Title: Major Outcomes With Personalized Dialysate TEMPerature: Pragmatic, Registry-Based, Cluster Randomized Controlled Trial

Protocol Trial Registration: NCT02628366

Date: September 6, 2022

Protocol Compilation

All documents are from the MyTEMP study

The original protocol was sent to participating centers on February 1, 2017, and approved by the research ethics board.

The final protocol was submitted for publication on September 9, 2019, and accepted for publication on September 23, 2019.

Summary of changes for the protocol posted online on August 14, 2020, at ClinicalTrials.gov NCT02628366. It documents changes between the original protocol version on February 1, 2017, and the protocol published in the Canadian Journal of Kidney Health and Disease on September 23, 2019.

The original and only version of the statistical analysis plan was submitted for publication on April 27, 2021, and accepted for publication on July 13, 2021.

Correction to the statistical analysis plan published online on July 6, 2022.

The original substudy protocol on patient-reported outcomes was approved by the research ethics board on August 30, 2019 (labeled as version 3 for internal purposes).

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* The numbers below refer to the page numbers in the pdf document.

MyTEMP

Major important outcomes with personalized dialysate TEMPerature

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Trial Summary

Title	**Major cardiovascular and other patient-important outcomes with personalized dialYsate TEMPerature (MyTEMP): A registry-based cluster randomized controlled trial**
Version & Date	**Version 1.0 completed on 08-Oct-2015 by Ahmed Al-Jaishi**
Motto	***"MY dialysis, MY temperature"***
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Study Size	75+ Hemodialysis Centres (~ 7500 patients)
Study Design	Cluster randomized controlled trial
Research Question	Do centres randomized to provide temperature-reduced personalized hemodialysis have a different rate for the composite outcome of all-cause mortality and major cardiovascular events compared with centres that provide standard-temperature hemodialysis?
Hypothesis	There will be at least a 15% relative rate reduction in the composite outcome of all-cause mortality and major cardiovascular events among centres that provide temperature-reduced personalized hemodialysis compared with centres that provide standard-temperature hemodialysis.
Inclusion Criteria	**1)** The medical director of the dialysis centre must provide informed consent and be willing adopt temperature-reduced personalized hemodialysis as their center protocol (if randomized to the intervention) or stay with a standard 36.5°C hemodialysis temperature protocol during the course of the trial (if randomized to the control group); and **2)** The centre must care for a minimum of 15 patients being treated with conventional in-centre hemodialysis.
Study Intervention & Control	Dialysis centres randomized to the intervention will provide temperature-reduced personalized hemodialysis. A nurse will set the temperature of the dialysate to **0.5-0.9 °C below each patient's body temperature** (measured just before starting the dialysis treatment). The remaining dialysis centres (the control group) will provide usual care, which is standard dialysis using a fixed dialysate temperature of 36.5°C (the current practice for over 90% of patients in Ontario centres).
Primary Outcome	A composite of all-cause mortality or hospitalization for ischemic stroke, myocardial infarction, or coronary revascularization (coronary artery bypass grafting or percutaneous coronary intervention).
Follow-up	Centres will be followed for a period of two years after the intervention start date (01-April-2017 to 31-March-2019).

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Protocol Summary

Background: For patients with kidney failure (23,000 in Canada, >2 million worldwide), hemodialysis provides a life-saving treatment option; however, mortality remains extremely high—30 times higher than age-matched controls from general population. Cardiovascular disease is the leading cause of morbidity and death. Standard therapies such as statins and anti-platelet drugs, which are effective for treating cardiovascular disease in the general population, have been largely *ineffective* in hemodialysis patients. We need to re-think our strategies to prevent cardiovascular events in this vulnerable population.

In this trial, we will test if temperature-reduced personalized hemodialysis reduces the composite rate of death and hospitalizations for major cardiovascular events. Preliminary results are promising: in a pilot trial, we showed that lowering the dialysate temperature to 0.5° C below a patient's core body temperature (temperature-reduced personalized hemodialysis) effectively reduced progressive brain and cardiac injury. However, this was a small trial (n = 73 patients) and no study to date has investigated long-term effects of using temperature-reduced personalized hemodialysis.

Research Question: Do centres randomized to provide temperature-reduced personalized hemodialysis have a different rate for the composite outcome of all-cause mortality and major cardiovascular events* compared with centres that provide standard-temperature hemodialysis?

*Hospital encounters for ischemic stroke, myocardial infarction, or receipt of coronary revascularization (CABG/PCI).

Hypothesis: There will be at least a 15% relative rate reduction in the composite outcome of all-cause mortality and major cardiovascular events among centres that provide temperature-reduced personalized hemodialysis compared with centres that provide standard-temperature hemodialysis.

Methods: We will conduct a registry-based, cluster randomized controlled trial. All hemodialysis centres (clusters) in Ontario that care for more than 15 patients are eligible to participate, and **all** renal programs overseeing these centres have already agreed to do so. We strategically designed this study to be inclusive of all facilities (including community hospitals that are normally excluded from trials) and patients treated within these facilities. Participating centres will be given resources and strategies to adhere to the allocated temperature therapy during the trial.

Baseline characteristics and follow-up for outcomes will be ascertained through healthcare administrative databases housed at the Institute for Clinical Evaluative Sciences (ICES), supplemented with primary data abstracted from patient dialysis run sheets.

Choice of Study Design: Hemodialysis patients receive all their treatments at the same centre, making this population ideal for a cluster-level intervention, where all patients in the cluster receive the randomly assigned therapy. There are two reasons why we chose this design:

1. *Enhanced uptake of MyTEMP within each dialysis centre*. From an administrative perspective, interventions such as MyTEMP are naturally applied at the level of the dialysis centre, where trained nurses follow a standard protocol for **all patients** under their care (e.g. for centres randomized to the intervention, nurses will measure each

patient's temperature and set the dialysate temperature to 0.5 °C below the patient's body temperature).

2. *Minimized cross-group contamination.* One limitation of patient-level randomization is the potential for cross-group contamination. For example, the same nurse cares for different patients in a dialysis centre and if a nurse observes that a patient with temperature-reduced personalized dialysis has fewer intra-dialytic hypotensive episodes, they may decide to apply this intervention to a patient randomized to the control group, negating the randomization and contaminating the control group. Cross-group contamination and treatment-effect dilution are less likely to occur in this setting with centre-level randomization.

Feasibility/Scalability: Temperature-reduced personalized hemodialysis is safe, well tolerated, and simple—requiring no additional resources to apply in hemodialysis centres. In the pilot trial (n=73), we found 100% adherence to the intervention achieving the target 1°C separation in mean dialysate temperature between the treatment and control group.

Public Health Impact: This simple and safe intervention warrants broad testing given its potential to reduce cardiovascular diseases, costs, and save lives in a vulnerable segment of the population Each year, more than 2,000 hemodialysis patients in Ontario die or are admitted to hospital for a major cardiovascular event. If this intervention is effective, even a modest 15% relative-risk reduction would translate into 300 fewer deaths or cardiovascular events each year (in Ontario alone!).

Health System Economic Impact: Dialysis patients have the highest per-person healthcare costs compared with the 16 of the most common chronic diseases. The total healthcare cost for dialysis patients exceeds $1.6 billion per year in Ontario, with ~80% of costs attributed to hospitalizations. A conservative estimate is that our intervention could save the Ontario healthcare system up to $1.5 million each year simply by reducing cardiovascular-related hospitalizations.

1.0 Background

Cardiovascular disease in hemodialysis patients: For those with kidney failure (~2 million worldwide and 23,000 in Canada), hemodialysis provides a life-saving treatment option; however a tragic **20-40% of patients die within one year of starting dialysis, and cardiovascular disease is the leading cause of death**.[1–3] Therapies such as statins (which help prevent major adverse cardiovascular events in many segments of the population) have proven largely *ineffective* in patients with advanced kidney disease.[4] This led the renal community to consider other causes of cardiovascular disease that are unique to patients receiving long-term dialysis.

Dr. Chris McIntyre (co-PI) has conducted a series of pivotal studies showing that the hemodialysis procedure *itself* directly damages the heart and brain through repeated episodes of hypotension and subclinical ischemia.[5–9] This paradigm-shifting concept took the nephrology community by surprise, but is now broadly accepted. We and others are altering various aspects of the hemodialysis procedure to determine which paramaters best prevent hemodialysis-induced ischemic injury. In small randomized controlled trials, we have shown that *reducing the temperature of a hemodialysis treatment* may prevent intra-dialytic hypotension and mitigate injury to the heart and brain (details provided in this protocol).[7,9–11]

We now propose to conduct a large-scale evaluation to determine whether **temperature-reduced personalized hemodialysis** (compared to standard-temperature dialysis) reduces the risk of major cardiovascular events (myocardial infarction, stroke, coronary revascularization) and death. We propose an efficient *Ontario-wide cluster-randomized registry trial* that will involve 75+ hemodialysis centres (~7500 hemodialysis patients). The name of this trial is MyTEMP.

How does hemodialysis cause ischemic injury?
When fluid is removed from the body during hemodialysis (~1-3 L per session), blood pressure often drops by 20-30 mmHg.[12,13] These intra-dialytic hypotensive episodes occur in up to 50% of dialysis sessions. Not only are these extremely unpleasant for patients, but physiologically, these episodes cause repeated ischemic injury to the heart and brain.[13–15] Using magnetic resonance imaging, Dr. McIntyre demonstrated that hemodialysis causes direct cardiac injury, myocardial stunning, and reversible left ventricular regional wall motion defects.[7,9] Over time, the cumulative effect of these subclinical ischemic insults can lead to myocardial infarction, stroke, and even death.[6,12,16]

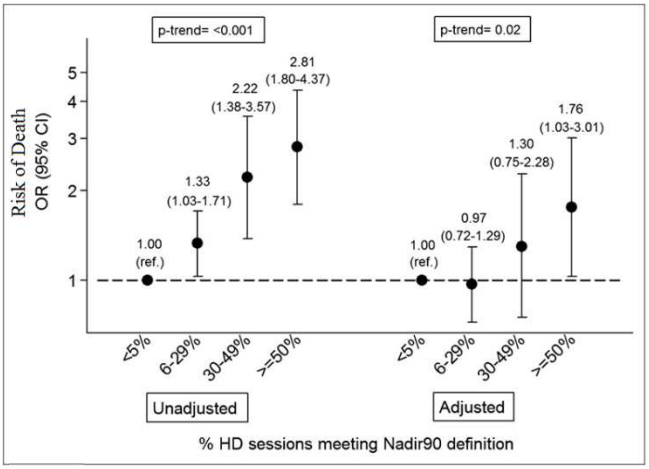

Figure 1: Association between intra-dialytic hypotension and mortality. Analyses were adjusted for demographics, clinical factors, and medications. Error bars indicate 95% CI.[13]

In a cohort of 1409 hemodialysis patients, a greater frequency of intra-dialytic hypotension was associated with an incrementally greater risk of death in both unadjusted and adjusted analyses

(**Figure 1**).[13] Patients who had the lowest nadir blood pressure during dialysis also had the highest risk of death.

One strategy to maintain stable blood pressure and tissue oxygenation during hemodialysis is to use temperature-reduced personalized hemodialysis.

2.0 Rationale

2.1 How does temperature-reduced hemodialysis prevent ischemic injury?

Approximately 120 L of dialysate is used during a hemodialysis treatment. This dialysate circulates through the dialysis machine at a set temperature, where a semi-permeable membrane separates the dialysate from a patient's blood which is also circulating through the machine. A higher dialysate temperature means a patient will have a higher core body temperature during their dialysis treatment.

A nurse sets the dialysis temperature at the beginning of each hemodialysis treatment (and it remains constant during that treatment). The current practice in Ontario is to set the temperature of the dialysate to 36.5ºC.[17] However, this practice is largely based on clinical tradition, not evidence. There is now strong evidence that a cooler dialysate can improve patients' hemodynamic response to dialysis and reduce the frequency of intra-dialytic hypotension.[18–25]

Human body temperature is maintained within a narrow range, where 0.3°C to 0.8°C separates the thresholds for skin vasodilation and shivering.[17] Exposure to a warm dialysate warms a patient's core temperature, which causes the skin to vasodilate, and this may increase the risk of hypotension from decreased peripheral vascular resistance. However, a cooler dialysate increases peripheral vascular resistance, improves cardiac output, and alters the level of vasoactive peptides, all which decrease the risk of intra-dialytic hypotension.[18–25]

2.2 Pilot Trial

In a small parallel-group randomized controlled trial (73 patients), we examined the effect of lowering the dialysate temperature to 0.5°C below **each patient's** body temperature, which was measured at the beginning of their dialysis treatment (**temperature-reduced *personalized* dialysis**).[9] For example, a patient who started dialysis with a body temperature of 36.2°C had their dialysis machine temperature set to 35.7°C, while another patient who started dialysis with a body temperature of 35.9°C had their dialysis temperature set to 35.4°C. Compared with standard-temperature dialysis, patients who received temperature-reduced *personalized* dialysis had improved dialysis tolerability and improved blood pressure stability; fewer patients stopped their treatment session prematurely and adherence to the intervention was 100% with no adverse events (no patients complained about feeling uncomfortably cold on dialysis). Most importantly, this intervention **protected patients from progressive brain and cardiac injury** as observed on magnetic resonance imaging over one year.[7,9]

2.3 Meta-Analysis

Following our pilot trial, we updated our systematic review and identified 26 randomized controlled trials (484 patients in total) that compared temperature-reduced and standard-temperature hemodialysis. This meta-analysis was led by Dr. Mustafa (co-investigator) and is registered at prospero.com (CRD42011001104). The manuscript is published in *Clinical Journal*

of American Society of Nephrology.[26] Compared with standard-temperature dialysis (36-38.5°C), temperature-reduced hemodialysis (34-35.5°C) lowered the rate of intra-dialytic hypotension by 70% (95% CI: 49-89%) and increased the intra-dialytic mean arterial pressure by 12 mmHg (95% CI: 8 to 16 mmHg).

