Study Protocol-Clinical Research

Major Outcomes With Personalized Dialysate TEMPerature (MyTEMP): Rationale and Design of a Pragmatic, Registry-Based, Cluster Randomized Controlled Trial

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Abstract

Background: Small randomized trials demonstrated that a lower compared with higher dialysate temperature reduced the average drop in intradialytic blood pressure. Some observational studies demonstrated that a lower compared with higher dialysate temperature was associated with a lower risk of all-cause mortality and cardiovascular mortality. There is now the need for a large randomized trial that compares the effect of a low vs high dialysate temperature on major cardiovascular outcomes.

Objective: The purpose of this study is to test the effect of outpatient hemodialysis centers randomized to (1) a personalized temperature-reduced dialysate protocol or (2) a standard-temperature dialysate protocol for 4 years on cardiovascular-related death and hospitalizations.

Design: The design of the study is a pragmatic, registry-based, open-label, cluster randomized controlled trial.

Setting: Hemodialysis centers in Ontario, Canada, were randomized on February 1, 2017, for a trial start date of April 3, 2017, and end date of March 31, 2021.

Participants: In total, 84 hemodialysis centers will care for approximately 15 500 patients and provide over 4 million dialysis sessions over a 4-year follow-up.

Intervention: Hemodialysis centers were randomized (1:1) to provide (1) a personalized temperature-reduced dialysate protocol or (2) a standard-temperature dialysate protocol of 36.5°C. For the personalized protocol, nurses set the dialysate temperature 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.

Primary outcome: A composite of cardiovascular-related death or major cardiovascular-related hospitalization (a hospital admission with myocardial infarction, congestive heart failure, or ischemic stroke) captured in Ontario health care administrative databases.

Planned primary analysis: The primary analysis will follow an intent-to-treat approach. The hazard ratio of time-to-first event will be estimated from a Cox model. Within-center correlation will be considered using a robust sandwich estimator. Observation time will be censored on the trial end date or when patients die from a noncardiovascular event.

Trial Registration: www.clinicaltrials.gov; identifier: NCT02628366.

Abrégé

Contexte: De petits essais à répartition aléatoire ont montré que l'utilisation d'un dialysat à basse température réduisait le risque d'hypotension intra-dialytique. De même, certaines études observationnelles ont démontré qu'un dialysat à basse température était associé à un plus faible risque de mortalité toute cause ou d'origine cardiovasculaire. Le temps est venu de procéder à un vaste essai à répartition aléatoire comparant les effets d'un dialysat à basse température et à température standard sur les principaux résultats cardiovasculaires.

Objectif: Répartir aléatoirement des centres d'hémodialyse ambulatoire pour qu'ils suivent pendant quatre ans (i) un protocole personnalisé de dialysat à basse température ou (ii) un protocole de dialysat à température standard, et tester l'effet sur les hospitalisations et la mortalité attribuables à des événements cardiovasculaires.

Type d'étude: Un essai clinique à répartition aléatoire en grappes.

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Cadre: Le 1er février 2017, des centres d'hémodialyse de l'Ontario (Canada) ont été répartis aléatoirement en vue d'un essai qui a débuté le 3 avril 2017 et qui se poursuivra jusqu'au 31 mars 2021.

Participants: Quatre-vingt-quatre centres d'hémodialyse qui prendront en charge environ 15 500 patients pendant les quatre ans de suivi.

Intervention: Les centres d'hémodialyse ont été répartis aléatoirement (1:1) pour offrir (i) un protocole personnalisé de dialysat à température réduite ou (ii) un protocole de dialysat à 36,5°C. Pour le protocole personnalisé, les infirmières règlent la température du dialysat entre 0,5 et 0,9°C sous la température corporelle du patient mesurée avant la dialyse, jusqu'à une température minimale de 35,5°C.

Principaux résultats: Un ensemble d'hospitalisations attribuables à un événement cardiovasculaire majeur (accident ischémique cérébral non fatal, infarctus du myocarde ou insuffisance cardiaque congestive) et de décès d'origine cardiovasculaire consignés dans les bases de données de santé de l'Ontario.

Principale analyse envisagée: L'analyse primaire adoptera une approche fondée sur l'intention de traiter. Un modèle de Cox servira à estimer le rapport de risque du temps écoulé jusqu'au premier événement. La corrélation intra-centre sera prise en compte à l'aide d'un estimateur sandwich robuste. Le temps d'observation sera censuré à la date de fin de l'essai ou au moment d'un décès non lié à un événement cardiovasculaire.

What was known before

- The results of small randomized clinical trials suggest that a cooler dialysate temperature (≤35.5°C) compared with a standard dialysate temperature (≥36.0°C) lessens the drop in systolic blood pressure during hemodialysis treatments.
- In some observational studies, using a cooler dialysate temperature (≤35.5°C) vs a standard dialysate temperature (≥36.0°C) was associated with a lower rate of all-cause and cardiovascular-related death in adults receiving in-center hemodialysis.

What this adds

- The Major Outcomes with Personalized Dialysate TEMPerature (MyTEMP) trial will generate robust information on whether providing a personalized dialysate temperature (set 0.5°C below a patient's body temperature measured prior to each dialysis session) vs usual dialysate temperature (36.5°C) as a hemodialysis center policy for 4 years alters the risk of cardiovascular-related death or cardiovascular-related hospitalization.

Background

Maintenance hemodialysis provides a life-saving treatment for patients with end-stage kidney disease (approximately 3 million worldwide and 23 000 in Canada); however, 20% to 40% of patients die within 1 year of starting dialysis, which is often due to cardiovascular-related causes.[1-5] Evidence from magnetic resonance imaging showed hemodialysis itself can injure the heart, brain, and other vital organs through repeated episodes of intradialytic hypotension and subclinical ischemia.[6-13] During a hemodialysis session, blood pressure often drops by 20 mm Hg or more, and this can lead to coronary hypoperfusion and myocardial stunning,[14,15] which is associated with left ventricular dysfunction.[8,10,16-18] This results in the heart losing some of its ability to compensate for the reduced blood volume that occurs during dialysis, and this may lead to further hypotensive events and related ischemic organ damage (more detail in Supplemental Appendix 1—Section 1.1). In observational research, a greater frequency of intradialytic hypotension was associated with an incrementally greater risk of death, and patients with the lowest nadir blood pressure during dialysis had the highest risk of death.[13]

Reducing the dialysate temperature is one strategy to help stabilize blood pressure during hemodialysis. The measures used to describe blood pressure differences between cooler dialysate temperature (≤35.5°C) vs a standard dialysate temperature (≥36.0°C) in prior individual-level randomized controlled trials (RCTs) have not been consistent; with some reporting mean intradialytic systolic blood pressure, nadir systolic blood pressure, and predialysis and postdialysis blood pressure. Nevertheless, these trials reported that cooler compared with standard dialysate temperature led to (1) higher intradialytic nadir systolic blood pressure readings, (2) a smaller drop in postdialysis blood pressure from predialysis blood pressure, and (3) a smaller drop in nadir intradialytic blood pressure from predialysis blood pressure (more detail in Supplemental Appendix 1—Section 1.2 and eTable 1).[15,19-28]

