysis.¹¹ For crossovers, where a patient transfers to a center providing the other allocated temperature protocol, the observation time for the second center will begin after 30 days, and events that occur after this date will be attributed to the second center.

In the as-treated analysis, transfer to a dialysis center providing the other allocated temperature protocol (for >30 consecutive days) will be treated as a time-varying exposure variable. The patient's observation time will end when they (1) switch to another type of dialysis for >30 consecutive days (eg, home hemodialysis, peritoneal dialysis, in-center nocturnal hemodialysis, or in-center self-care hemodialysis), (2) transfer to a center not participating in the trial for >30 consecutive days, (3) receive a kidney transplant, or (4) no longer receive any form of kidney replacement therapy for at least 90 consecutive days. These events will be treated as competing-risk events in the as-treated analysis (see section "Additional Analyses," below, for more details). In addition, for patients at a small proportion of centers that started delivering the allocated temperature protocol after the trial start date (ie, after April 3, 2017) due to delays in ethics and institutional approvals, the patients' observation time will begin after the center started delivering the allocated treatment protocol. Finally, as in the intent-to-treat analysis, we will assume all patients in a given center received hemodialysis using the temperature protocol allocated to that center; as described above in section "Adherence and Protocol Deviations," we expect $>80\%$ of hemodialysis treatments on average will be adherent to the allocated protocol.

Trial Population

Eligibility Criteria

The MyTEMP trial had 2 center-level inclusion criteria: (1) The hemodialysis center had to expect to treat a minimum of 15 outpatients with maintenance in-center hemodialysis at the start of the trial period and (2) the medical director of the hemodialysis center (who acted as the center's gatekeeper) had to allow their center to implement the randomly allocated dialysate temperature protocol for the duration of the trial. On February 1, 2017 (the randomization date), 84 of Ontario's 97 hemodialysis centers met the trial's eligibility criteria and were included in the trial.

At the time of the analysis, we will restrict the trial's analysis population to patients who received maintenance in-center hemodialysis at a trial center between April 3, 2017, and March 1, 2021 (to allow for at least 30 days of follow-up). To minimize the inclusion of transient patients and those receiving temporary dialysis, we will further restrict the analysis to patients who received dialysis at the same participating study center for at least 90 days, which will be the patient's index date (see Al-Jaishi et al.)¹. We term this the *90-day stability rule*. Patients who met the stability rule before April 3, 2017, will have an index date of April 3, 2017 (the trial start date). Patients who started maintenance in-center hemodialysis after April 3, 2017 (eg, patients new to in-center hemodialysis, or patients returning to in-center hemodialysis from home dialysis or a failed transplant), will

be assigned an index date on the date they meet the stability rule. The index date is start of the patient's observation time in the trial.

We will exclude patients who are not Ontario residents, patients with missing data on age or sex, and patients with an invalid health card number. We will also exclude patients older than 105 years, given the possibility the value was entered in error (a common exclusion used in ICES studies). These exclusions are primarily for data cleaning purposes to ensure that we can link patients across the different data sets, and we expect to exclude very few patients for these reasons. We will also exclude patients younger than 18 years because they are not recorded in the ORRS registry.

Flow Diagram

We will report the number of eligible and recruited centers, and the corresponding patients included in the analyses by the allocation group in a flow diagram (Figure 1 in the Supplemental Material).

Withdrawal and Loss to Follow-up

No centers withdrew from the study during the trial period. One dialysis center closed, and patients assigned to this center before it closed will continue to be followed up for the trial period. In addition, one center divided into two centers after the trial started; these centers will be treated as a single cluster for the primary intent-to-treat analysis. Given that patient follow-up is performed through provincial administrative health care data, the only reason for loss to follow-up is emigration from the province, which occurs at a rate of 0.5% per year for the general population;¹² however, we can ascertain any outcomes that occur before emigration.

Baseline Patient Characteristics

Baseline characteristics will be obtained through administrative data and center-level survey reporting. A list of baseline characteristics and database sources is available in appendix 7 of Al-Jaishi et al.¹ Continuous data will be summarized using means (standard deviations) or medians (25th, 75th percentiles) as appropriate. Binary and categorical variables will be summarized using counts and percentages. We expect to report a key set of baseline characteristics in the primary paper, with additional characteristics provided in an appendix.