2.4 The need to determine whether temperature-reduced personalized hemodialysis prevents major adverse cardiovascular events

Evidence from small clinical trials (6-128 patients) consistently shows that temperature-reduced personalized hemodialysis is a simple and safe intervention that effectively reduces intra-dialytic hypotension and protects the heart and brain from hemodialysis-induced ischemic injury. As well, one observational study showed that patients who received cooler dialysis had a reduced risk of death and cardiovascular events.[27] However, to influence practice, we need at least one large, high-quality multi-centre randomized controlled trial to determine whether this intervention reduces the risk major cardiovascular events and death. While this is the next logical trial to do, current trials of temperature-reduced hemodialysis registered on clinicaltrials.gov have sample sizes of 100 patients or less. Thus, we propose to efficiently conduct a large Ontario-wide cluster-randomized registry trial to determine if **temperature-reduced personalized hemodialysis** compared to standard-temperature hemodialysis reduces the rate of death and major cardiovascular events.

3.0 Plan

We are planning a large trial to determine if using temperature-reduced personalized hemodialysis reduces rates of major cardiovascular events and death.

In this intervention (MyTEMP), the dialysate temperature will be set to **0.5-0.9 °C below each patient's body temperature**, where the body temperature is measured just prior to starting a hemodialysis treatment. We are using this personalized approach because it adjusts for individual and diurnal variations. This differs from a fixed-colder temperature approach, where all patients, for example, receive a dialysis temperature of 35.5°C irrespective of their body temperature at the beginning of a dialysis treatment. In our pilot trial, a personalized-temperature approach achieved all the benefits of cooler dialysis without any patient concerns about feeling cold (no patient stopped their dialysis session early). This intervention is easily applied on standard dialysis machines, including all machines in Ontario.

4.0 Methods

4.1 Primary Research Question

Do centres randomized to provide temperature-reduced personalized hemodialysis have a different rate for the composite outcome of all-cause mortality and major cardiovascular events compared with centres that provide standard-temperature hemodialysis?

4.2 Hypothesis

There will be at least a 15% relative rate reduction in the composite outcome of all-cause mortality and major cardiovascular events among centres that provide temperature-reduced personalized hemodialysis compared with centres that provide standard-temperature hemodialysis.

4.3 Trial Design

The MyTEMP trial is an Ontario-wide registry-based, cluster randomized controlled trial.
Registry: routinely collected healthcare data that are housed at ICES.
Cluster: the unit of randomization and analysis (dialysis centres).

Using a cluster-design, we will randomize hemodialysis centres (rather than individual patients), to ensure that all patients in each centre are studied, including subgroups of patients who are normally excluded from trials.

4.4 Justification of Study Design:

Hemodialysis patients receive all their treatments at the same centre, making this population ideal for a cluster-level intervention, where all patients in the cluster receive the randomly assigned therapy. There are two reasons we chose this design:

1. Enhanced uptake of MyTEMP intervention within each dialysis centre: From an administrative perspective, interventions such as MyTEMP are naturally applied at the level of the dialysis centre, where trained nurses follow a standard protocol for **all patients** under their care (e.g. for centres randomized to the intervention, nurses will measure each patient's temperature and set the dialysate temperature to 0.5-0.9 °C below the patient's body temperature).
2. Minimize cross-group contamination: One limitation of patient-level randomization is the potential for cross-group contamination. For example, the same nurse cares for different patients in a dialysis centre and if the nurse observed that a patient with temperature-reduced personalized dialysis had fewer intra-dialytic hypotensive episodes, they may decide to apply this intervention to a patient randomized to the control group, negating the randomization and contaminating the control group. Cross-group contamination and treatment-effect dilution are less likely to occur in cluster-level interventions.

4.5 Inclusion/Exclusion Criteria

This pragmatic trial has only two inclusion criteria:

1) The medical director of the dialysis centre must be willing to adopt temperature-reduced personalized hemodialysis as the routine protocol for their centre (if the centre is randomized to the intervention) or stay with the standard 36.5°C hemodialysis temperature protocol during the course of the trial (if the centre is randomized to the control group); and

2) The centre must care for a minimum of 15 patients being treated with conventional in-centre hemodialysis.

These broad inclusion criteria mean our study will include many types of patients who are normally excluded from clinical trials. For example, we analyzed historic data from the same ICES healthcare databases that will used for this trial. In our preliminary analysis of 7,446 hemodialysis patients in Ontario who would comprise our trial population, our study would include 4,989 patients with multiple comorbidities, and 673 patients living in rural or remote locations. The **Ontario data below**, while not exhaustive, provides a simple overview of patient diversity and high expected levels of clinically significant co-morbidities among patients that will be included in our trial.

Patients living in rural or remote locations	673 (9%)
Women	3019 (42%)
Lowest income quintile	2049 (28%)
Patients older than 65 years	4468 (60%)
Patients older than 80 years	1580 (21%)
Patients with multiple (>4) comorbidities	4989 (67%)
Coronary artery disease	4617 (62%)
Congestive heart failure	3797 (51%)
Diabetes	4728 (63%)
Dementia	1117 (15%)

As approved by Research Ethics Review Board at Western University, medical directors will provide approval for the participation of their dialysis centre, and the standard protocol used in the hemodialysis center for the trial will be the randomly allocated dialysis temperature treatment (see the Ethic Section 5.0 of this protocol for further details). In routine care, any given patient or their nephrologist have the option of pursuing a dialysis temperature other than the routine temperature protocol for that centre. The same will be true during the course of this trial; we expect such protocol deviations from the randomly allocated temperature will be uncommon. By including patients from a variety of medical, ethnic, geographic, and socioeconomic backgrounds, the results of our trial should be **broadly generalizable**.

4.6 Participating Dialysis Centres:

Ontario has 97 hemodialysis centres that care for ~7800 patients. We have ***already recruited 80+ dialysis centres*** that meet the eligibility requirements for this trial (~7,000 dialysis patients). Thirteen centres were excluded because they care for fewer than 15 patients (less than 225 patients in Ontario) or the centre director did not agree to randomization.

4.7 Intervention and Control

Dialysis centres randomized to the intervention will provide temperature-reduced personalized hemodialysis. A nurse will set the temperature of the dialysate to **0.5-0.9°C below each patient's body temperature** measured just before starting the dialysis treatment (**Appendix 1**). We are aware that some dialysis machines (e.g. Fresenius 5008) are only able to modify dialysate temperature by 0.5°C increments. For centres with those machines, the temperature should be lowered by a minimum of 0.5°C and a maximum of 0.9°C (**Appendix 2**). The remaining dialysis centres (the control group) will provide usual care, which is standard dialysis using a fixed dialysate temperature of 36.5°C (the current practice for over 98% of patients in Ontario centres).

All participating centres have agreed to adhere to their randomly allocated temperature therapy for **two years** after randomization. We expect that this intervention will be easily deployed. Nonetheless, to maximize intervention uptake, we performed semi-structured interviews of 18 health professionals (nephrologists, nurses, and technicians) and 3 dialysis patients to identify any behaviours that may hinder or influence intervention uptake. We used principles of theory-based knowledge translation, and respondents were purposely sampled from a wide range of practice settings across Ontario.[28–30] The results from these interviews informed our final implementation strategy for this trial, which is provided to the centre PI for the renal program.

Dr. Jeremy Grimshaw (Canada Research Chair, Health Knowledge Transfer and Uptake) at the *Ottawa Provincial Knowledge Translation and Exchange Network* helped develop and guide the implementation plan for our intervention (both during and after the trial).

4.8 Data Collection and Follow-Up

All data, including baseline characteristics, study outcomes, other patient-selected outcomes, and economic data will be obtained from data sources housed at the *Institute for Clinical Evaluative Sciences* (*ICES*). Common data sources used at ICES are described in **Appendix 3**.

4.8.1 Additional Data Collection

We will ask each dialysis centre (both intervention and control centres) to send additional data from 15 random patients (no patient identifiers will be requested) including pre-dialysis patient temperatures, pre-dialysis systolic and diastolic blood pressure, the temperature of the dialysate, and the nadir systolic with its accompanying diastolic blood pressure. To ascertain baseline information, we will request this data be sent monthly starting as early as October 2015 until March 2017.

Beginning April 2017, we will ask each centre to send weekly reports for the first month of the trial, bi-weekly for the second month, and monthly thereafter. All of these data elements are available in the patient's dialysis run sheet as part of routine care. These data will allow us to assess adherence to the treatment allocation, and assess differences in average dialysis temperature and blood pressure between the two groups of dialysis centres.

4.8.1.1 Measuring Patient's Temperature

In Canada and abroad, all patients have their vital signs (including temperature) measured before initiating a hemodialysis session. In this pragmatic trial, participating centres will continue with their usual method of temperature measurement (e.g. oral or tympanic).

4.8.1.2 Measure Blood Pressure

Blood pressure measurements should be completed before starting dialysis and while the patient is sitting down using standard centre equipment. For instances where the patient has multiple measurements before dialysis, please record the first blood pressure reading.

Centres can enter their monthly data using the following link:
https://mytemp.lawsonresearch.ca/account/login.aspx

User Name:
Password:

4.9 Outcomes

4.9.1 Primary Outcome

Composite outcome of all-cause mortality or hospitalization for ischemic stroke, myocardial infarction, or coronary revascularization (coronary artery bypass grafting or percutaneous coronary intervention).

Datasets housed at ICES contain vital statistics and reasons for hospital admission for all Ontarians. Hospital encounters for cardiovascular events will be ascertained using ICD-10 codes recorded in CIHI-DAD. These codes have high accuracy (**Appendix 4**); demonstrating high sensitivity and specificity when compared to manual chart review. We will also use the registered persons database (RPDB) to ascertain all-cause mortality (recorded with 99% accuracy).[31]

We can reliably track the major outcomes in the MyTEMP trial (as we have done in other published studies) with validated algorithms applied to the large healthcare databases held at ICES.[31–34]

4.9.2 Secondary Outcomes

We will estimate the relative rate reduction for each component of the primary composite outcome.

Other Important Outcomes

In consultation with patient representatives, we discussed several patient-important outcomes that: *1)* may be responsive to our intervention, and *2)* can be reliably assessed using the administrative data sources. Patient representatives prioritized four other outcomes for this trial:

Amputation: Patients on HD, especially those with diabetes, have a high incident rate of amputation with 3% of patients having a lower or upper limb amputation each year. This high rate of amputations is associated with cardiovascular risk factors and likely linked to vascular injury caused by HD-induced ischemia, which complicates pre-existing arterial disease and diabetes related injury. We will compare the amputation rate for the two groups for all-amputations (excluding digit amputation) and separately for upper and lower limb amputations.

Major fall and Fractures: Many patients on dialysis are frail and prone to falling, which may also predispose them to suffer a fracture. Bone fractures are an important outcome and can result in morbidity, high economic, costs, and mortality. The three-year incidence of falls requiring a hospitalization ranges from 3 to 12% for patients on dialysis, with elderly females being at the highest risk.[35] Fractures (hip, forearm, pelvis, or proximal humerus) are also common occurring in nearly 5% of patients each year.[35]

Intra-dialytic hypotension might increase the rate and severity of falls after a HD session leading to additional fractures requiring hospitalizations. We will estimate the rate of falls and fractures for both groups.

The ability to live independently: Temperature-reduced personalized HD may help patients maintain health, cognition and mobility through direct neuro-protection.

Intensity use of blood pressure medications: This outcome will be restricted to patients covered by the Ontario Drug Benefit (ODB) Program; this program covers most of the cost of 4,400 prescription drug products, some nutrition products and some diabetic testing agents. Individuals eligible for ODB include [i] all patients 65 years and older; [ii] patients living long-term care or a

home for special care; [iii] patients enrolled in the Home Care Program; [iv] patients registered in the Trillium drug plan; and [v] patients on social assistance through Ontario Works or the Ontario Disability Support Program.

We will include the following blood pressure prescription medication classes:

- Diuretics;
- renin-angiotensin system blockers (angiotensin-converting enzyme inhibitors and angiotensin receptor blockers);
- β-blockers (selective, nonselective, and α-β-blocker agents);
- calcium channel blockers (nondihydropyridines and dihydropyridines);
- centrally acting antiadrenergic agents; and
- other (i.e., peripheral acting antiadrenergic agents or vasodilators).