A cooler dialysate may also improve peripheral vascular resistance, improve cardiac function, and alter the level of vasoactive peptides—all of which may stabilize intradialytic blood pressure.[24,29-35] Compared with a dialysate temperature of 37°C (standard dialysate temperature in the United Kingdom, where the trial took place), a cooler personalized dialysate temperature (ie, 0.5°C below the patient's predialysis body temperature) showed less injury to both the brain and the heart over a 12-month period, as observed on magnetic resonance imaging (more detail in Supplemental Appendix 1—Section 1.2).[8,10]

In a meta-analysis of 26 randomized clinical trials (total 484 patients), a cooler dialysate temperature (ie, 34°C-35.5°C vs the control, where the control in different regions ranged from 36°C to 38.5°C) reduced the rate of intradialytic hypotension by 70% (95% confidence interval: 49%-89%), significantly increased the intradialytic mean arterial pressure by 12 mm Hg (95% confidence interval: 8-16 mm Hg).[36] Several trials reported a smaller drop in average intradialytic nadir systolic blood pressure and postdialysis systolic blood pressure compared with predialysis systolic blood pressure.[19,21,22,36] Dialysis adequacy (measured using Kt/V was not statistically different between patients treated with cooler vs standard dialysate temperature.[36] Most trials enrolled fewer than 30 patients and only 3 trials followed patients for longer than 6 sessions; mortality and major adverse events were not evaluated.[23,24,37] In observational studies, the use of a cooler dialysate has been associated with a reduced risk of cardiovascular mortality[38,39] and all-cause mortality in some,[38] but not all studies[39,40] (more detail in Supplemental Appendix 1—Section 1.3).

Currently, the dialysate temperature used in most centers in Canada and the United States ranges from 36.5°C to 36.7°C (97.7°F-98.1°F) (more detail in Supplemental Appendix 1—Section 1.4).[41] This practice comes largely from clinical tradition rather than empirical evidence (with the historic rationale being that the dialysate temperature should be similar to the average body temperature). While a cooler dialysate shows promise for stabilizing intradialytic blood pressure and improving patient outcomes, current trials investigating this question (registered on clinicaltrials. gov) plan to enroll fewer than 150 patients and will therefore lack statistical power to test the effect of this intervention on many important outcomes. To inform clinical practice, evidence from a large, pragmatic, high-quality, multicenter randomized clinical trial is needed.[36,42,43]

A Pragmatic Cluster Randomized Clinical Trial of Dialysate Temperature

This protocol describes the design and statistical analysis plan for a cluster randomized clinical trial that will test the effect of randomizing hemodialysis centers to provide a personalized reduced-temperature dialysate protocol vs a standard-temperature protocol (ie, 36.5°C) for 4 years on the rate of

cardiovascular-related death or hospitalization in outpatients receiving maintenance hemodialysis. The personalized dialysate temperature-reduced approach proposed in this trial accounts for individual, diurnal, and seasonal variations in body temperature. In contrast, a nonpersonalized protocol of dialysate temperature might be fixed at a specific temperature (eg, 35.5°C) for all patients, irrespective of their body temperature. In a clinical trial of 73 patients, a personalized approach achieved the hemodynamic benefits of cooler hemodialysis without any major patient concerns about feeling cold (no patient stopped their hemodialysis session early).[8,10] More details on how the dialysate temperature is set and maintained during hemodialysis and patient effects are provided in Supplemental Appendix 1—Sections 1.5 and 1.6.

Objective

The purpose of this study is to test the effect of randomizing hemodialysis centers to provide (1) a personalized temperature-reduced dialysate protocol of 0.5°C to 0.9°C below the patient's predialysis body temperature measured before each dialysis session, to a minimum dialysate temperature of 35.5°C, vs (2) a standard-temperature dialysate protocol of 36.5°C, for a period of 4 years, on a composite outcome of cardiovascular-related death or hospitalization for major cardiovascular events in outpatients receiving maintenance hemodialysis.

Methods

Study Design and Overview

The *M*ajor outcomes with personalized dial*y*sate *TEMP*-erature (MyTEMP) is a pragmatic, 2-arm, parallel-group, registry-based, open-label, cluster RCT. The trial started on April 3, 2017, and enrolled 84 (of the 97) hemodialysis centers in Ontario, Canada, at that time. This province-wide trial is embedded into routine care with center-wide implementation of the intervention delivered by dialysis unit personnel rather than research staff (Supplemental Appendix 1—Section 1.7). Patient characteristics and outcomes will be largely obtained from administrative health care databases. This pragmatic design allows broad inclusion of dialysis centers and a large representative sample of patients that should yield highly generalizable findings (Figure 1).[44,45]

Hemodialysis centers were randomized (1:1) to provide (1) a personalized temperature-reduced dialysate protocol (see "Intervention" section) or (2) a standard dialysate temperature of 36.5°C, which reflects usual practice at Ontario hemodialysis centers. Randomization with concealed allocation was conducted centrally on February 1, 2017, and centers were notified of their group allocation by the study team 2 months before the intervention start date. The primary outcome is a composite of cardiovascular-related death or hospital admission with myocardial infarction, congestive heart
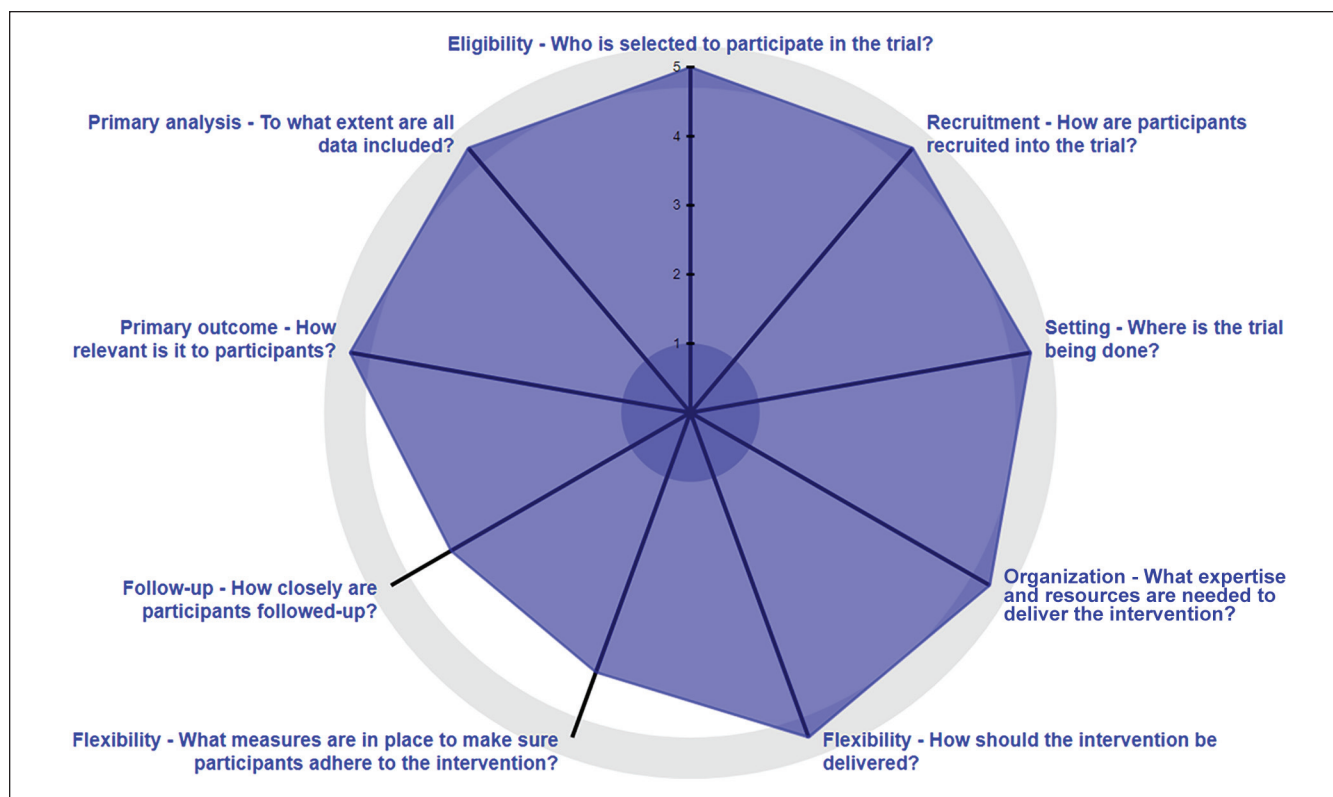
Figure 1. Precis-2 wheel highlighting the pragmatism of MyTEMP trial for 9 domains.
Note. Small reductions in pragmatism relate to (1) monthly data collection from centers to assess intervention adherence and (2) contact with centers that had less than 80% adherence. MyTEMP = Major Outcomes with Personalized Dialysate TEMPerature.