We will use the Registered Persons Database supplied from the Ontario Ministry of Health and Long-term Care and enriched with other data sources at ICES to obtain demographic information. Kidney characteristics will be obtained from ORRS and the Canadian Organ Replacement Registry. Baseline outpatient medication dispensing will be obtained through the Ontario Drug Benefit (ODB) database using a 120-day lookback before the index date. Health care use in the year before the index date and baseline characteristics in

the 5 years before the index date will be assessed using the Ontario Health Insurance Plan Claims Database (OHIP), the Canadian Institute for Health Information Discharge Abstract Database (CIHI-DAD), CIHI's Same Day Surgery database, and the National Ambulatory Care Reporting System database. The OHIP Claims Database is supplemented with the ICES Physician Database and the Corporate Provider Database to obtain data on health care use with specific provider types. Long-term care status will be obtained from ODB, OHIP, and the Continuing Care Reporting System. Baseline laboratory information in the year before the index date will be obtained through the Ontario Laboratories Information System. We will use ICES-derived cohorts to determine the history of certain chronic conditions such as diabetes,¹³ congestive heart failure,¹⁴ hypertension,^{15,16} and chronic obstructive pulmonary disease.¹⁷ Whenever possible, we will use validated algorithms to define baseline variables that have been used in multiple prior studies.

Analysis

Outcome Definitions

The *primary outcome* is a composite of cardiovascular-related death or hospital admission with myocardial infarction,¹⁸ congestive heart failure,¹⁴ or ischemic stroke.^{19,20} Cardiovascular-related hospitalization will be defined using main diagnostic codes from CIHI-DAD. Data on cause of death will be obtained from the ORGD, which uses a modified version of Becker's groupings based on *International Classification of Diseases 10th Revision (ICD-10)* coding.²¹ The specific algorithm for the primary composite outcome is provided in the trial protocol.¹

The *key secondary outcome* is the mean drop in intradialytic systolic blood pressure. To calculate this, we will subtract each patient's nadir intradialytic systolic blood pressure from their predialysis systolic blood pressure, and then average these values at the center level for each of the 48 timepoints during the 4-year trial period. As described in section "Timing of Outcome Assessments" above, anonymized data on patients' predialysis systolic blood pressure and their intradialytic systolic blood pressure were collected from a random sample of 15 patients at monthly intervals from each dialysis center. These blood pressure data will be averaged monthly for each center. As such, during the 4-year trial period, we will have a total of 48 summary measures (ie, 1 a month), for each of the 84 centers in our trial.

The *other secondary outcomes* are a composite of all-cause mortality or cardiovascular-related hospitalization, all-cause mortality, and the components of the primary outcome examined separately: hospital admission with myocardial infarction, hospital admission with congestive heart failure, hospital admission with ischemic stroke, and cardiovascular-related mortality.

We will also examine a composite of all-cause emergency room visits or all-cause hospitalizations (each will also be examined separately as the number of visits and hospitalizations, respectively), a hospital encounter with lower limb amputation, and a hospital encounter with a major fall or fracture.²²⁻²⁴

Finally, we will examine four definitions of intradialytic hypotension using the same blood pressure data as for the key secondary outcome at the cluster level. We will examine the center's proportion of patients (weighted by the dialysis center size) whose (1) systolic blood pressure dropped from ≥ 90 mm Hg before dialysis to < 90 mm Hg during dialysis; (2) nadir intradialytic systolic blood pressure was $\geq 25\%$ lower than their predialysis level *or* whose systolic blood pressure dropped from ≥ 90 mm Hg before dialysis to < 90 mm Hg during dialysis; (3) nadir intradialytic systolic blood pressure was $\geq 25\%$ lower than their predialysis level; and (4) nadir intradialytic systolic blood pressure was ≥ 35 mm Hg lower than their predialysis level.

Analytic Methods

For both the intervention and control groups, we will summarize the weighted proportion of the patients' observation time spent receiving hemodialysis at an index center (or a center providing the same allocated temperature protocol as the index center), the time spent receiving hemodialysis at other centers, and the time spent receiving other forms of kidney replacement therapy (as described in the "Adherence and Protocol Deviations" section, above, and in Figure 2 in the Supplemental Material). Patient crossovers between the intervention and control arms will also be reported.

Analysis of the primary outcome. The primary analysis will follow an intention-to-treat approach. Eligible patients will be analyzed according to their index center's treatment allocation (regardless of whether they transitioned to other dialysis centers or received other types of kidney replacement therapy in follow-up). Patients will be followed up until they experience the primary outcome, emigrate from Ontario, or die of a noncardiovascular cause (which will be treated as a competing-risk event).