We will calculate the daily intensity of blood pressure medication by dividing the total defined daily dose (DDD) by the number of days under observation for each patient. Each daily dose will be converted to a standardized daily dose based on the corresponding DDD proposed by the World Health Organization International Working Group for Drug Statistics Methodology.[36] The intensity will be classified in three categories: Low (0 to <0.2 DDD), moderate (0.2-2.5 DDD), or high (>2.5 DDD).[37] We will estimate the intensity of BP medication for ODB eligible patients for both groups.

4.9.3 Economic Outcomes

ICES contains information on all costs borne by the Ontario health care system. We will compare our two groups on the average healthcare cost per patient per month alive (to account for differences in mortality), which will include the hospitalization costs for any major cardiovascular events.

4.10 Randomization

On a single date, we will randomize all participating HD centres to the intervention or control group in a 1:1 ratio using computer-generated randomization. We are using the method of covariate-constrained randomization, where we will run a large number of random allocations from all possible allocations. We will select random allocations where a set of important covariates are well balanced — a scheme was considered to have good balance if the between-group standardized differences on the constrained variables were within 10% caliper. This standardized difference translates to group means/proportions for each trial arm having less than ~8% non-overlap in the two populations. At this stage, we will select one overall randomization scheme from the list of all "good" allocation schemes.[38] This method ensures the two groups are comparable at baseline on important measured prognostic factors and has been shown to produce un-biased results.[39,40] It should be noted, because of the way administrative data are captured, the two groups will be compared on baseline prognostic factors for prevalent HD patients in the two-years prior to trial start (i.e. April 01, 2017).

4.11 Blinding

Because of the nature of MyTEMP trial, it is not feasible to blind the patients, nurses, or nephrologists who care for these patients to the intervention assignment. However, outcome adjudication (e.g. myocardial infarction) at/within hospital admission will be diagnosed by physicians who are blinded to the MyTEMP intervention.

4.12 Statistical Analysis

4.12.1 Analysis of Primary Outcome

The statistical analysis is being supervised by Dr. Allan Donner, a Professor of Biostatistics at Western University and a world authority on the statistics of cluster-randomized trials. Trial centres will be analyzed according to their random allocation (i.e. intention to treat). We will assume a closed cohort, where only patients that are on dialysis on April 31st, 2017 will be included in our analyses (we will assume an open cohort in additional analyses). We will fit a Poisson regression model to the individual (i.e. patient) level data, including potential confounders, but without the intervention variable. We will calculate the residual (the difference between the observed and fitted values using the adjusted model without intervention status) for each patient. The individual-level residual includes the effects of random variation and explanatory factors not included in the model, one of which is the intervention.[41]

The analysis is unaffected by whether the data are analyzed as one observation per individual or as one summary observation per combination of covariates.[41] Therefore, we will aggregate the individual-level residuals, rather than the raw incident rate, for each cluster using inverse probability weighting using centre's sample size. Using the calculated aggregate cluster residuals, we will fit an ordinary Poisson model including an indicator variable for the intervention. All analyses will be conducted using SAS version 9.4 (SAS Institute Inc.).

4.12.2 Economic Analysis

There is no incremental cost for administering temperature-reduced personalized hemodialysis compared with standard-temperature hemodialysis. While there is an initial one-time education cost for the nursing staff in the intervention group (nurses will require ~15 minutes of training to deliver personalized dialysis temperature for all subsequent hemodialysis treatments), the educational package for the MyTEMP intervention will be bundled into standard education processes already available to nurses at each participating centre. Most programs have clinical educators that update dialysis nurses on new policies and procedures. This education is often efficiently delivered to groups of nurses at one time.

If our intervention is successful, a reduced annual rate of cardiovascular-related hospitalizations may result in cost savings to the healthcare system. If (as anticipated) costs are the same or lower in the intervention group (and outcomes better) relative to the control group (i.e. dominant strategy), a cost-effectiveness analysis will not be necessary.

We are planning to conduct a cost-analysis from a healthcare system perspective. We will use data from ICES on total (and hospitalization only) resource consumption to estimate the average healthcare cost per patient per month alive (to address differences in mortality) accounting for within-centre clustering. Full details of the economic analysis are provided in **Appendix 5**. The economic analysis will be supervised by Dr. Walter Wodchis, Associate Professor of Health Economics and an authority on healthcare costing studies using ICES datasets.

4.12.3 Subgroup Analysis

We have not pre-specified any subgroup analyses. As subgroup analyses often have inadequate statistical power for modest interactions, we will simply perform exploratory subgroup analyses in this trial looking at rates of our composite outcomes for: 1) incident (starting dialysis <1

month) and prevalent patients (on dialysis for longer than one month); and 2) Previous History of cardiovascular disease.

4.13 Loss to follow-up

We expect that less than 7% of patients during the follow-up period will transfer to home peritoneal dialysis or receive a kidney transplant. In the primary analysis, patients will be followed after these transitions; however, in additional analyses we will censor the observation period at the time of these transitions.

Using healthcare administrative databases, we expect little loss to follow-up (< 0.2% per year who emigrates from Ontario).

4.13.1 Patients Switching Centres

We expect that a proportion of patients will switch centres. Some patients will likely switch from a centre on the MyTEMP intervention to a centre in the control group (or *vice versa*). For these instances, the patient temperature prescription should follow the new centre's protocol. That is, if a patient switches to a centre in the control group, their dialysate temperature prescription should change to a fixed temperature of 36.5 °C.

4.13.2 Inpatient Hemodialysis Sessions

Patients hospitalized will use the hosting hospital's standard dialysate temperature protocol whilst in hospital. In most cases, physicians will likely deviate back to standard temperature of 36.5 °C.

4.14 Missing Data

Using healthcare administrative databases, we will have near-complete data for all study variables. We will use recommended methods to investigate missing data, including a model-based multiple imputation technique.[42] We will also conduct sensitivity analyses to investigate whether conclusions are sensitive to assumptions about the missing-data mechanism.

4.15 Sample Size

Based on 2013 ICES data, the rate of our primary composite outcome was 0.30 events per person-year with an average dialysis centre size of 90 patients (range 16 to 325). To detect a 10% relative-rate reduction between our intervention and control group with 80% power (two-tailed alpha 0.05 and coefficient of variation of 0.07) over a follow-up of 2 years, we require 35 dialysis centres per group. However, based on the strong advice of our methods experts, we have recruited all eligible 80+ dialysis centres in Ontario for three reasons: 1) to minimize the chance baseline imbalance between groups (which could bias our trial results), 2) to improve the generalizability of the results, and 3) to increase the statistical power for analyzing components of the primary outcome. The Table below shows the required number of clusters needed per group for various scenarios.

		Incidence rate of the primary composite outcome (per person-year)			
		0.20	0.25	0.30	0.35
	10%	49	41	35	31

Minimum detectable relative-rate reduction	15%	21	18	15	14
	20%	12	10	9	8

Assumptions (as observed in 2013 ICES data)**:** Mean cluster size=90 patients; Coefficient of variation=0.07; α=0.05; β=0.2 (power=0.8). Based on these assumptions, we have a sufficient number of clusters to detect a statistically significant difference for all of the above scenarios, except the one shaded cell. The coefficient of variation is defined as the ratio of the standard deviation to the mean – it shows the extent of variability in relation to the mean of the population.

4.16 Summary of Trial Design and Method

We will conduct a trial of 80+ dialysis centres (~7000 patients) across Ontario. We will randomize half of the centres to use temperature-reduced personalized hemodialysis (0.5 ºC below the patient's body temperature). The other centres will use fluid at the standard temperature. We will follow all patients for at least 2 years. At the end of the trial, we will compare rate of the primary outcomes between centres randomized to the intervention and control using Poisson regression.

5.0 Ethical Standards

5.1 Ethical Considerations

In 2001, Canada's three federal research agencies, the Canadian Institutes for Health Research (CIHR), the Natural Sciences and Engineering Research Council (NSERC), and the Social Sciences and Humanities Research Council (SSHRC), jointly developed the Tri-Council Policy Statement (TCPS). Endorsed by the Government of Canada, the mandate was to promote the ethical conduct of research involving human participants.

Cluster randomized trials have unique ethical challenges. Consent to enter this study can be theoretically obtained at multiple levels (e.g. patient, physician, or HD medical director). MyTEMP met the necessary criteria for altered patient consent as outlined in the Tri-Council Policy Statement for the following reasons: (i) the research poses a clear benefit to society and unlikely to adversely affect patient welfare; (ii) the intervention was considered to be of minimal risk to patients (similar to a quality-control measure that could be implemented by a dialysis centre director); (iii) an informed consent model is impossible and impracticable given our research design and resources; and (iv) there is a plan to provide a debriefing which also offers patients the possibility of refusing the intervention.[43]

The medical directors of the dialysis centres (see inclusion criteria) will provide the overall approval for their HD centre(s) to participate in the MyTEMP trial. We also have approval to obtain de-identified information on all patients in each cluster through administrative data sets held at the Institute for Clinical and Evaluative Sciences (ICES), which has special status with the privacy commissioner of Ontario.

5.2 Access to Data

All baseline and outcome data will be retrieved from routinely collected administrative healthcare data housed at ICES. ICES is a prescribed entity for the purposes of section 45 Ontario's Personal Health Information Privacy Act (PHIPA). This means that health information custodians — like physicians, hospitals or long-term care homes — are permitted to disclose

personal health information about their patients to ICES without consent. This information is for statistical analysis in order to evaluate and monitor aspects of the health system. ICES may also use personal health information under the authority of PHIPA's section 44 for approved research projects. Data custodians outside the health sector may disclose personal information to ICES for specified use under the authority of FIPPA or other data-governing statutes. This project has already been approved by the ICES Privacy Office to access to the entire provincial repository of 75 linked databases with information on all hemodialysis patients in Ontario (~7,500 patients). ICES data provides the flexibility to link individual records across a large breadth of data.

5.3 Data Destruction

Any data generated by ICES as part of the proposed studies, will be destroyed within 8 years of study completion (expected date of study completion is March 31st, 2019, expected date of destruction is March 31st, 2027). Study data specified for destruction will be destroyed according to ICES standard operating procedures, which include document shredding, electronic erasure, and physical destruction of electronic media. These policies are also in line with Western University and Lawson Health Research Institute's policies.

5.4 Protecting Privacy

We will follow all rules and policies implemented by ICES to protecting the information collected. To achieve this, ICES implements the privacy policies and practices required by the Ontario's Information and Privacy Commissioner under section 45 of PHIPA. These include implementation of a range of physical and logical controls to control access to information, like use of secure zones within ICES facilities, complex passwords and encryption. In addition, ICES has adopted the following key principles to protect information:

1. ICES limits the information it collects to what is necessary and lawful.
2. ICES restricts access to information within ICES by role.
3. ICES administers access to information on a project-by-project basis. Scientists must apply for and justify each element of information.
4. ICES prohibits identification of individuals and uses techniques like coding and de-identification to prevent it. Direct personal identifiers, including names and health card numbers and other identifying numbers, are removed and replaced by a confidential code promptly after it is collected.
5. ICES requires all employees and scientists to be trained in the privacy policies and procedures relevant to their role, and agree to uphold them.

Monthly additional data (blood pressures, patient temperature, and dialysate temperature) collected from centres will be entered into a secure and password protected website hosted by Lawson Health Research Institute Web- and database-server. No patient identifiers will be collected and we will ask the centre to send a random group of patients each time.

6.0 Study Timeline and Milestones

We will be able to complete this project within 3 years. Year 3 will be used to support activities including finalization of the dataset (accounting for the time it takes information to be compiled at ICES), completion of the analysis, presentation and publication of the results and implementation of the knowledge dissemination plan. The Table below summarizes study progress and key milestones.

Year 1* (April 2017 – Mar 2018)	Year 2 (April 2018 – March 2019)	Year 3 (April 2019 – March 2020)
- Finalize, register, and publish the trial protocol - Onboard and randomize all dialysis centres to the intervention/control group.	- Monitor dialysis centres monthly for uptake and adherence to the intervention - Publish manuscript on the implementation strategy used maximize adherence to cold dialysis temperature across 40+ hemodialysis centres - Complete follow-up	- Complete data linkages and cleaning - Conduct the analysis - Present and publish the results - Present results to key knowledge users including the Ontario Renal Network - Develop and implement knowledge dissemination plan

*We will start collecting monthly preliminary data starting October 2015 or when we have Institutional and Ethics Approval. This data will include pre-dialysis core temperature, setting of dialysate temperature, pre-dialysis systolic BP, pre-dialysis diastolic BP, nadir systolic BP during dialysis session for 15 random patients.

7.0 References

1. Foley RN, Collins AJ. End-stage renal disease in the United States: an update from the United States Renal Data System. *J Am Soc Nephrol*. 2007;18(10):2644-2648. doi:10.1681/ASN.2007020220.

2. Foote C, Ninomiya T, Gallagher M, et al. Survival of elderly dialysis patients is predicted by both patient and practice characteristics. *Nephrol Dial Transplant*. 2012;27(9):3581-3587. doi:10.1093/ndt/gfs096.