failure, or ischemic stroke. Follow-up for study outcomes will continue until March 31, 2021.

Choice of study design. In this trial, the unit of randomization is the cluster (ie, the hemodialysis center) and the unit of analysis is the patient (for the primary and most secondary outcomes). For the secondary outcome of mean drop in systolic blood pressure (see "Secondary Outcomes" section), the unit of randomization and the unit of analysis is the cluster because we sample a subset of hemodialysis sessions each month to represent the entire cluster (see "Data Collection" section). We chose a cluster randomized design to enhance intervention uptake and adherence (logistical convenience) and to minimize cross-group contamination. Hemodialysis patients typically receive all their treatments at the same center, making this population suitable for cluster-level interventions. Delivery of the MyTEMP intervention in this cluster trial follows what occurs in routine care, where all nurses in each center are trained to follow the same dialysis protocol or policy for patients under their care.

Eligibility Criteria

This trial had 2 inclusion criteria at the level of the hemodialysis center:

1. The hemodialysis center must have cared for a minimum of 15 outpatients being treated with maintenance in-center hemodialysis on January 1, 2017.
2. The medical director of the hemodialysis center (who acted as the center's gatekeeper) must have been willing for their center to adopt the randomly allocated dialysate temperature protocol for the duration of the trial.

Hemodialysis medical centers and patients. On February 1, 2017 (the randomization date), Ontario had 97 hemodialysis centers that were overseen by 26 medical directors. Nine centers (less than a total of 135 patients) cared for fewer than 15 patients, and 4 centers (less than a total of 120 patients) were not included at the request of the medical director. Thus, 84 hemodialysis centers (caring for approximately 7500 hemodialysis patients at the randomization date) met the trial's eligibility criteria. Figure 2 shows the geographical locations of all participating centers.

At the time of the analysis, we will restrict the study cohort to outpatients who received in-center maintenance hemodialysis at a participating study center between April 3, 2017, and March 31, 2021. To minimize the inclusion of patients who leave the study or switch centers soon after starting in-center hemodialysis, we will restrict the cohort to
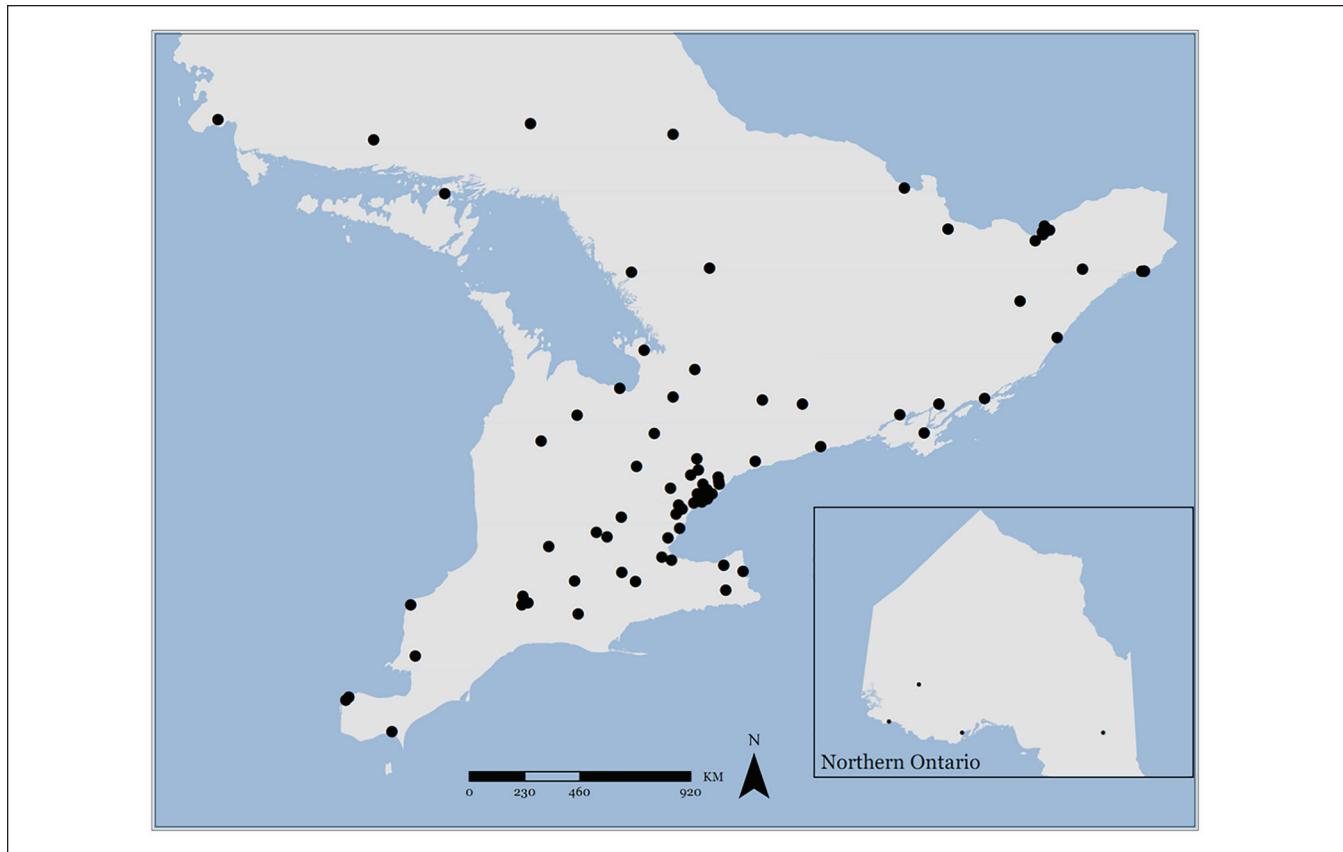
Figure 2. Map of Ontario, Canada, depicting participating centers across the province.
Note. Each black dot represents one of the 84 participating hemodialysis centers that in total care for approximately 7500 patients at any time. During the 4-year trial period, these 84 centers will care for approximately 15 550 patients and will provide over 4 million hemodialysis sessions.

patients who received treatment at the same participating study center for at least 90 days before their cohort entry date (the index date), after which the patient's observation time will begin (termed the 90-day rule). This added restriction would exclude (1) patients who quickly recover renal function (eg, patients with acute kidney injury), (2) early scheduled transfers to home dialysis or those receiving kidney transplants, and (3) those with arranged dialysis treatments away from home (transient dialysis). In our analysis of historic data, approximately 40% of patients were excluded from the cohort as a result of the 90-day rule (in the 90 days observation period prior to cohort entry, patients may have died, recovered their renal function, switched to home dialysis, received a kidney transplant, or emigrated out of the province).