We will report the crude frequency (%) and crude event rate (number of events per 100 person-years) for the time to first event for the primary composite outcome. We will create a graph of the nonparametric cumulative incidence function (CIF) showing the time followed, number of events, and patients at risk during regular intervals in the trial for the intervention and control groups.²⁵ Noncardiovascular death will be treated as a competing-risk event.²⁶ We will present the curves for visualization purposes only (no statistical tests will be conducted for differences between curves); we will simultaneously present the curves of the primary outcome, the components of the composite outcome, and the competing risk of noncardiovascular death.

We will assess the intervention's effect on the rate of the primary outcome using the multivariable generalized-estimating-equations extension for the Fine and Gray's subdistribution proportional hazards, with an exchangeable covariance matrix, to account for the clustering of patients within hemodialysis centers and the competing risk of noncardiovascular death.²⁶⁻²⁸ We will supplement the primary analysis with the cause-specific hazard model for both the primary outcome and competing-risk of noncardiovascular death.^{26,29-31} We also will explore the composite of our primary event with the competing risk as described in the "Additional Analyses" section below.

As our study used covariate-constrained randomization, we will adjust for constrained covariates in our analyses; these patient-level covariates include age, biological sex, rural status, race, modified Charlson comorbidity index,^{32,33} number of unique hospital admissions (in the 12 months before the index date), number of unique hypertensive prescriptions, referral to a nephrologist < 3 months before initiating dialysis, type of vascular access on the index date, serum albumin on the index date, and the following baseline comorbidities: myocardial infarction, congestive heart failure, peripheral vascular disease, and diabetes mellitus. We will also adjust for the cluster-level historical rate of the composite outcome of cardiovascular-related death and major cardiovascular-related hospitalization.

We will evaluate and report the model assumptions for the clustered subdistribution hazard and cause-specific hazards models. Appropriate techniques will be applied when model assumptions are violated. Specifically, this model assumes a linear relationship between the log hazard and covariates. We will assess the assumption for linearity using residual plots. From historic data, we expect that the linearity assumption will be violated for our continuous covariates. If this occurs, we plan to correct for the nonlinear covariates using restricted cubic splines. We will assess the proportionality of the hazard visually and use the Schoenfeld test for the intervention. If the assumption of proportionality is violated, we will consider alternative methods so that the model remains valid (ie, a time-stratified model to identify constant hazard ratios within appropriate time intervals).

If we observe a statistically significant effect of the intervention on the rate of the primary outcome, we will provide the absolute risk difference (and 95% CI) of the CIF for the intervention and control groups at different time points during follow-up (including the median time points).

Bayesian analysis of the primary outcome. Our trial is powered to detect a hazard rate reduction in the primary composite outcome of at least 20% (corresponding to a hazard ratio of 0.80).¹ We acknowledge that effects smaller than 20% could still be clinically meaningful. While we will give precedence to the results of the frequentist analysis, we will additionally conduct a prespecified Bayesian analysis to examine the probability that the intervention reduces the rate of the primary composite outcome by 5%, 10%, and 15% compared with the control

group based on the trial results. This analysis is motivated by advice that prespecified Bayesian analyses can complement frequentist analyses in the interpretation of the results of randomized clinical trials.^{34,35}

We will conduct and report a Bayesian analysis based on existing guidelines.³⁶ We aim to determine the probability that the intervention (1) affects the primary outcome and (2) reduces the hazard rate of the primary outcome by 5% to 30%, given the observed data. The range of hazard ratios will be presented in a figure. We considered a minimum 5% hazard rate reduction (ie, hazard ratio = 0.95) in the primary composite outcome as clinically relevant, as adopting the intervention with such an effect would still prevent many major cardiovascular-related hospitalizations and/or deaths each year.

We will explore a range of prior distributions (see Appendix 1 and Table 1 in the Supplemental Material) that can condition the posterior distribution. We will use priors to reflect varying degrees of enthusiasm and skepticism for the benefit of a personalized temperature-reduced dialysate before starting MyTEMP. The parameter's estimate and standard errors will be obtained from the analysis (as described in the "Analysis of the primary outcome" section above) and combined with prior distributions to obtain the model's posterior distributions. We will estimate the Bayes factor and credible intervals using Markov chain Monte Carlo sampling techniques with at least 3 parallel chains. We will report the probability of the truth of our conclusions. This approach enables the specification of prior information, controls the sampling, and obtains posterior summary statistics and convergence diagnostics. The convergence of the generated Markov chain will be assessed by examining the trace plot, autocorrelation function plot, and posterior density plot.