3. Jassal S, Trpeski L, Zhu N, S F, Hemmelgarn B. Changes in survival among elderly patients initiating dialysis from 1990 to 1999. *Can Med …*. 2007;177(9):1033-1038. http://www.cmaj.ca/content/177/9/1033.short. Accessed January 7, 2015.

4. Palmer SC, Craig JC, Navaneethan SD, Tonelli M, Pellegrini F, Strippoli GFM. Benefits and harms of statin therapy for persons with chronic kidney disease: a systematic review and meta-analysis. *Ann Intern Med*. 2012;157(4):263-275. doi:10.7326/0003-4819-157-4-201208210-00007.

5. Burton JO, Jefferies HJ, Selby NM, McIntyre CW. Hemodialysis-induced cardiac injury: determinants and associated outcomes. *Clin J Am Soc Nephrol*. 2009;4(5):914-920. doi:10.2215/CJN.03900808.

6. Burton JO, Jefferies HJ, Selby NM, McIntyre CW. Hemodialysis-induced repetitive myocardial injury results in global and segmental reduction in systolic cardiac function. *Clin J Am Soc Nephrol*. 2009;4(12):1925-1931. doi:10.2215/CJN.04470709.

7. Eldehni MT, Odudu A, McIntyre CW. Randomized Clinical Trial of Dialysate Cooling and Effects on Brain White Matter. *J Am Soc Nephrol*. September 2014. doi:10.1681/ASN.2013101086.

8. McIntyre CW. Effects of hemodialysis on cardiac function. *Kidney Int*. 2009;76(4):371-375. doi:10.1038/ki.2009.207.

9. Odudu A, Eldehni MT, McCann GP, McIntyre CW. Randomized Controlled Trial of Individualized Dialysate Cooling for Cardiac Protection in Hemodialysis Patients. *Clin J Am Soc Nephrol*. May 2015. doi:10.2215/CJN.00200115.

10. Selby NM, Burton JO, Chesterton LJ, McIntyre CW. Dialysis-induced regional left

ventricular dysfunction is ameliorated by cooling the dialysate. *Clin J Am Soc Nephrol*. 2006;1(6):1216-1225. doi:10.2215/CJN.02010606.

11. Mustafa R, Bdair F, Akl EA, et al. Effect of cool dialysis in chronic hemodialysis: A systematic review and meta-analysis. *Clin J Am Soc Nephrol*. 2015;Under revi.

12. K/DOQI Clinical Practice Guidelines for Cardiovascular Disease in Dialysis Patients. *Am J Kidney Dis*. 2005;45(4):16-153. doi:10.1053/j.ajkd.2005.01.019.

13. Flythe JE, Xue H, Lynch KE, Curhan GC, Brunelli SM. Association of mortality risk with various definitions of intradialytic hypotension. *J Am Soc Nephrol*. 2015;26(3):724-734. doi:10.1681/ASN.2014020222.

14. Santoro A, Mancini E, Paolini F, Cavicchioli G, Bosetto A, Zucchelli P. Blood Volume Regulation During Hemodialysis. *Am J Kidney Dis*. 1998;32(5):739-748. doi:10.1016/S0272-6386(98)70128-3.

15. Veljančic L, Popović J, Radović M, et al. Simultaneous blood temperature control and blood volume control reduces intradialytic symptoms. *Int J Artif Organs*. 2011;34(4):357-364. doi:10.5301/IJAO.2011.7746.

16. Stefánsson B V, Brunelli SM, Cabrera C, et al. Intradialytic hypotension and risk of cardiovascular disease. *Clin J Am Soc Nephrol*. 2014;9(12):2124-2132. doi:10.2215/CJN.02680314.

17. Pérgola PE, Habiba NM, Johnson JM. Body temperature regulation during hemodialysis in long-term patients: is it time to change dialysate temperature prescription? *Am J Kidney Dis*. 2004;44(1):155-165. doi:10.1053/j.ajkd.2004.03.036.

18. Maggiore Q, Pizzarelli F, Zoccali C, Sisca S, Nicolò F, Parlongo S. Effect of extracorporeal blood cooling on dialytic arterial hypotension. *Proc Eur Dial Transplant Assoc*. 1981;18:597-602. http://www.ncbi.nlm.nih.gov/pubmed/7329988. Accessed January 7, 2015.

19. Jefferies HJ, Burton JO, McIntyre CW. Individualised dialysate temperature improves intradialytic haemodynamics and abrogates haemodialysis-induced myocardial stunning, without compromising tolerability. *Blood Purif*. 2011;32(1):63-68. doi:10.1159/000324199.

20. Maggiore Q, Pizzarelli F, Santoro A, et al. The effects of control of thermal balance on vascular stability in hemodialysis patients: results of the European randomized clinical trial. *Am J Kidney Dis*. 2002;40(2):280-290. http://www.ncbi.nlm.nih.gov/pubmed/12148100. Accessed November 20, 2014.

21. Maggiore Q. Isothermic dialysis for hypotension-prone patients. *Semin Dial*. 15(3):187-190. http://www.ncbi.nlm.nih.gov/pubmed/12100456. Accessed November 20, 2014.

22. Maggiore Q, Dattolo P, Piacenti M, et al. Thermal balance and dialysis hypotension. *Int J Artif Organs*. 1995;18(9):518-525. http://www.ncbi.nlm.nih.gov/pubmed/8582769. Accessed November 20, 2014.

23. Enia G, Catalano C, Pizzarelli F, et al. The effect of dialysate temperature on haemodialysis leucopenia. *Proc Eur Dial Transplant Assoc Eur Ren Assoc*. 1985;21:167-172. http://www.ncbi.nlm.nih.gov/pubmed/3991497. Accessed November 20, 2014.

24. Pizzarelli F, Sisca S, Zoccali C, et al. Blood temperature and cardiovascular stability in hemofiltration. *Int J Artif Organs*. 1983;6(1):37-41. http://www.ncbi.nlm.nih.gov/pubmed/6840887. Accessed November 20, 2014.

25. Maggiore Q, Pizzarelli F, Sisca S, et al. Blood temperature and vascular stability during hemodialysis and hemofiltration. *Trans Am Soc Artif Intern Organs*. 1982;28:523-527. http://www.ncbi.nlm.nih.gov/pubmed/7164293. Accessed November 20, 2014.

26. Mustafa RA, Bdair F, Akl EA, et al. Effect of Lowering the Dialysate Temperature in Chronic Hemodialysis: A Systematic Review and Meta-Analysis. *Clin J Am Soc Nephrol*. 2016;11(3):442-457. doi:10.2215/CJN.04580415.

27. Hsu H-J, Yen C-H, Hsu K-H, et al. Association between cold dialysis and cardiovascular survival in hemodialysis patients. *Nephrol Dial Transpl*. 2012;27(6):2457-2464. doi:10.1093/ndt/gfr615.

28. Michie S, Johnston M, Abraham C, Lawton R, Parker D, Walker A. Making psychological theory useful for implementing evidence based practice: a consensus approach. *Qual Saf Health Care*. 2005;14(1):26-33. doi:10.1136/qshc.2004.011155.

29. French SD, Green SE, O'Connor DA, et al. Developing theory-informed behaviour change interventions to implement evidence into practice: a systematic approach using the Theoretical Domains Framework. *Implement Sci*. 2012;7:38. doi:10.1186/1748-5908-7-38.

30. Francis JJ, Stockton C, Eccles MP, et al. Evidence-based selection of theories for designing behaviour change interventions: using methods based on theoretical construct domains to understand clinicians' blood transfusion behaviour. *Br J Health Psychol*. 2009;14(Pt 4):625-646. doi:10.1348/135910708X397025.

31. Quinn RR, Laupacis A, Austin PPC, et al. Using administrative datasets to study outcomes in dialysis patients: a validation study. *Med Care*. 2010;48(8):745-750. doi:10.1097/MLR.0b013e3181e419fd.

32. Fleet JL, Dixon SN, Shariff SZ, et al. Detecting chronic kidney disease in population-based administrative databases using an algorithm of hospital encounter and physician claim codes. *BMC Nephrol*. 2013;14(1):81. doi:10.1186/1471-2369-14-81.

33. Stukel TA, Fisher ES, Alter DA, et al. Association of hospital spending intensity with mortality and readmission rates in Ontario hospitals. *JAMA*. 2012;307(10):1037-1045. doi:10.1001/jama.2012.265.

34. Garg AX, Pouget J, Young A, et al. Fracture Risk in Living Kidney Donors: A Matched Cohort Study. *Am J Kidney Dis*. 2012;59(6):770-776. doi:10.1053/j.ajkd.2012.01.013.

35. Naylor KL, McArthur E, Leslie WD, et al. The three-year incidence of fracture in chronic kidney disease. *Kidney Int*. 2014;86(4):810-818. doi:10.1038/ki.2013.547.

36. Wessling A, Boëthius G. Measurement of drug use in a defined population. Evaluation of the defined daily dose (DDD) methodology. *Eur J Clin Pharmacol*. 1990;39(3):207-210. http://www.ncbi.nlm.nih.gov/pubmed/2257853. Accessed July 13, 2016.

37. Tinetti ME, Han L, Lee DSH, et al. Antihypertensive Medications and Serious Fall Injuries in a Nationally Representative Sample of Older Adults. *JAMA Intern Med*. 2014;174(4):588. doi:10.1001/jamainternmed.2013.14764.

38. Yang D, Dalton JE. A unified approach to measuring the effect size between two groups using SAS ®. *Pap 335-2012 Present 2012 SAS Glob Forum*. 2012:1-6.

39. Raab GM, Butcher I. Balance in cluster randomized trials. *Stat Med*. 2001;20(3):351-365. doi:10.1002/1097-0258(20010215)20:3<351::AID-SIM797>3.0.CO;2-C.

40. Carter BR, Hood K, Fisher R, et al. Balance algorithm for cluster randomized trials. *BMC*

Med Res Methodol. 2008;8(1):65. doi:10.1186/1471-2288-8-65.

41. Bennett S, Parpia T, Hayes R, Cousens S. Methods for the analysis of incidence rates in cluster randomized trials. *Int J Epidemiol*. 2002;31(4):839-846. http://www.ncbi.nlm.nih.gov/pubmed/12177032.

42. Little RJ, D'Agostino R, Cohen ML, et al. The prevention and treatment of missing data in clinical trials. *N Engl J Med*. 2012;367(14):1355-1360. doi:10.1056/NEJMsr1203730.

43. Canadian Institutes for Health Research the Natural Sciences, Natural Sciences and Engineering Research Council of Canada, Social Sciences and Humanities Research Council of Canada. *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans*.; 2014.

44. Kokotailo R a, Hill MD. Coding of stroke and stroke risk factors using international classification of diseases, revisions 9 and 10. *Stroke*. 2005;36(8):1776-1781. doi:10.1161/01.STR.0000174293.17959.a1.

45. Andrade SE, Harrold LR, Tjia J, et al. A systematic review of validated methods for identifying cerebrovascular accident or transient ischemic attack using administrative data. *Pharmacoepidemiol Drug Saf*. 2012;21 Suppl 1:100-128. doi:10.1002/pds.2312.

46. Juurlink D, Preyra C, Croxford R, et al. *Canadian Institute for Health Information Discharge Abstract Database: A Validation Study ICES Investigative Report*. Toronto; 2006.

47. Lee DS, Verocai F, Husain M, Al Khdair D, Wang X, Freeman M IR. Cardiovascular outcomes are predicted by exercise-stress myocardial perfusion imaging: Impact on death, myocardial infarction, and coronary revascularization procedures. *Am Hear J*. 2011;161(5):900-907.

48. Wodchis WP, Bushmeneva K, Nikitovic M, McKillop I. *Guidelines on Person-Level Costing Using Administrative Databases in Ontario*. Vol 1. Toronto, Ontario, Canada; 2013.

49. Manning WG, Mullahy J. Estimating log models: to transform or not to transform? *Heal Econ*. 2001;20(4):461-494.

50. Hausman JA. Specification Tests in Econometrics. *Econometrica*. 1978;46(6):1251-1271.

Appendices

Appendix 1: Patient Temperature and setting of the dialysate temperature for the intervention group. Centres that have dialysis machines able to change by increments of 0.1°C

Patient Temperature** (°C)	Dialysate Temperature (°C)
37.5 and greater	36.5 (or standard centre protocol)
37.4	36.9
37.3	36.8
37.2	36.7
37.1	36.6
37	36.5
36.9	36.4
36.8	36.3
36.7	36.2
36.6	36.1
36.5	36
36.4	35.9
36.3	35.8
36.2	35.7
36.1	35.6
36	35.5
35.9	35.5
35.8	35.5
35.7	35.5
35.6	35.5
35.5 and less	35.5 (or standard centre protocol)

When to measure patient temperature: before starting the dialysis session using your standard thermometer.

If temperature out of ordinary (e.g. patient consuming cool/warm beverage or just came from the cold outside in the winter), **then**: please start the patient on a reasonable dialysate temperature and re-check the body temperature in a few minutes.