Intervention

Hemodialysis centers were randomly allocated (as described above) to provide a personalized temperature-reduced dialysate protocol or a standard-temperature dialysate protocol. On April 3, 2017, 62 participating centers utilized hemodialysis machines that were able to modify the dialysate temperature by steps of 0.1°C, and the remaining 22 centers

were able to modify the dialysate temperature by steps of 0.5°C. The predialysis body temperature was measured by a nurse as done in usual care before each dialysis session; 41 centers used tympanic, 33 used oral, 6 used a combination of tympanic and oral, and 4 used forehead thermometers.

For the personalized protocol, a nurse sets the dialysate temperature between 0.5°C and 0.9°C below each patient's predialysis body temperature, to a minimum dialysate temperature of 35.5°C (Supplemental Appendices 2 and 3). For machines that can only lower the dialysate temperature by steps of 0.5°C, nurses were asked to lower the temperature to the next increment, to a maximum of 0.9°C below the patient's temperature. For example, if a patient's body temperature is 36.7°C, then the dialysate temperature is set to 36.0°C (Supplemental Appendix 3). The set dialysate temperature remains fixed for the duration of the dialysis session. For the intervention arm, the lowest recommended setting is 35.5°C and the highest is 36.5°C.

Protocol adherence. Participating centers were asked to apply the randomly allocated temperature protocol for all patients and hemodialysis sessions. If necessary, individual patients, in consultation with their nephrologist, may opt to use a different dialysate temperature. In this pragmatic trial, our goal

is to have at least 80% adherence to the center's allocated protocol at any given time. This level of adherence is expected to achieve a target between-group difference in the median dialysate temperature of approximately 0.5°C (ie, the median dialysate temperature is expected to be 36.5°C for centers in the control arm and 36.0°C for centers in the intervention arm). This estimate is based on a preliminary analysis of 12 012 hemodialysis sessions during the 6-month period before the trial start date, where patients had a median predialysis body temperature of 36.3°C (25th, 75th percentiles: 35.9°C, 36.6°C). As described in the "Data Collection" section, we will monitor center adherence by randomly sampling hemodialysis sessions from each center in both groups during the trial follow-up. We have shown that this sampling accurately reflects overall center adherence (see Supplemental Appendix 4). If center adherence drops below 80%, we contact the local site investigator, and where applicable, a nurse educator, charge nurse, or hemodialysis program manager, to explore reasons for low adherence and discuss possible solutions (Table 1). We will also examine the proportion of time patients spend in their index center's initial allocation (ie, if their initial center was allocated to the intervention arm, what proportion of follow-up time did patients spend in a center allocated to the intervention arm).

Implementation Strategy

We used a framework of behavioral change (the Theoretical Domains Framework) to assess and address potential barriers to intervention implementation before the trial started. The results from this work are detailed elsewhere.[48] Briefly, through semistructured interviews with physicians and nurses, we identified some potential barriers that we were able to address before the trial started. These included aligning the intervention protocol with local policies and procedures, addressing concerns about thermometer accuracy, patient comfort, and beliefs about the potential impact of the intervention on patients.[48] This information was incorporated into the trial's educational and training materials, which were delivered by study staff, nurse educators, or charge nurses to the other dialysis nurses. Training sessions included opportunities to discuss and address other additional concerns or barriers to maximize intervention uptake and adherence.

Ethical Considerations

This trial was designed and is being conducted in accordance with the second edition of the Tri-Council Policy Statement (TCPS-2).[49] 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 (CTO), an independent not-for-profit organization established with support from the Government of Ontario. Ethics approval for this trial was given on behalf of 13 institutions (overseeing 45 hemodialysis centers at the time) participating in CTO's streamlined ethics review process. The remaining institutions received ethics approval from their local research ethics boards. The medical directors of the dialysis centers (see "Eligibility Criteria" section) acted as the center's gatekeeper and provided overall approval for their hemodialysis center(s) to participate and be randomized. We also received approval to obtain de-identified baseline and follow-up information on all patients in each participating dialysis center through administrative data sets held at ICES (previously known as the Institute for Clinical Evaluative Sciences), which has special status with the privacy commissioner of Ontario (see "Data Collection" section).

The trial received research ethics approval with a waiver of written patient consent for enrollment, receiving the allocated temperature protocol, and data collection; the criteria for this waiver are detailed in Supplemental Appendix 5. All patients receiving hemodialysis at a participating center were notified about the trial and of their right to opt out of their center's allocated treatment protocol; however, given our data sources (see "Data Collection" section), it is not possible for patients to opt out of data collection or data analysis (where encoded information on all patients receiving hemodialysis at each center is analyzed and aggregated without knowledge of whether a specific patient adhered to the randomly allocated treatment). Participating centers were provided with an information letter to give to patients; the letter described the center's allocated temperature protocol and patients' right to dialyze at a different temperature should they, or their treating physician choose (see "Protocol Adherence" section). As well, posters describing the trial were placed in a highly accessible area (eg, the patient waiting area, near the scale where all patients are weighed before each treatment).

Presentations to Patient and Family Advisory Councils

We presented MyTEMP trial details to several Renal Patient and Family Advisory Councils across Ontario and sought feedback and advice on the trial, the intervention, and on what patient-important outcomes should be considered.[50] These discussions influenced how the trial was communicated to patients (including in the patient information letter) and we are now designing an independent substudy that will assess patient-reported symptoms (eg, itching, tiredness, time to recovery after treatment) in a subset of centers (details of this substudy are not included in this protocol).

Data Collection

Data on patient characteristics and study outcomes will be obtained through administrative data sources housed at

Table 1. Potential Techniques to Address Low Adherence at a Center Depending on the Allocated Group.