Analysis of the key secondary outcome. The between-group difference in the key secondary outcome (the mean drop in patients' intradialytic systolic blood pressure) will be obtained using an unadjusted, generalized linear mixed model on the cluster-period summaries that accounts for the repeated measurements at the cluster level over time using longitudinal analysis methods,³⁷ and appropriate CIs will be generated as described in section "Confidence Intervals and *P* Values: Level of Statistical Significance" in the "Statistical Principles" section above.

Analysis of other secondary outcomes. We will use the same analytic approach as for the primary outcome to examine each component of the primary outcome separately and the other secondary time-to-event outcomes (ie, see secondary outcomes listed in "Confidence Intervals and *P* Values: Level of Statistical Significance" and "Outcome Definitions" sections). Death (or noncardiovascular-related death) will be treated as a competing-risk event in these analyses when not part of the outcome. The model assumptions will be assessed as described in the "Analysis of the primary outcome" section, above.

The number of all-cause hospital admissions and emergency department visits during the study period will be analyzed using a negative binomial model relevant for count data while adjusting for clustering of dialysis centers with generalized estimating equations and using the log of time as an offset. We have chosen a negative binomial model because the historic data show a propensity for overdispersion (ie, the mean and variance of all-cause hospitalization and emergency room visits appear to be different). We will assess model assumptions and evaluate the fit of our model. From historic data, we expect that 85% of our cohort will have at least 1 hospital admission and/or emergency department visit in follow-up, and we also expect this outcome to be right skewed. We will perform and report model diagnostics.

The four definitions of intradialytic hypotension will be analyzed at the center level in a similar manner as the key secondary outcome (ie, unadjusted, generalized linear mixed model on the cluster-period summaries).

Additional Analyses

We will conduct several additional analyses to assess the robustness of the results of the primary analysis. We will conduct an as-treated analysis (see the "Analysis Populations" section, above). We will also conduct a additional competing-risk analysis, a recurrent-event analysis, and prespecified subgroup analyses.

Competing-risk events. Additional events that may influence a patient's chance of experiencing the primary outcome include receipt of a kidney transplant, switching to a non-center hemodialysis modality, and emigrating from the province. As such, we will conduct additional analyses and treat these events as competing risks.^{31,38} We will report how often these events occur during the follow-up period (see Figure 2 in the Supplemental Material for more detail) and examine the extent to which treating these as competing events impacts our estimate of the intervention effect.²⁶

Recurrent events. In an analysis of historical data, over a 4-year follow-up period predating the trial, we found that 19% of patients experienced at least one event in our primary composite outcome. Only 4% of all patients experienced more than one event. Given the infrequent number of recurrent events, we decided to use a parsimonious approach of time-to-first event model for the primary analysis. However, we will repeat the primary analysis using a recurrent-event model such that patients may contribute multiple outcome events during the trial period. We will use a cluster analog of the mean and rate functions in a recurrent-event multivariate regression model³⁹ to accommodate multiple events per patient while accommodating the clustered design using a marginal approach (ie, a common baseline rate function).⁴⁰ We will define a hospitalization episode of care as a direct admission to an acute care hospital from which the patient has subsequently been discharged home (ie, a hospital discharge and admission within the same day is considered to all be part of the same episode of care, as this could be simply a transfer between hospitals).

Subgroup analyses. In our protocol, we have prespecified two subgroup analyses for the MyTEMP trial. We will simply provide point estimates and corresponding 95% CIs for subgroups and will not perform significance testing. First, a subgroup analysis of patients with preexisting cardiovascular disease (ie, patients hospitalized with myocardial infarction, ischemic stroke, or congestive heart failure at least once before study entry). Second, a subgroup of new hemodialysis patients, that is, those starting in-center hemodialysis for the first time during the trial period. These analyses will follow the same approaches as described above. We hypothesize that the intervention may confer a larger absolute benefit to these 2 subgroups of patients. To examine the presence of additive interaction, we will calculate the hazard ratios (and 95% CI) between the intervention and control groups in patients with and without preexisting cardiovascular disease, and in new hemodialysis patients versus those who were already receiving dialysis when the trial started on April 3, 2017.