Appendix 2: Patient Temperature and setting of the dialysate temperature for the intervention group. Centres that have dialysis machines able to change by increments of 0.5°C

Patient Temperature** (°C)	Dialysate Temperature (°C)
37.5 and greater	36.5 (or standard centre protocol)
37.4	36.5
37.3	36.5
37.2	36.5
37.1	36.5
37	36.5
36.9	36
36.8	36
36.7	36
36.6	36
36.5	36
36.4	35.5
36.3	35.5
36.2	35.5
36.1	35.5
36	35.5
35.9	35.5
35.8	35.5
35.7	35.5
35.6	35.5
35.5 and less	35.5 (or standard centre protocol)

When to measure patient temperature: before starting the dialysis session using your standard thermometer.

If temperature out of ordinary (e.g. patient consuming cool/warm beverage or just came from the cold outside in the winter), **then**: please start the patient on a reasonable dialysate temperature and re-check the body temperature in a few minutes.

Appendix 3: Common data sources used for population-based studies

Database (Source)	Description	Key Data Variables
Health Services		
Discharge Abstract Database (CIHI)	Hospital discharge abstracts for acute, chronic and rehabilitative care (1988 onward)	Diagnoses; Procedures; Comorbidities; Length of Stay
National Ambulatory Care Reporting System (CIHI)	Emergency department visits, same day surgery, outpatient clinics (e.g., dialysis, cancer clinics) (2002 onward)	Reason for visit; Triage level; Interventions; Mode of arrival
Ontario Drug Benefit Database (MOHLTC)	Claims for prescribed drugs covered by the Ontario Drug Formulary for adults aged 65+ and those receiving social assistance (1990 onward)	Drug ID number; Drug quantity; Cost
Ontario Health Insurance Plan (MOHLTC)	Reimbursement claims made by fee-for-service physicians and community based labs (1991 onward)	Service provided; Diagnosis codes ; Fee paid; Physician specialty
Registry		
Ontario Renal Reporting System (ORRS)	Collects and records the incidence, prevalence, treatment changes, and outcomes of all chronic dialysis and solid organ transplant patients in Ontario (2010 onward)	Hemodialysis start; vascular access use; nephrology referral; comorbid and baseline conditions; centre characteristics
Population and Demographics		
Registered Persons Database (MOHLTC)	Basic demographic information about anyone who has received an Ontario HCN. (1990 onward)	Date of birth; Date of death; Sex; Geographic information
Care Providers		
ICES Physicians Database	This data set contains yearly information about all physicians in Ontario (1992 onward)	Annual demographics; Specialization; Workload
Laboratory Datasets		
Ontario Gamma Dynacare	Outpatient laboratory values for all Gamma Dynacare laboratories in Ontario (2002 onward, > 59 million tests)	Creatinine levels, lipid panels, urine protein
Cerner Data stream	Laboratory values from an electronic medical record operating in 12 hospitals in Southwestern Ontario (2000 onward, > 2 million tests).	Creatinine levels. Outpatient, emergency room and inpatient values.
Ontario Laboratories Information System (pending linkage)	OLIS is a cornerstone information system that connects hospitals, community laboratories, public health laboratories and practitioners to facilitate the secure electronic exchange of laboratory test orders and results. ICES has signed and currently executing a Data Sharing Agreement to link Ontario-wide laboratory results to the Ontario-wide data holdings housed at ICES.	Creatinine levels, lipid panels, urine protein Outpatient, emergency room and inpatient values.

MOHTC: Ministry of Health and Long-term Care, CIHI – Canadian Institutes for Health Information

Appendix 4: Primary outcome codes and performance measures

Outcome	Algorithm	Position of code	Performance
Death	Registered Person's Database	N/A	Accuracy=99% [31]
Hospital admission with Ischemic Stroke	***ICD-10:*** I63 (excl. I63.6), I64, H341	Primary Diagnosis	PPV= 85% [44,45]
Hospital admission with Myocardial infarction	***ICD-10:*** I21, I22	Primary Diagnosis	Sn= 89%, PPV= 87% [46]
Coronary revascularization (includes CABG/PCI):	***CCI:*** 1IJ50, 1IJ57, 1IJ76, 1IJ54GQAZ	N/A	Sn= 99-100%, PPV= 97-100% [46] **

Abbreviations: ICD = International Classification of Disease; OHIP = Ontario Health Insurance Plan; Sn=Sensitivity; PPV= Positive Predictive Value.

** Juurlink *et al.*[46] only validated the codes 1IJ50 and 1IJ76. However, previous studies have reported the use of additional codes, which likely increases the sensitivity of capturing coronary revascularizations.[47]

Appendix 5: Full details of economic analysis

Cost Measurement

Nominal costs for each encounter with the health system are ascribed using algorithms that have been implemented at ICES, based on methods for costing using administrative data.[48] Costs for each encounter where an encounter-specific payment is made (e.g. for prescriptions, fee for service physician visits, assistive devices claims) use that payment information. Costs for acute, rehabilitation, complex continuing care and mental health hospital encounters use the appropriate resource intensity weight for that particular care setting (e.g. resource intensity weight for acute care) and the setting-specific weighted cost derived based on Ontario spending.[48] Costs for long-term care are measured as a fixed per diem based on prevailing government payment rates. Capitation payments for primary care physicians are calculated based on the payment rate and the particular model of primary care for each patient's physician in each month of the study period. Team-based payments for family health teams and physician bonus payments for pay-for-performance are not ascribed to individual patients and are not included in the analysis. Emergency department and oncologist physicians receive substantial alternative payments that are not visit-related and the algorithms also ascribed these payments, generally on an average per-patient approach.

Analysis

We will compare two-year costs associated with standard and personalized treatments. Costs are a useful summative measure of intensity of health system use. Costs are modeled using a generalized linear model (e.g. linear model of log-costs etc.) or two part model if necessary depending on the structure of the observed cost distributions. The dependent variable in the cost analysis will be average cost per month alive in order to account for differences in survival between the two population groups. The independent variable will be the treatment group assignment. Additional covariates will be added to the model if treatment and control groups are not balanced on measured clinical variables. The appropriate model for the cost estimation will be selected following Manning and Mullahy.[49] Clustering at the hospital level will be addressed by including a random-effect for within-centre clustering (or fixed effect if covariates are included and random effects are identified to be inconsistent [biased] based on a Heckman specification test).[50]

The results will also be used to produce estimates of the incremental cost per year alive as an estimate of cost-effectiveness. Bootstrap analysis will be used to calculate standard errors and 95% confidence intervals for the difference in average costs. The bias corrected and accelerated (BCa) method will be used to obtain confidence intervals for the estimates of cost per year alive. Given a hypothesis that the intervention will provide improved life expectancy with lower costs, we anticipate this estimate will be negative indicating a strictly dominant strategy.

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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.

[1]London Health Sciences Centre, ON, Canada
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[7]Sault Area Hospital, Sault Ste. Marie, ON, Canada
[8]Michael Garron Hospital, Toronto, ON, Canada
[9]Renfrew Victoria Hospital, ON, Canada
[10]Health Sciences North, Sudbury, ON, Canada
[11]Grand River Hospital, Kitchener, ON, Canada
[12]Ottawa Hospital Research Institute, ON, Canada
[13]University of Ottawa, ON, Canada
[14]Peterborough Regional Health Centre, ON, Canada
[15]Kingston Health Sciences Centre, ON, Canada
[16]University Health Network, Toronto, ON, Canada
[17]University of Kansas Medical Center, Kansas City, USA
[18]Mackenzie Health, Richmond Hill, ON, Canada
[19]Humber River Regional Hospital, Toronto, ON, Canada
[20]Sunnybrook Health Sciences Centre, Toronto, ON, Canada
[21]University of Toronto, ON, Canada
[22]Halton Healthcare, Oakville, ON, Canada
[23]Timmins and District Hospital, ON, Canada
[24]Trillium Health Partners, Mississauga, ON, Canada
[25]Niagara Health System, St. Catharines, ON, Canada
[26]St. Joseph's Health Centre, Toronto, ON, Canada
[27]North Bay Regional Health Centre, ON, Canada
[28]Lakeridge Health Corporation, Oshawa, ON, Canada
[29]Scarborough Health Network, ON, Canada
[30]Orillia Soldiers' Memorial Hospital, ON, Canada
[31]William Osler Health Centre, Brampton, ON, Canada
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[33]St. Joseph's Healthcare, Hamilton, ON, Canada
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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.

Keywords
cluster randomized controlled trial, pragmatic trial, dialysis, dialysis solutions, personalized dialysate temperature, cardiovascular events, mortality

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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

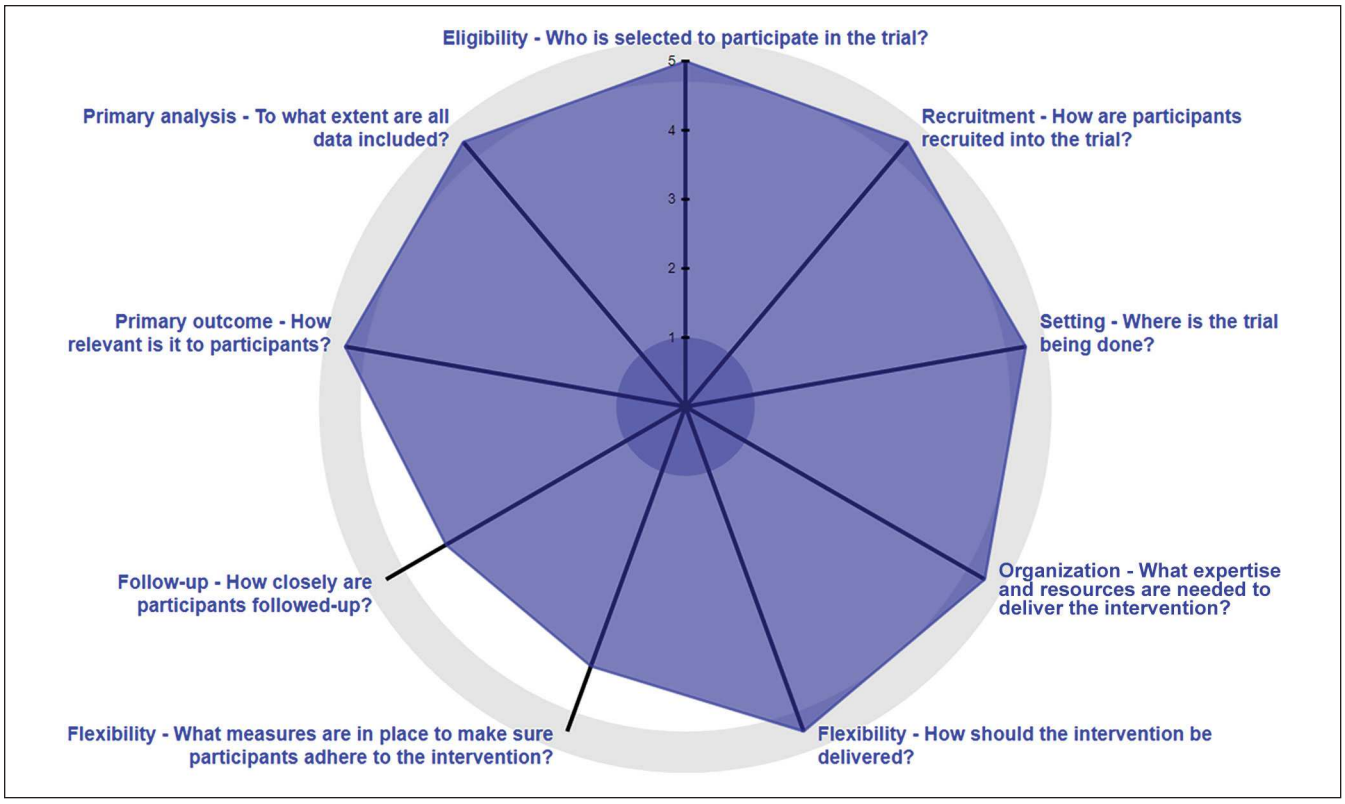

Figure 1. Precis-2 wheel highlighting the pragmatism of MyTEMP trial for 9 domains.
Note. Small reductions in pragmatism relate to (1) monthly data collection from centers to assess intervention adherence and (2) contact with centers that had less than 80% adherence. MyTEMP = Major Outcomes with Personalized 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