Potential reason for low compliance	How the issue may be addressed
Control arm	
Patients are hypotensive and may require cooler dialysate temperature	When patients are at high risk of intradialytic hypotension, and the treating physician wishes to lower the dialysate temperature, we ask their treating physician to consider lowering the dialysate temperature at increments of 0.5°C rather than prescribing a set temperature below 36°C. This recommendation aligns with guidelines from the Canadian Society of Nephrology and other organizations[46,47]
Nurses forget to use the prescribed dialysate protocol	Nurse educator or charge nurse is asked to highlight the importance of following the prescribed dialysate temperature during their regular rounds and educational sessions. Specific nurses not following the prescribed dialysate temperature protocol are approached separately for retraining/education
Intervention arm	
Nurses forget to use the prescribed dialysate protocol	See "Nurses forget to use the prescribed dialysate protocol" above
Nurses set a warmer temperature for patients who are *hyper*tensive	In centers when this occurs, we ask the lead site investigator to speak directly with those nurses regarding the potential impact of raising the dialysate temperature beyond the patient's body temperature. We suggest avoiding externally/actively warming patients by increasing the dialysate temperature beyond the patient's body temperature. During the hemodialysis session, core temperature increases, which may lead to peripheral vasodilation counteracting the normal vascular response to a decline in blood volume. Increasing the dialysate temperature may exacerbate that process and lead to a sudden and significant drop in blood pressure. Also, increasing the dialysate temperature may increase the core body temperature resulting in reduced tissue oxygenation
Patients are unable to tolerate the MyTEMP intervention protocol	Whenever patients decline the intervention due to cold symptoms, we ask nurses to follow the protocol below
	Accommodate patients as per usual care and suggest any of the following, if available, at the unit:
	✓ Suggest that patients bring a blanket to their hemodialysis session
	✓ Suggest that patients bring or wear additional layers to their hemodialysis session
	✓ Offer a warm blanket to keep the patient comfortable
	If the patient continues to feel uncomfortable and unable to tolerate the prescribed dialysate temperature, we suggest physicians and/or nurses increase the dialysate temperature to 36°C to a maximum of 36.5°C
Patients decline the MyTEMP intervention protocol	We ask the treating physician to discuss with their patients the potential benefits of personalized dialysate temperature. Physicians explain that personalized dialysate temperature is the new center protocol because current evidence suggests it may be beneficial for patients. Previous research shows it reduces the frequency in drops in blood pressure and reduces the feeling of fatigue from these drops in blood pressure. As an added benefit, we think by following this new way of setting the machine temperature, our patients may be less likely to experience events like heart attacks and strokes
	When messaging to patients, rather than saying "we are *cooling* the dialysate temperature," please consider messaging the intervention as "personalizing the machine temperature to your [the patient's] body temperature"
	If the patient is willing, the physician/nurse can ask the patient to try personalized dialysate temperature for at least 3 sessions to see how they feel during *and* after the hemodialysis session. Patients were assured they can still use a warm blanket or bring additional layers if they feel cold symptoms during their session
	If a patient wishes to use a different dialysate temperature after these discussions, the treating physician will not adhere to the MyTEMP protocol and prescribe a different temperature moving forward. If the treating physician is prescribing a different temperature, we ask them to consider a dialysate temperature of 36°C rather than 36.5°C

Note. MyTEMP = Major Outcomes with Personalized Dialysate TEMPerature.

Table 2. Expected Number of Prevalent Patients at Any Specific Time and the Expected Total Number of Patients and Hemodialysis Sessions Over the 4-Year Follow-Up.

	Personalized reduced dialysis temperature 0.5°C predialysis core body temperature	Fixed dialysis temperature of 36.5°C
Number of hemodialysis centers	42	42
Expected number of prevalent hemodialysis patients per center Median (25th, 75th percentiles)	Average: 103 Median: 81 (32, 130)	Average: 89 Median: 56 (30, 132)
Expected number of patients per center over the 4-year follow-up[a] Median (25th, 75th percentiles)	Average: 189 Median: 136 (60, 262)	Average: 174 Median: 100 (49, 253)
Expected total number of patients over the 4-year follow-up	7750	7750
Expected number of sessions over 4-year follow-up period[b]	2 184 000	2 184 000
Expected number of sampled hemodialysis sessions over 4-year follow-up period[c]	32 760	32 760

[a]Includes both prevalent patients who were on dialysis as of April 3, 2017, and new patients who start hemodialysis over the 4-year follow-up.
[b]Using historic data, we estimate there will be approximately 31 314 patient-years of follow-up (over a 4-year period). We also assume there will be at least 3500 patients dialyzing at any one point in time per group. Assuming 3 hemodialysis sessions/week regimen, there will be approximately 156 hemodialysis sessions per patient-year [3 sessions/week × 52 weeks/year]. Thus, 3500 patients × 156 hemodialysis sessions per patient-year × 4 years of follow-up is equal to 2 184 000 sessions. (Note: These calculations assume that the number of prevalent patients remains constant overtime and is similar in both groups. The true hemodialysis sessions count will likely be higher because the number of patients on hemodialysis is increasing each year.)
[c]Based on 15 hemodialysis sessions randomly selected per month and 42 centers over a 48-month period. It should be noted, in April and May 2017, we collected data weekly and biweekly, respectively.

ICES. ICES is a prescribed entity for the purposes of Section 45 Ontario's Personal Health Information Privacy Act, which means that health information custodians, including physicians, hospitals, or long-term care homes, are permitted to disclose personal health information about their patients to ICES without patient consent. Secure access to these data is governed by policies and procedures that are approved by the Information and Privacy Commissioner of Ontario. These data sets will be linked using unique encoded identifiers and analyzed at ICES. More information about the databases and variables that will be used in this study is provided in Supplemental Appendices 6 and 7.

The following data, collected as part of routine care, will be obtained from the hemodialysis run sheet as part of patients' medical record: the patient's predialysis body temperature (measured as described in the "Intervention" section), the patient's predialysis systolic and diastolic blood pressure (typically measured while seated), the patient's nadir systolic with accompanying diastolic blood pressure during the hemodialysis session, and the prescribed dialysate temperature. Baseline data on these variables will be obtained from a random sample of 15 hemodialysis sessions from each center during the 2-month period before the intervention start date. After the intervention start date, these data will be collected from a random sample of 15 hemodialysis sessions weekly for the first month, biweekly for the second month, and monthly thereafter. Data will be collected on either the last Friday or Saturday of the data collection period. During the 4-year study follow-up, we expect to sample approximately 65 500 of 4.2 million hemodialysis sessions (Table 2).

Primary Outcome

The primary outcome is a composite of cardiovascular-related death or major cardiovascular-related hospitalization (a hospital admission with myocardial infarction, congestive heart failure, or ischemic stroke; the coding algorithm is provided in Supplemental Appendix 8). Data on cause of death will primarily be obtained from the Office of the Registrar General Deaths (ORGD) database, which records the cause of death for all deaths in Ontario; however, the release of these data is lagging by 2 years. Thus, at the time of the analysis (anticipated in Spring 2023), to avoid delays in the publication of results, ORGD cause-of-death data will be available for all deaths that occur between April 3, 2017, and December 31, 2020 (which is 88% of the follow-up period). Deaths that occur in the last 3 months of follow-up will be captured using the Registered Persons Database,[51] and cause of death will be defined as cardiovascular-related if the patient dies in hospital (or the emergency department) with a cardiovascular event as the main diagnosis on the discharge summary. For the subset of deaths that occur outside of hospital in the last 3 months of follow-up, cause of death will be unknown; using historic data, approximately 33% of cardiovascular-related deaths were missed because they occurred outside of hospital. Hospital encounters for cardiovascular events will be ascertained using the 10th version of the International Classification of Diseases (ICD-10) codes. These codes have high accuracy (Supplemental Appendix 8), demonstrating high sensitivity and specificity in the general population against adjudication of medical charts as the reference standard.[51-55]

Justification for using a primary composite outcome. The primary composite outcome will provide an overall measure of the intervention's impact on cardiovascular-related morbidity and mortality. The outcome components are each expected to respond similarly to the intervention (ie, be reduced by a similar magnitude) and have a similar rate of occurrence, and each is clinically important—appreciating that while death is far worse than a cardiovascular-related hospitalization—avoiding the latter is also important to patients. A detailed justification for each component is provided in Supplemental Appendix 9.