Missing Data

Given that our trial follow-up is through administrative health care data held at ICES, we anticipate no missing data for our outcomes unless a patient emigrated from Ontario during follow-up (anticipated in <0.5%), which will be treated as a censoring event in the primary analysis.

From previous work, we anticipate a small amount of missing data on some baseline characteristics. We will recode missing data on rural status as urban, missing data on race as Caucasian, and missing data on the modified Charlson comorbidity index as 2 (the minimum value associated with kidney failure).⁴¹ If there is <10% missing data on baseline serum albumin, we will use simple imputation; if there is between 10% and 40% missing, we will use multiple imputation; if there is >40% missing, we will exclude serum albumin from the adjusted analyses.

Harms

As described in prior studies (summarized in the protocol),¹ the MyTEMP intervention is well tolerated by patients. It was deemed a minimal risk to patients by the Research Ethics Review Boards which approved MyTEMP (further details in the protocol).¹ There was a waiver of patient consent for enrollment into MyTEMP, and patients were notified through posters and letters about their dialysis center's allocation. A patient or their nephrologist retained the option to opt out of the random allocation (ie, receipt of the treatment); however, patients could not opt out of data collection of the primary analysis as data are obtained as secondary use of routinely collected data. There are no prior data to suggest the intervention will increase the risk of our primary or secondary outcomes compared with the control group (although our hypothesis testing approach will examine for this possibility). We have undertaken a separate independent substudy in

a small set of centers to confirm there are no large between-group differences on patient-reported symptoms (eg, feeling cold on dialysis). We are also linking some electronic dialysis medical records to the ICES databases, to confirm in an observational cohort that the intervention is not associated with an altered risk of missed dialysis treatments or coming off hemodialysis treatments early.

Statistical Software

The primary analyses will be performed in SAS software version 9.4 (NC, Cary). We may use additional software (eg, R Project, STAN or WinBUGS) for some analyses (eg, Bayesian analysis).

Trial Status

Eligible hemodialysis centers in Ontario were randomized on February 1, 2017. Centers began delivering the intervention on April 3, 2017. The last day of follow-up is March 31, 2021. Eligible patients receiving in-center hemodialysis between April 3, 2017, and March 1, 2021, will be included in the analysis.

Discussion

We designed a pragmatic, cluster-randomized registry trial to compare the effect of using a personalized, temperature-reduced dialysate protocol versus a fixed dialysate temperature of 36.5°C on the rate of cardiovascular-related mortality and hospitalizations. This work provides a comprehensive outline of the analytic plan for the MyTEMP trial. We discussed the methods used for our prespecified primary, key secondary, and other secondary outcomes. We also provided details on additional analyses, which will be used to assess the robustness of the findings in our primary analysis. We hope this article will aid in the interpretation of MyTEMP and the design and analysis of other hemodialysis cluster-randomized trials in the future.

Ethics Approval

The Health Sciences Research Ethics Board at Western University centrally approved the research ethics application for Ontario through the Streamlined Research Ethics Review System managed by Clinical Trials Ontario (Application Number: CTO-0736). 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 and does not require review by a Research Ethics Board.

Consent to Participate

The Research Ethics Board approved our application with alteration to the informed consent process as described in the protocol.

Consent for Publication

Consent for publication was obtained from all authors.

Availability of Data and Materials

The ICES Analyst and Scientist involved in the study will have access to the trial data obtained through ICES. 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 (e-mail: 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. The study investigators will have access to the trial data collected outside of ICES. These data will not be available to the public.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: G.N. has received consulting fees from Baxter Healthcare and Amgen. M.J.O. is the owner of Oliver Medical Management Inc, which licenses Dialysis Management Analysis and Reporting System software. He has received honoraria for speaking from Baxter Healthcare and participated on advisory boards for Janssen and Amgen. R.W. has received unrestricted research support from Baxter. The other authors declare no potential conflicts of interest to disclose.

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Data Monitoring

The Data Safety Monitoring Board (DSMB) (Drs Lehana Thabane, John Eikelboom, and Clara Bohm) are experts in clinical trials and hemodialysis. The DSMB reviewed the protocol, statistical analytic


plan, and other trial documents. No interim analyses were conducted beyond assessing protocol adherence.

Dissemination Policy

We plan to disseminate the results of the MyTEMP trial through peer-reviewed publication.

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Supplemental Material

Supplemental material for this article is available online.

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