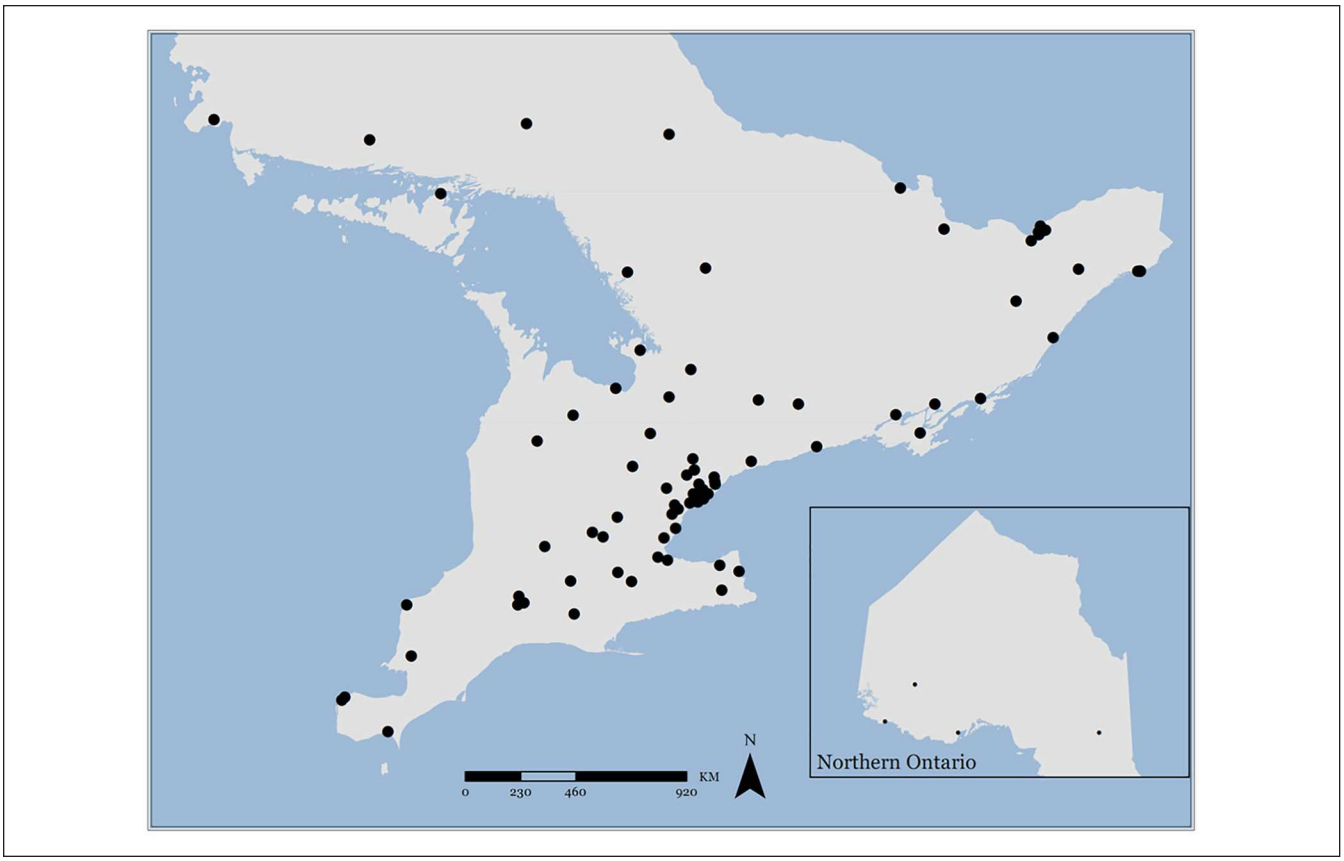

Figure 2. Map of Ontario, Canada, depicting participating centers across the province.
Note. Each black dot represents one of the 84 participating hemodialysis centers that in total care for approximately 7500 patients at any time. During the 4-year trial period, these 84 centers will care for approximately 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	Average: 103	Average: 89
Median (25th, 75th percentiles)	Median: 81 (32, 130)	Median: 56 (30, 132)
Expected number of patients per center over the 4-year follow-up[a]	Average: 189	Average: 174
Median (25th, 75th percentiles)	Median: 136 (60, 262)	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.

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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

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Supplemental Material

Supplemental material for this article is available online.

References

1. Liyanage T, Ninomiya T, Jha V, et al. Worldwide access to treatment for end-stage kidney disease: a systematic review. *Lancet*. 2015;385(9981):1975-1982. doi:10.1016/S0140-6736(14)61601-9.
2. Canadian Institutes for Health Information. CORR annual statistics 2019. Date unknown. https://www.cihi.ca/en/organ-replacement-in-canada-corr-annual-statistics-2019. Accessed January 29, 2020.

3. Foley RN, Collins AJ. End-stage renal disease in the United States: an update from the United States Renal Data System. *J Am Soc Nephrol*. 2007;18(10):2644-2648. doi:10.1681/ASN.2007020220.
4. Foote C, Ninomiya T, Gallagher M, et al. Survival of elderly dialysis patients is predicted by both patient and practice characteristics. *Nephrol Dial Transplant*. 2012;27(9):3581-3587. doi:10.1093/ndt/gfs096.
5. Jassal S, Trpeski L, Zhu NSF, Fenton S, Hemmelgarn B. Changes in survival among elderly patients initiating dialysis from 1990 to 1999. *CMAJ*. 2007;177(9):1033-1038. doi:10.1503/cmaj.061765.
6. Burton JO, Jefferies HJ, Selby NM, McIntyre CW. Hemodialysis-induced cardiac injury: determinants and associated outcomes. *Clin J Am Soc Nephrol*. 2009;4(5):914-920. doi:10.2215/CJN.03900808.
7. Burton JO, Jefferies HJ, Selby NM, McIntyre CW. Hemodialysis-induced repetitive myocardial injury results in global and segmental reduction in systolic cardiac function. *Clin J Am Soc Nephrol*. 2009;4(12):1925-1931. doi:10.2215/CJN.04470709.
8. Eldehni MT, Odudu A, McIntyre CW. Randomized clinical trial of dialysate cooling and effects on brain white matter. *J Am Soc Nephrol*. 2015;26:957-965. doi:10.1681/ASN.2013101086.
9. McIntyre CW. Effects of hemodialysis on cardiac function. *Kidney Int*. 2009;76(4):371-375. doi:10.1038/ki.2009.207.
10. Odudu A, Eldehni MT, McCann GP, McIntyre CW. Randomized controlled trial of individualized dialysate cooling for cardiac protection in hemodialysis patients. *Clin J Am Soc Nephrol*. 2015;10(8):1408-1417. doi:10.2215/CJN.00200115.
11. Santoro A, Mancini E, Paolini F, Cavicchioli G, Bosetto A, Zucchelli P. Blood volume regulation during hemodialysis. *Am J Kidney Dis*. 1998;32(5):739-748. doi:10.1016/S0272-6386(98)70128-3.
12. Veljančic L, Popović J, Radović M, et al. Simultaneous blood temperature control and blood volume control reduces intradialytic symptoms. *Int J Artif Organs*. 2011;34(4):357-364. doi:10.5301/IJAO.2011.7746.
13. Flythe JE, Xue H, Lynch KE, Curhan GC, Brunelli SM. Association of mortality risk with various definitions of intradialytic hypotension. *J Am Soc Nephrol*. 2015;26(3):724-734. doi:10.1681/ASN.2014020222.
14. McIntyre CW, Burton JO, Selby NM, et al. Hemodialysis-induced cardiac dysfunction is associated with an acute reduction in global and segmental myocardial blood flow. *Clin J Am Soc Nephrol*. 2008;3(1):19-26. doi:10.2215/CJN.03170707.
15. Selby NM, Burton JO, Chesterton LJ, McIntyre CW. Dialysis-induced regional left ventricular dysfunction is ameliorated by cooling the dialysate. *Clin J Am Soc Nephrol*. 2006;1(6):1216-1225. doi:10.2215/CJN.02010606.
16. Singh N, Langer A, Freeman MR, Goldstein MB. Myocardial alterations during hemodialysis: insights from new noninvasive technology. *Am J Nephrol*. 1994;14(3):173-181.
17. Galetta F, Cupisti A, Franzoni F, Carpi A, Barsotti G, Santoro G. Acute effects of hemodialysis on left ventricular function evaluated by tissue Doppler imaging. *Biomed Pharmacother*. 2006;60(2):66-70. doi:10.1016/j.biopha.2005.10.008.
18. Selby NM, Lambie SH, Camici PG, Baker CS, McIntyre CW. Occurrence of regional left ventricular dysfunction in patients undergoing standard and biofeedback dialysis. *Am J Kidney Dis*. 2006;47(5):830-841. doi:10.1053/j.ajkd.2006.01.012.
19. Beerenhout C, Dejagere T, van der Sande FM, Bekers O, Leunissen KM, Kooman JP. Haemodynamics and electrolyte balance: a comparison between on-line pre-dilution haemofiltration and haemodialysis. *Nephrol Dial Transplant*. 2004;19(9):2354-2359. doi:10.1093/ndt/gfh315.
20. Tsujimoto Y, Tsujimoto H, Nakata Y, et al. Dialysate temperature reduction for intradialytic hypotension for people with chronic kidney disease requiring haemodialysis. *Cochrane Database Syst Rev*. 2019;7:CD012598.
21. Beerenhout CH, Noris M, Kooman JP, et al. Nitric oxide synthetic capacity in relation to dialysate temperature. *Blood Purif*. 2004;22(2):203-209. doi:10.1159/000076854.
22. Chesterton LJ, Selby NM, Burton JO, McIntyre CW. Cool dialysate reduces asymptomatic intradialytic hypotension and increases baroreflex variability. *Hemodial Int*. 2009;13(2):189-196. doi:10.1111/j.1542-4758.2009.00355.x.
23. Cruz DN, Mahnensmith RL, Brickel HM, Perazella MA. Midodrine and cool dialysate are effective therapies for symptomatic intradialytic hypotension. *Am J Kidney Dis*. 1999;33:920-926. doi:10.1016/s0272-6386(99)70427-0.
24. Maggiore Q, Pizzarelli F, Santoro A, et al. The effects of control of thermal balance on vascular stability in hemodialysis patients: results of the European randomized clinical trial. *Am J Kidney Dis*. 2002;40(2):280-290. doi:10.1053/ajkd.2002.34506.
25. Parker KP, Bailey JL, Rye DB, Bliwise DL, Van Someren EJ. Lowering dialysate temperature improves sleep and alters nocturnal skin temperature in patients on chronic hemodialysis. *J Sleep Res*. 2007;16(1):42-50. doi:10.1111/j.1365-2869.2007.00568.x.
26. van der Sande FM, Kooman JP, Burema JH, et al. Effect of dialysate temperature on energy balance during hemodialysis: quantification of extracorporeal energy transfer. *Am J Kidney Dis*. 1999;33(6):1115-1121. doi:10.1016/S0272-6386(99)70149-6.
27. Kaufman AM, Morris AT, Lavarias VA, et al. Effects of controlled blood cooling on hemodynamic stability and urea kinetics during high-efficiency hemodialysis. *J Am Soc Nephrol*. 1998;9(5):877-883.
28. Zitt E, Neyer U, Meusburger E, et al. Effect of dialysate temperature and diabetes on autonomic cardiovascular regulation during hemodialysis. *Kidney Blood Press Res*. 2008;31(4):217-225. doi:10.1159/000141926.
29. Maggiore Q, Pizzarelli F, Zoccali C, Sisca S, Nicolò F, Parlongo S. Effect of extracorporeal blood cooling on dialytic arterial hypotension. *Proc Eur Dial Transplant Assoc*. 1981;18:597-602.
30. Jefferies HJ, Burton JO, McIntyre CW. Individualised dialysate temperature improves intradialytic haemodynamics and abrogates haemodialysis-induced myocardial stunning, without compromising tolerability. *Blood Purif*. 2011;32(1):63-68. doi:10.1159/000324199.
31. Maggiore Q. Isothermic dialysis for hypotension-prone patients. *Semin Dial*. 2002;15(3):187-190.
32. Maggiore Q, Dattolo P, Piacenti M, et al. Thermal balance and dialysis hypotension. *Int J Artif Organs*. 1995;18(9):518-525.