Secondary Outcomes

The key mechanism through which a personalized dialysate temperature may be beneficial is through preventing drops in intradialytic systolic blood pressure. As a key secondary outcome, we will examine the between-group mean difference in the drop in intradialytic systolic blood pressure. A blood pressure drop is defined as the predialysis systolic blood pressure minus the intradialytic nadir systolic blood pressure, where the greater the number (in the positive direction), the larger the drop (see "Data Collection" section).

Most definitions of intradialytic hypotension are defined by a specified drop (eg, ≥20 mm Hg) in systolic blood pressure. In this trial, we have limited statistical power to detect clinically important between-group differences in the proportion of patients who experience intradialytic hypotension. Thus, the outcome of intradialytic hypotension will only be considered in additional post hoc analyses (Supplemental Appendix 10).

The following secondary outcomes will also be examined: a composite of all-cause death or cardiovascular-related hospitalization, all-cause death, and components of the primary composite outcome examined separately.

Other Important Outcomes

We will examine additional patient-important outcomes that (1) may be responsive to the intervention based on prior literature or biologic rationale and (2) can be reliably assessed using our administrative data sources. These outcomes include a composite of emergency department visits and all-cause hospitalization (also each examined separately), a hospital encounter with major lower limb amputation, and a hospital encounter with a major fall or fracture.

Randomization

Sequence generation, allocation concealment, and implementation. Centers were randomly allocated to the intervention or control arm (1:1) using covariate-constrained randomization (detailed below). The allocation scheme was computer-generated at a central location (ICES Western, London, Ontario, Canada) on February 1, 2017, using SAS version 9.4 (SAS Institute Inc, Cary, North Carolina) and concealed from study investigators and centers. The study team notified each hemodialysis center of their assigned allocation approximately 2 months before the intervention start date (the 2-month lead time was chosen to give centers enough time to update their standard operating procedures and to conduct nurse training sessions on delivering the allocated temperature protocol).

Covariate-constrained randomization. We performed the covariate-constrained randomization in the following series of steps (this method has been shown to produce intervention groups that are well balanced on measured baseline characteristics).[56-58] We first generated a large number of randomized allocation schemes from 1.68×10^{24} possible schemes, and selected those with good balance on a set of patient-level baseline characteristics—a scheme was considered to have good balance if the between-group standardized differences on the constrained variables were within 10% caliper.[59] This caliper size was chosen because it was expected to result in the trial arms having over 90% overlap on the distributions of the measured baseline characteristics. We then randomly selected one randomization scheme from the set with good balance. Given that ICES data sources lag by approximately 6 to 12 months, the baseline data used in the covariate-constrained randomization were based on patient and center records from April 1, 2016. New patients will initiate hemodialysis during the trial follow-up period, and these patients are also counted in the primary analysis. Therefore, at the final analytic stage, we will conduct analyses to confirm that the groups are similarly balanced on baseline characteristics at their trial entry date (April 3, 2017, for patients receiving dialysis at the beginning of the trial or, for new patients, on the date they started outpatient hemodialysis).

Blinding. The nature of the intervention makes it infeasible to blind patients, nurses, or nephrologists to the treatment assignment; however, the primary outcome will be recorded by medical coders who are unaware of the trial or the center's treatment assignment. In Ontario, medical coders review the medical charts of all patients with health care encounters, and code all diagnoses and procedures using ICD-10 coding system; this information is then entered into the Canadian Institute for Health Information Discharge Abstract Database. Medical coders only consider physician-recorded diagnoses in the patient's medical chart when assigning the codes, and it is highly unlikely that physicians' recorded diagnoses will be influenced by knowledge of the trial. Moreover, most patients admitted to hospital with major cardiovascular complications are admitted under a most responsible physician who is not their primary nephrologist.

Statistical Power

Power calculations for the primary composite outcome of this trial are based on a comparison of hazard rates (accounting for clustering).[60] To inform these calculations, we conducted a historical analysis of 15 233 patients who received maintenance hemodialysis at 84 Ontario centers in the 4-year period before the trial start date. Each center cared for a median of 122 patients (range, 17-736) and contributed a median follow-up of 258 person-years (range, 35-1524). During this period, the hazard rate for the composite outcome of cardiovascular-related death or hospitalization was 0.095 events per person-year (termed the baseline hazard). We used a coefficient of variation (the ratio of the between-cluster variance to the average baseline hazard rate) of 0.216, and a cluster harmonic mean of the total person-time follow-up of 163 person-years.[60,61] Based on these data, our trial will have 80% power to detect a hazard rate reduction of at least 20% (corresponding to a hazard ratio of 0.80; 2-sided $\alpha = 0.04$; 0.04 chosen to control the family-wise error rate, see "Statistical Significance" section). Supplemental Appendix 11a shows the statistical power achieved for various hazard rate reductions, coefficients of variation, and annual baseline hazard rates for the primary composite outcome. We also confirmed our power calculations through computer simulations that took into account other complex aspects of the study design, including variable cluster sizes, censoring, and different patient follow-up times (these analyses are detailed in Supplemental Appendix 11b and confirmed the trial will have 81% power for a 20% hazard rate reduction [or a hazard ratio of 0.80] in the primary composite outcome [2-sided $\alpha = 0.04$]).[62-65]

Assumptions for power calculations for the key mechanistic secondary outcome are presented in Supplemental Appendix 11c. We have 84% power to detect a 4 mm Hg between-group difference in the mean drop in systolic blood pressure with a 2-tailed $\alpha = 0.01$ (0.01 was chosen to control the family-wise error rate, see "Statistical Significance" section), a standard deviation of 7.2, 6 repeated observations, constant conservative intraclass correlation coefficient (ICC) of 0.4, and an average drop across all sites and periods of 28 mm Hg.

Statistical Analysis Plan

Cohort creation and observation time. The study cohort will include outpatients receiving maintenance hemodialysis at a study center at any time between April 3, 2017, and March 31, 2021. The patient's cohort entry date is their index date. Patients will be analyzed according to their initial center's random allocation on their index date (ie, all outcome events will be attributed to that center [the index center] according to the intention-to-treat principle); for new patients who initiate dialysis during the trial follow-up, the index center is the dialysis center where they entered the cohort. Patients will be followed for study outcomes until death or the trial end date on March 31, 2021. Based on emigration rates in Ontario, we estimate that 0.5% of patients will permanently leave the province every year during follow-up[66] and approximately 85% of patients' observation time will be spent receiving maintenance hemodialysis at their index center (or at another center with the same random treatment allocation). The treatment allocation does not follow patients who transfer to another hemodialysis center during follow-up; rather patients follow the new center's dialysate temperature protocol.

Analysis of adherence to the allocated temperature protocol. Prior to the analysis of the primary outcome, we will assess adherence to the allocated temperature protocol for each month during follow-up and overall for each arm of the trial. The adherence at the center level will be weighted by center size. We will also report the proportion of time patients spend on their index center's treatment allocation.

Analysis of the primary outcome. Our analyses will account for the design and covariate-constrained randomization. In the primary intention-to-treat analyses, we will also assess the effect of the intervention on the rate of the composite outcome of cardiovascular-related death or hospitalization using the multivariable generalized-estimating-equations extension for the Cox proportional hazard model, with an exchangeable covariance matrix, to account for the clustering of individuals within hemodialysis centers.[67,68] Patients will be censored at end of study follow-up or earlier if they die due to a non-cardiovascular-related cause. Patients who recover renal function, switch to a hemodialysis center with the alternative or no temperature allocation, receive a kidney transplant, or switch to home dialysis will be followed for outcomes according to their initial random allocation (see "Additional Exploratory Analyses" section).

Analysis of secondary outcomes. Between-group mean differences in the drop of mean systolic blood pressure is the key secondary outcome, because it examines the mechanism through which a lower dialysate temperature is expected to improve outcomes. This outcome will be analyzed at the center level using a repeated-measures random-effects linear mixed model. This model will provide an estimate (with 99% confidence intervals—see "Statistical Significance" section) of the absolute mean difference in the intradialytic drop in systolic blood pressure between the 2 groups.

For the analysis of the other secondary outcomes, the same approach described for the primary outcome will be used to analyze each component individually (eg, cardiovascular-related death, hospital admission with myocardial infarction) and the other secondary time-to-event composite outcomes (ie, all-cause mortality or cardiovascular-related hospitalization). Noncardiac death (except for outcomes that include all-cause mortality) will be treated as censoring events in these analyses. Model fit will be assessed to ensure

that all assumptions are met (eg, proportional hazards). If proportional hazard assumption is violated, we will explore using a time-stratified Cox model.

Bayesian analysis of the primary outcome. We will assess the robustness of the primary findings (based on the classical frequentist analytic approach) to various assumptions about the use of prior information from various sources. As a supplement, we will conduct and report a Bayesian analysis based on existing guidelines.[69] Our aim is to determine the probability that the intervention (1) has any effect on the primary outcome and (2) reduces the hazard rate of the primary outcome by at least 5%, 10%, 15%, 20%, and 30% given the observed data. We considered a minimum 5% hazard rate reduction (ie, hazard ratio = 0.95) in the primary composite outcome as clinically relevant as it would translate to an estimated 150 lives saved or major cardiovascular-related hospitalizations prevented every year in Canada.

We will explore several prior distributions (Table 3) that can condition the posterior distribution and provide insight about the sensitivity of the primary results. We are using priors to reflect varying degrees of enthusiasm and skepticism for the benefit of personalized dialysate temperature before the start of the MyTEMP trial. See Supplemental Appendix 12 for more details.

Analysis of other outcomes. For the analysis of emergency department visits and all-cause hospitalizations (number of visits and length of stay), the incident rate ratio (visits/events per person-year) will be estimated using either Poisson regression or a negative binomial regression model (depending on the level of dispersion) accounting for within-center clustering. For the analysis of hospital encounters with major lower limb amputation and hospital encounters with major falls or fractures, the hazard ratio for time to first event will be estimated from a Cox model as described above for the primary outcome.

Additional exploratory analyses. We will perform several exploratory analyses to assess the robustness of the primary analysis. These analyses may include treating some events as competing rather than censoring events in follow-up and repeated events per patient (for the primary analysis)—see Supplemental Appendix 13 for more details.

In the literature, the credibility of subgroup effects is generally low, even when claims about the treatment effect made by the researchers are strong.[70] We will visually examine the point estimate of the hazard ratio for the primary outcome with its accompanying 95% confidence intervals across subgroups for consistency of the effect. Two prespecified subgroups of interest, where a personalized dialysis temperature may have a larger treatment effect, are (1) patients with a baseline prior hospitalization with myocardial infarction, ischemic stroke, or congestive heart failure, and (2) incident patients, defined as new patients starting in-center hemodialysis during follow-up

(based on historical data, approximately 9000 patients will start hemodialysis at a study center during the 4-year trial period).

Economic Analysis

We are designing a cost-effectiveness analysis that will model the costs and health outcomes for implementing a personalized dialysate temperature compared with a usual dialysate temperature. The primary outcome is the incremental cost-effectiveness ratio (ICER), where the costs will be considered from the perspective of a universal health care system and health outcome will be life-years.

We will use a multilevel model to allow for the correlation between costs and outcomes while accounting for clustering.[71] The results will produce an estimate of the incremental cost per month alive with an accompanying 95% confidence intervals. We will supplement our base case analysis with a probabilistic sensitivity analysis to quantify the level of confidence in relation to uncertainty in the model inputs (ie, relative treatment effects, transition probabilities, costs, and outcomes). Details of this substudy are not included in this protocol.

Statistical Significance

In keeping with recommended practice, our aim is to avoid type I errors due to multiple comparisons.[72-75] We will use the parallel gatekeeping procedure[76] to control the overall family-wise error rate at 0.05. The first family of hypotheses includes both the primary and key secondary hypotheses (composite primary outcome and drop in intradialytic systolic blood pressure), with weights of 0.8 and 0.2, respectively. If the intervention improves at least 1 of the 2 outcomes in the first family of hypotheses, outcomes in a second family of hypotheses will be tested in the following order at a level of significance that maintains the overall error rate across all prior testing at .05: all-cause mortality or cardiovascular-related hospitalization, all-cause mortality, hospital admission with myocardial infarction, hospital admission with congestive heart failure, and hospital admission with ischemic stroke. Any reported confidence intervals that maintain the family-wise error rate at .05 will be adjusted for the tested level of significance.

The reporting of treatment effects on outcomes including secondary outcomes examined after the family-wise error rate exceeds 0.05, additional outcomes, prespecified and post hoc subgroup analyses, and exploratory analyses will be limited to point estimates with 95% confidence intervals (without *P* values), and we will indicate that these interval widths are not adjusted for multiple testing, so that inferences drawn from them may not be reproducible.[72,74]

Discussion

This protocol describes the design and statistical analysis plan for MyTEMP, a pragmatic cluster randomized clinical

Table 3. Characteristics of Reference Prior Probability Distributions Representing Prior Beliefs About Primary Composite Endpoint Benefit.