33. Enia G, Catalano C, Pizzarelli F, et al. The effect of dialysate temperature on haemodialysis leucopenia. *Proc Eur Dial Transplant Assoc Eur Ren Assoc*. 1985;21:167-172.
34. Pizzarelli F, Sisca S, Zoccali C, et al. Blood temperature and cardiovascular stability in hemofiltration. *Int J Artif Organs*. 1983;6(1):37-41.
35. Maggiore Maggiore Q, Pizzarelli F, Sisca S, et al. Blood temperature and vascular stability during hemodialysis and hemofiltration. *Trans Am Soc Artif Intern Organs*. 1982;28:523-527.
36. Mustafa RA, Bdair F, Akl EA, et al. Effect of lowering the dialysate temperature in chronic hemodialysis: a systematic review and meta-analysis. *Clin J Am Soc Nephrol*. 2016;11(3):442-457. doi:10.2215/CJN.04580415.
37. Fine A, Penner B. The protective effect of cool dialysate is dependent on patients' predialysis temperature. *Am J Kidney Dis*. 1996;28(2):262-265. doi:10.1016/s0272-6386(96)90310-8.
38. Hsu H-J, Yen C-H, Hsu K-H, et al. Association between cold dialysis and cardiovascular survival in hemodialysis patients. *Nephrol Dial Transplant*. 2012;27(6):2457-2464. doi:10.1093/ndt/gfr615.
39. Dasgupta I, Thomas GN, Clarke J, et al. Associations between hemodialysis facility practices to manage fluid volume and intradialytic hypotension and patient outcomes. *Clin J Am Soc Nephrol*. 2019;14(3):385-393. doi:10.2215/CJN.08240718.
40. Gray KS, Cohen DE, Brunelli SM. Dialysate temperature of 36°C: association with clinical outcomes. *J Nephrol*. 2018;31:129-136. doi:10.1007/s40620-016-0369-3.
41. Ye X, Usvyat LA, Jiao Y, Kotanko P, Maddux FW. Patient and dialysate temperature characteristics in incident hemodialysis patients: results from a large U.S. population. *J Am Soc Nephrol*. 2015;26:281A-282A.
42. Sakkas GK, Krase AA, Giannaki CD, Karatzaferi C. Cold dialysis and its impact on renal patients' health: an evidence-based mini review. *World J Nephrol*. 2017;6(3):119-122. doi:10.5527/wjn.v6.i3.119.
43. Roumelioti M-E, Unruh ML. Lower dialysate temperature in hemodialysis: is it a cool idea? *Clin J Am Soc Nephrol*. 2015;10(8):1318-1320. doi:10.2215/CJN.06920615.
44. Loudon K, Treweek S, Sullivan F, Donnan P, Thorpe KE, Zwarenstein M. The PRECIS-2 tool: designing trials that are fit for purpose. *BMJ*. 2015;350:h2147. doi:10.1136/BMJ.H2147.
45. Mc Cord KA, Hemkens LG. Using electronic health records for clinical trials: where do we stand and where can we go? *CMAJ*. 2019;191(5):E128-E133. doi:10.1503/cmaj.180841.
46. Jindal K, Chan CT, Deziel C, et al. Hemodialysis clinical practice guidelines for the Canadian society of nephrology: vascular access. *J Am Soc Nephrol*. 2006;17(suppl 1):S1-S27.
47. Ashby D, Borman N, Burton J, et al. Renal association clinical practice guideline on haemodialysis. *BMC Nephrol*. 2019;20(1):379. doi:10.1186/s12882-019-1527-3.
48. Presseau J, Mutsaers B, Al-Jaishi AA, et al. Barriers and facilitators to healthcare professional behaviour change in clinical trials using the Theoretical Domains Framework: a case study of a trial of individualized temperature-reduced haemodialysis. *Trials*. 2017;18(1):227. doi:10.1186/s13063-017-1965-9.
49. Canadian Institutes of Health Research, Natural Sciences and Engineering Research Council of Canada, Social Sciences and Humanities Research Council of Canada. *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans*. Ottawa, Ontario, Canada; 2018.
50. Ward JM, Getchell L, Garg AX; for MyTEMP Investigators. Patient and caregiver involvement in a multicentre clustered hemodialysis trial. *CMAJ*. 2018;190(suppl):S32-S33. doi:10.1503/cmaj.180403.
51. Quinn RR, Laupacis A, Austin PC, et al. Using administrative datasets to study outcomes in dialysis patients: a validation study. *Med Care*. 2010;48(8):745-750. doi:10.1097/MLR.0b013e3181e419fd.
52. Kokotailo R, Hill MD. Coding of stroke and stroke risk factors using International Classification of Diseases, Revisions 9 and 10. *Stroke*. 2005;36(8):1776-1781. doi:10.1161/01.STR.0000174293.17959.a1.
53. Andrade SE, Harrold LR, Tjia J, et al. A systematic review of validated methods for identifying cerebrovascular accident or transient ischemic attack using administrative data. *Pharmacoepidemiol Drug Saf*. 2012;21(suppl 1):100-128. doi:10.1002/pds.2312.
54. Juurlink D, Preyra C, Croxford R, et al. *Canadian Institute for Health Information Discharge Abstract Database: A Validation Study*. Toronto, Ontario, Canada: Institute for Clinical Evaluative Sciences; 2006.
55. Schultz SE, Rothwell DM, Chen Z, Tu K. Identifying cases of congestive heart failure from administrative data: a validation study using primary care patient records. *Chronic Dis Inj Can*. 2013;33(3):160-166.
56. Ivers NM, Halperin IJ, Barnsley J, et al. Allocation techniques for balance at baseline in cluster randomized trials: a methodological review. *Trials*. 2012;13(1):120. doi:10.1186/1745-6215-13-120.
57. Moulton LH. Covariate-based constrained randomization of group-randomized trials. *Clin Trials*. 2004;1(3):297-305. doi:10.1191/1740774504cn024oa.
58. Raab GM, Butcher I. Balance in cluster randomized trials. *Stat Med*. 2001;20(3):351-365. doi:10.1002/1097-0258(20010215)20:3<351::AID-SIM797>3.0.CO;2-C.
59. Yang D, Dalton JE. A unified approach to measuring the effect size between two groups using SAS®. Paper 335-2012 present at SAS Glob Forum; 2012. http://support.sas.com/resources/papers/proceedings12/335-2012.pdf. Accessed October 30, 2019.
60. Hayes RJ, Moulton LH. *Cluster Randomised Trials*. Boca Raton, FL: CRC Press; 2009.
61. Hayes RJ, Bennett S. Simple sample size calculation for cluster-randomized trials. *Int J Epidemiol*. 1999;28(2):319-326.
62. Reich NG, Myers JA, Obeng D, Milstone AM, Perl TM. Empirical power and sample size calculations for cluster-randomized and cluster-randomized crossover studies. *PLoS ONE*. 2012;7(4):e35564. doi:10.1371/journal.pone.0035564.
63. Arnold BF, Hogan DR, Colford JM Jr, Hubbard AE. Simulation methods to estimate design power: an overview for applied research. *BMC Med Res Methodol*. 2011;11:94. doi:10.1186/1471-2288-11-94.
64. Wicklin R. *Simulating Data With SAS®*. Cary, NC: SAS Institute; 2013.
65. Gelman A, Hill J. Causal inference using regression on the treatment variable. In: Alvaerz M, Beck N, Wu L, eds. *Data Analysis Using Regression and Multilevel/Hierarchical Models*. New York, NY: Cambridge University Press; 2006:167-194.

66. Munger A. *Components of Population Growth, Q4 2018 and Average for 2013-2017*. Toronto, Ontario, Canada; 2019.
67. Lin DY. Cox regression analysis of multivariate failure time data: the marginal approach. *Stat Med*. 1994;13(21):2233-2247. doi:10.1002/sim.4780132105.
68. Donner A, Klar N. *Design and Analysis of Cluster Randomization Trials in Health Research* (Gooster L and Ueberberg A, eds.). London, England: Arnold; 2000.
69. Van Doorn J, van den Bergh D, Boehm U, et al. The JASP guidelines for conducting and reporting a Bayesian analysis. *PsyArXiv*. 2019. doi:10.31234/osf.io/yqxfr.
70. Sun X, Briel M, Busse JW, et al. Credibility of claims of subgroup effects in randomised controlled trials: systematic review. *BMJ*. 2012;344:e1553. doi:10.1136/bmj.e1553.
71. Grieve R, Nixon R, Thompson SG. Bayesian hierarchical models for cost-effectiveness analyses that use data from cluster randomized trials. *Med Decis Making*. 2010;30(2):163-175. doi:10.1177/0272989X09341752.
72. Harrington D, D'Agostino RB, Gatsonis C, et al. New guidelines for statistical reporting in the journal. *N Engl J Med*. 2019;381(3):285-286. doi:10.1056/NEJMe1906559.
73. Food and Drug Administration. Guidance for industry and FDA staff: guidance for the use of Bayesian statistics in medical device clinical trials. http://www.rkstatistics.com/files/public/Knowledge_Bank/FDA-Bayesian_Stats_in_Medical_Device_Trials.pdf Published 2010. Accessed January 11, 2019.
74. US Department of Health & Human Services, US Food & Drug Administration, Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research. *Multiple Endpoints in Clinical Trials: Guidance for Industry*. Silver Spring, MD: US Food & Drug Administration; 2017.
75. Massachusetts Medical Society. Submitting to NEJM: statistical reporting guidelines. Date unknown. https://www.nejm.org/author-center/new-manuscripts. Accessed September 4, 2019.
76. Dmitrienko A, Offen WW, Westfall PH. Gatekeeping strategies for clinical trials that do not require all primary effects to be significant. *Stat Med*. 2003;22(15):2387-2400. doi:10.1002/sim.1526.
77. Wijeysundera DN, Austin PC, Hux JE, Beattie WS, Laupacis A. Bayesian statistical inference enhances the interpretation of contemporary randomized controlled trials. *J Clin Epidemiol*. 2009;62(1):13-21.e5. doi:10.1016/j.jclinepi.2008.07.006.
78. Gupta SK. Use of Bayesian statistics in drug development: advantages and challenges. *Int J Appl Basic Med Res*. 2012;2(1):3-6. doi:10.4103/2229-516X.96789.
79. Lewis RJ, Angus DC. Time for clinicians to embrace their inner Bayesian? *JAMA*. 2018;320(21):2208-2210. doi:10.1001/jama.2018.16916.

Appendices

Appendix 1: Detailed Background and Rationale for the MyTEMP Trial

Maintenance hemodialysis provides a life-saving treatment for persons whose kidneys have permanently failed (approximately 3 million worldwide and 23,000 in Canada).[1,2] However, over 400,000 individuals worldwide (2,500 persons in Canada) are admitted to hospital- or die from a major cardiovascular-related event each year.[3–5]

In most hemodialysis centers, the default dialysate temperature setting is in the range of 36.5 °C to 37.0 °C. Lowering the dialysate temperature below a patient's core body temperature (such a value of 35 °C to 36 °C) is a promising intervention that has the potential to reduce the risk of cardiovascular-related mortality and major adverse cardiovascular events.[6–8] Lowering the dialysate temperature stabilizes intradialytic blood pressure and decreases the risk of experiencing hypotensive events during hemodialysis treatments[9] – experiencing frequent hypotensive events during hemodialysis is associated with a greater risk of all-cause mortality and cardiovascular events.[10]

1.1 Physiology of intradialytic hypotension

There is evidence showing hemodialysis itself injures the heart, brain, and other vital organs through repeated episodes of intradialytic hypotension and subclinical ischemia.[10–17] Most intradialytic hypotensive events are attributed to the ultrafiltration that occurs during dialysis and an inadequate cardiovascular compensation to replace the loss in blood volume.[18] When fluid is removed from the body during hemodialysis, systolic blood pressure often drops by an average of 20 mmHg to 30 mmHg and diastolic blood pressure drops by 7 mmHg to 10 mmHg.[10,19] The normal physiological response to reductions in blood volume for healthy individuals is an increase of peripheral vascular resistance, an increase in the heart stroke volume, and/or a faster heart rate. Healthy individuals can tolerate up to a 20% loss in circulating blood volume before they experience hypotension.[20,21] However, many patients

on hemodialysis are unable to mount the response seen in healthy persons, and hypotension occurs with a smaller decline in blood volume.[22] This inability to mount a normal response has been partly attributed to impairment in myocardial contractile reserve due to cardiomyopathy.[23,24] Beyond ultrafiltration, there are multiple patient and dialysis-associated factors that contribute to intra-dialytic hypotension including poor sympathetic responsiveness,[25] poor cardiac function,[26,27] older age (possibly related to increasing comorbid conditions),[28] medication use (e.g. use of anti-hypertensive agents),[29] body heating,[30–32] release of vasodilator agents,[33,34] and osmolar and electrolyte changes.[35–38]

Large drops (greater than 20 mmHg) in blood pressure complicate up to 50% of hemodialysis sessions.[22] Intradialytic hypotension increases the risk of coronary hypoperfusion that can lead to myocardial stunning,[39,40] which is associated with left ventricular dysfunction.[13,15,41–43] When the left ventricle starts losing its ability to pump blood, the heart's compensatory mechanisms further loses the ability to compensate for the loss in blood volume during ultrafiltration – possibly leading to further hypotensive events and the damage of vital organs. Over time, the cumulative effect of intra-dialytic hypotensive events – each time resulting in small ischemic insults – may lead to a higher risk of major adverse cardiovascular events and cardiovascular-related death.[12,19,44]

1.2 Physiologic effects of reduced dialysate temperature

One strategy to help stabilize blood pressure during hemodialysis is to reduce the temperature of the dialysate. A cooler dialysate temperature increases peripheral vascular resistance, improves cardiac function, and alters the level of vasoactive peptides — all which may stabilize blood pressure.[30,32,45–50] [10] The measures used to described blood pressure differences between cooler dialysate temperature (≤35.5 °C) vs. a standard dialysate temperature (≥36.0 °C) in prior individual level RCTs has not been consistent; with some reporting mean intra-dialytic systolic blood pressure, nadir intra-dialytic systolic

blood pressure, and pre- and post-dialysis blood pressure. Nevertheless, these studies reported with a cooler compared to standard dialysate temperature there was a: (i) higher nadir systolic blood pressure; (ii) a smaller drop in post-dialysis from pre-dialysis blood pressure; and (3) a smaller drop in nadir intra-dialytic from pre-dialysis blood pressure - (***eTable 1***).[40,47,51–58]