Prior belief	Assumed HR	Assumed SD of log HR	Pretrial probability of treatment effect greater than or equal to a specified HR threshold						Rationale for specifying distribution characteristics
			<1.00	<0.95	<0.90	<0.85	<0.80	<0.70	
Uninformative[a]	1.0	10	50%	50%	50%	49%	49%	49%	All possible values for treatment effect for log HR are equally likely
Strongly enthusiastic	0.8	0.1	99%	96%	88%	73%	50%	9%	Based on historic data from our data sources, the standard deviation is generally less than 0.1, and published observation studies have shown the intervention can have less than an HR of 0.8[38,39]
Moderately enthusiastic	0.8	0.135	95%	90%	81%	67%	50%	16%	Probability of observing a treatment effect greater than that assumed in MyTEMP trial design (HR = 0.8) is 50%; probability of no benefit is 5%
Moderately skeptical	0.9	0.125	80%	67%	50%	32%	17%	2%	Probability of observing a treatment effect greater than an HR of 0.90 is 50%; probability of any benefit is 80%
Skeptical	1.0	0.135	50%	35%	22%	11%	5%	0%	Probability of observing a treatment effect greater than that assumed in MyTEMP trial design (HR = 0.8) is 5%; probability of any benefit or harm is equivalent
Strongly skeptical	1.0	0.07	50%	23%	7%	1%	0%	0%	Probability of observing a treatment effect greater than that assumed in MyTEMP trial design is <5%; probability of any benefit or harm is equivalent

Note. HR = hazard ratio; MyTEMP = Major Outcomes with Personalized dialysate TEMPerature trial.
[a]An uninformative prior assigns an equal probability to all possibilities of treatment effects.

trial currently running at 84 hemodialysis centers in Ontario. The trial will test the effect of randomizing hemodialysis centers to provide a personalized temperature-reduced dialysate protocol vs a standard-temperature dialysate protocol (ie, 36.5°C) for 4 years on the rate of cardiovascular-related death or hospitalization in outpatients receiving maintenance hemodialysis.

This province-wide pragmatic trial will include outpatients receiving maintenance in-center hemodialysis in participating centers. The study population will include groups of patients who are commonly excluded from clinical trials, such as high-risk patients with multiple comorbidities and those with cognitive impairment or disabilities. By including patients from a variety of medical, ethnic, geographic, and socioeconomic backgrounds, the results of this trial should be broadly generalizable.

The setting of hemodialysis is well suited for trials that employ cluster randomization of interventions implemented at the individual level; patients typically receive all treatments at the same center (3 times or more per week), and all patients in a given center receive care using a uniform set of standard operating procedures. We used a behavioral change framework to systematically identify barriers and facilitators to implementing a personalize dialysate temperature in hemodialysis centers.[48] The results of this study informed our intervention implementation strategy, which should improve fidelity to the intervention and the trial's internal validity. This approach to implementation also lends itself well to wide-scale uptake of the intervention, should it prove beneficial in this trial.

This study has some limitations. First, even in a randomized trial of 84 hemodialysis units, imbalance on unmeasured patient-level and center-level prognostic factors is possible. To protect against this, we used covariate-constrained randomization to randomly select an allocation scheme from a list of acceptable allocations to ensure the 2 trial arms were balanced on baseline variables.

Second, we will have limited statistical power to detect a risk reduction below 20%, yet a risk reduction of even 5% (ie, hazard ratio of 0.95) could be clinically meaningful. In the absence of any harm, even a small risk reduction on the primary outcome would likely convince dialysis providers worldwide to adopt a personalized temperature-reduced dialysate protocol as the standard of care. To address this limitation, we will conduct a prespecified Bayesian analysis to examine the probability that the intervention is effective under differing thresholds that could be clinically relevant, in keeping with advice that investigators should prespecify both frequentist and Bayesian analyses as part of their statistical analysis plan for randomized clinical trials.[73,77-79]

Third, our administrative data sources lack information on patient symptoms (eg, postdialysis fatigue, restless legs, discomfort from being cold on dialysis, changes in cognition). To address this, we will conduct a substudy to assess patient-reported symptoms in a subset of centers (details of this substudy are currently under development). Key caveats are the reliability of such measures in a setting where patients are aware of the dialysate temperature they receive, and limited statistical power to detect the minimal clinically relevant effects with a subset of centers.

Fourth, our data sources lack information on patients who were and were not adherent to the randomly allocated temperature protocol. The observed effect of the intervention could be attenuated if (1) there is a high level of nonadherence in either the control or intervention arms, (2) a large proportion of patients transfer to centers that have a different treatment allocation than their index center (ie, treatment contamination), or (3) the level of nonadherence is associated with the risk of intradialytic hypotension (eg, patients at high risk of experiencing intradialytic hypotension in the control arm are prescribed a cooler dialysate temperature). We will monitor and report adherence to the allocated therapy during the trial, with a target between-group difference in the delivered dialysate temperature of 0.5°C.

Fifth, the primary data source that will be used to identify patients receiving maintenance in-center hemodialysis was not developed for research or clinical purposes, but rather to assess the funding and business needs of the Ontario Renal Network, which oversees the delivery of chronic kidney disease services in the province. As such, there is a possibility of including patients who temporarily switch to in-center hemodialysis or who are not on chronic hemodialysis. To overcome this issue, we are using the 90-day rule to focus the analysis on stable patients who are receiving chronic hemodialysis (see "Hemodialysis Medical Centers and Patients" section). The cardiovascular outcomes used in this trial are well coded in administrative data when compared with adjudicated outcomes in clinical trials of the general population.[51-55]

Sixth, we are testing a strategy of adopting a personalized dialysate temperature protocol for all patients treated in a hemodialysis center. As such, we will not be able to comment on the treatment effect of personalized dialysate temperature in patients at high risk of intradialytic hypotension. An individual patient RCT, with more restrictive eligibility criteria, would be a better design to address the latter objective.

Trial Oversight

An independent Data and Safety Monitoring Board (DSMB) has convened and continues to assess the progress of this trial and the safety data from published literature. After each meeting, the DSMB provides recommendations to the study team. The main responsibilities of the DSMB are listed in Supplemental Appendix 14.

Conclusion

Lowering the dialysate temperature between 0.5°C and 0.9°C below a patient's predialysis temperature may stabilize intradialytic blood pressure, reduce the risk of intradialytic hypotension,

protect the heart and brain from cumulative subclinical ischemic injury, and improve cardiovascular outcomes. This Ontario-wide clinical trial will determine the effect of randomizing hemodialysis centers to provide a personalized temperature-reduced-dialysate protocol vs a standard-temperature dialysate protocol on the rate of cardiovascular-related death or hospitalization. The intervention will be embedded into routine clinical care and patient characteristics, and outcomes will be largely obtained from administrative health care databases. This pragmatic design will allow broad inclusion of dialysis centers and a large, representative sample of patients that should yield highly generalizable results. If effective in reducing cardiovascular-related death or hospitalization, a personalized dialysate temperature can be scaled and delivered on all hemodialysis machine in Ontario (and worldwide) at no added cost.

Authors' Note

The analyses, conclusions, opinions and statements expressed herein are solely those of the authors and do not reflect those of the funding or data sources; no endorsement is intended or should be inferred.

Ethics Approval and Consent to Participate

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 Research Ethics Board approved our application with alteration to the informed consent process as described in the "Ethical Considerations" section of this manuscript.

Consent for Publication

Consent for publication was obtained from all authors.

Availability of Data and Materials

The data sets from this study are held securely in coded form at Institute for Clinical Evaluative Sciences (ICES). While data sharing agreements prohibit ICES from making the data publicly available, access may be granted to those who meet prespecified criteria for confidential access, available at www.ices.on.ca/DAS. The full dataset creation plan and underlying analytic code are available from the authors upon request, understanding that the programs may rely upon coding templates or macros that are unique to ICES.

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: Dr Zager is the Medical Director for Dialysis Clinic Inc, which provided partial funding for Major Outcomes with Personalized Dialysate TEMPerature (MyTEMP). Dr Wald has received unrestricted research support from Baxter Healthcare. The remaining authors declare they have no other relevant interests.

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Supplemental Material

Supplemental material for this article is available online.

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