Compared to a dialysate temperature of 37 °C, personalized dialysate temperature (0.5 °C below pre-dialysis core body temperature) over a 12-month period reduced injury to both the brain and heart. In the brain, temperature-reduced hemodialysis protected patients against white matter changes as a result of less injuries to cerebral vascular beds.[13] In the heart, temperature-reduced hemodialysis resulted in positive (but not statistically significant) changes in resting ejection fraction, however, there was a statistically significant reductions in both left ventricular mass and left ventricular end-diastolic volumes, and aortic distensibility was preserved.[15] A cardio- and neuro-protective effect of cooler dialysate temperature may operate through several mechanisms beyond stabilizing blood pressure and reducing the risk of intra-dialytic hypotension. Other mechanisms may include: lowering cell metabolism, reducing the likelihood of experiencing calcium overload, reducing inflammatory factors, and increasing anti-apoptotic factors.[59–62]

1.3 Clinical effects of reduced dialysate temperature

We conducted a systematic review and meta-analysis that identified 26 randomized controlled trials (total 484 patients) investigating the effect of cooler dialysate temperature compared to a standard temperature. Most of the trials enrolled less than 30 patients and only three trials followed patients for longer than six sessions.[47,54,63] In this review, temperature-reduced hemodialysis (34-35.5 °C) compared to control (where in different jurisdictions ranged from 36 °C to 38.5 °C), reduced the rate of intra-dialytic hypotension by 70% (95% CI: 49% to 89%). The intra-dialytic mean arterial pressure increased by

an average of 12 mmHg (95% CI: 8 to 16 mmHg) for temperature-reduced hemodialysis compared to standard temperature hemodialysis, and several studies reported a smaller reduction in average intra-dialytic nadir and post-dialysis systolic blood pressure compared with pre-dialysis blood pressure reading.[9,51–53] The of risk adverse events was not statistically different compared with standard dialysate temperature. However, these results should be interpreted with caution as the methodological quality of the 26 trials was rated as low to very low using GRADE criteria (Grading of Recommendations Assessment, Development and Evaluation criteria).[64,65]

Observational studies have reported inconsistent results with regards to the effect of temperature-reduced hemodialysis on mortality in comparison to the control temperature. Hsu *et al.*[66] found the use of cooler dialysate temperature (<35.5 °C) was associated with a 35% lower risk of cardiac mortality and 25% lower risk of all-cause mortality compared to patients that used a dialysate temperature between 35.5 and 37 °C. Similarly, data on 8807 patients from 232 hemodialysis facilities across 12 countries in the Dialysis Outcomes and Practice Patterns Study (DOPPS) Phase 4 (2009-2012) showed cool dialysate was associated with a 24% reduction in the risk of cardiovascular-related mortality (HR=0.76; 99% CI: 58%-98%), but was not associated with an altered risk of all-cause hospitalization (HR=1.12; 99% CI 0.98-1.27), all-cause mortality (HR=1.04; 99% CI 0.87-1.24), or major cardiovascular events (HR=0.94; 99% CI 0.80-1.11).[67] In a study comparing outcomes of cool dialysate at a temperature of 36 °C (n=313 patients) with matched-control patients with a dialysate temperature of 37 °C (n=1565), Gray et al.[68] found no difference in the risk of hospitalization (incidence rate ratio [IRR]=1.10; 95% CI 0.94-1.29) or all-cause mortality (IRR=1.09; 95% CI 0.77-1.53).

Some have suggested that a cooler dialysate temperature may reduce uremic toxin removal compared to a warmer dialysate temperature; however, this was not supported in our systematic review above when all prior studies were considered.[9] As well, other studies investigating the effect of a cooler dialysate on urea removal found that urea-based dialysis adequacy is largely unaffected by dialysate

temperature.[9,57,69,70] However, others have suggested urea removal is not a good marker for toxin removal because of its small size and generally negligible inter-compartmental resistance.[71] There is an ongoing clinical study of 14 patients that aims to compare toxin removal for patients on cool and warm dialysate for both small and large-sized toxins.[71] Of note, if a cooler dialysis temperature enables a patient to receive more dialysis or more ultrafiltration than they would otherwise receive with a warmer dialysis temperature (e.g. dialysis treatments are stopped early for reasons of intra-dialytic hypotension or cramping) this would increase uremic toxin removal.

1.4 What is the dialysate temperature used in current practice?

Currently, the dialysate temperature used in most centres in Canada and the United States ranges from 36.5 °C to 36.7 °C (97.7°F to 98.1°F). In preparation for the MyTEMP trial, we collected data on the prescribed dialysate temperature and patients' pre-dialysis body temperatures for 12,012 hemodialysis sessions across 68 unique hemodialysis centres in Ontario over a six-month period (September 2016 to March 2017). Results are reported as the median (25^{th}, 75^{th} percentile). We confirmed the delivered dialysis temperature during this period was fixed for each dialysis session except for 5 of the 68 hemodialysis centres that used blood temperature monitoring. The prescribed dialysate temperature was 36.5 °C or 97.7 °F (36 °C [96.8 °F], 36.5 °C [97.7 °F]). The pre-dialysis body temperature was 36.3 °C or 97.3 °F (35.9 °C [96.6 °F], 36.6 °C [97.9 °F]) and 59% of hemodialysis sessions started with a pre-dialysis body temperature (measured using oral or tympanic instruments) less than 36.5 °C (97.7 °F). The difference between the pre-dialysis body temperature and prescribed dialysate temperature was 0.0 °C (0.3 °C lower, 0.4 °C higher than body temperature).

In the United States, it has been estimated that the average delivered dialysate temperature is 36.7 °C (98.1 ºF).[72] The prescribed dialysate temperature of 36.5 °C (97.7 °F) used by most nephrologists comes

from clinical tradition rather than empirical evidence; with the historic rationale that dialysate temperature should be similar to typical body temperature.

1.5 How is the dialysate temperature set and maintained?

There are several types of hemodialysis mechanisms that control the dialysate temperature. These methods include fixed, programmed, isothermic, thermoneutral, and negative energy hemodialysis prescriptions.[6] The fixed method uses a single non-variable dialysate temperature that is prescribed throughout a patient's hemodialysis session. The latter four methods use blood temperature monitoring to make constant adjustments to the dialysate temperature during hemodialysis in response to the measured body temperature.

The fixed dialysate temperature prescription is currently the most common prescription method used in Ontario and likely worldwide. All hemodialysis machines have the mechanisms and software to achieve a fixed dialysis temperature, which makes this method of temperature control popular. To set a fixed dialysate temperature, a physician or nurse practitioner prescribes a specific temperature for a patient's hemodialysis treatment, and a dialysis nurse programs the fixed temperature into the hemodialysis machine. The nurse monitors the patient during the treatment, and some have the authority to alter the dialysate temperature during the treatment according to the patient's symptoms (e.g. temperature may be adjusted as per patient's condition).

In Ontario, the most commonly used dialysis machines are the Fresenius 5008 and the Baxter Artis. Purified water enters the machine through an inlet valve at a temperature between 5 °C and 30 °C. Then, the purified water passes through a passive heat exchanger where the spent dialysate that passed through the dialyzer passively heats the incoming purified water entering the hemodialysis machine. The purified water is then further heated by a heating element at a power correlated to the fixed

dialysate temperature. The heated water is combined with bicarbonate and acid to form the base of the dialysate.

A temperature sensor measures the dialysate temperature to determine if it is equivalent to the programmed dialysate temperature. The communication between the dialysate temperature sensor and the heating element is in a constant feedback loop throughout the hemodialysis session to maintain the programmed dialysate temperature. The temperature sensor in the above-mentioned machines measures the temperature of the water leaving the heater assembly and controls the heater to ensure that the: (a) temperature is within operating range; (b) maximum temperature deviation is within acceptable range; and (c) response time is within acceptable range. The Fresenius 5008 and Baxter Artis machines have different temperature circuit specification as shown in **eTable 2**.

Continuous monitoring of the dialysate fluid temperature is monitored by the protection system throughout the treatment session (**eFigure 1**). If the dialysate temperature cannot be maintained within the allowable operating and accuracy range (as specified in **eTable 2**) due to a failure in the temperature circuit, for patient safety an alarm is activated to warn the nurse and the bypass function is activated for the patient's blood to bypass the dialyzer.

1.6 How does body temperature change in response to the dialysate temperature?

In general, human body temperature is maintained within a narrow range. Several studies show that during conventional hemodialysis with the dialysate temperature set at 36.5 to 37 °C, temperature can increase by 0.1 to 0.9 °C at various parts of the body, including the arterial fistula line, oral cavity, and skin surface.[73] In the skin, decreases in body temperature as small as 0.3 °C can alter vascular tone; whereas, reductions in skin temperature of 0.8 °C associates with symptoms of shivering.[73] Using historic data from 4407 sessions, **eTable 3** shows as the dialysate temperature becomes cooler, the

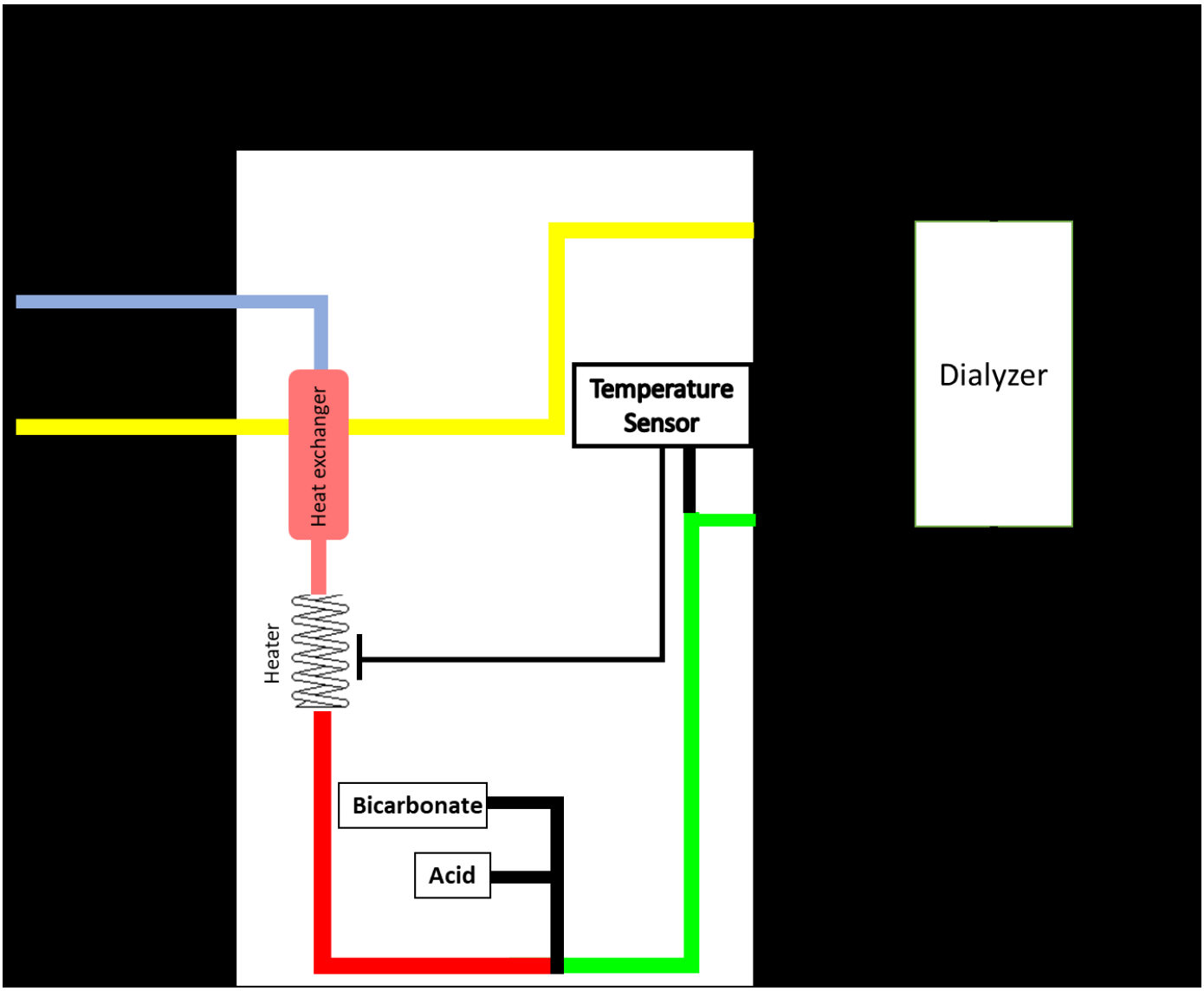
post-hemodialysis body temperature decreases after accounting for pre-hemodialysis body temperature.

Effects of temperature-reduced dialysis on patient symptoms. Some patients may experience feeling cold when using temperature-reduced hemodialysis.[9,40] In MyTEMP, we are *personalizing* the dialysate temperature for each patient, rather than using a single fixed cool temperature for all patients. In turn, this may improve tolerability for more patients. In a previous study, most patients using fixed temperature-reduced hemodialysis of 35 °C reported positive views of their experience and wanted to continue using the cooler temperature after study completion.[7,74] Patients also reported perceived benefits such as having more energy, better cognition, less post-hemodialysis fatigue, and a quicker time to recovery after their hemodialysis session.[9,74–76]

1.7 The need for large multi-centre trials of temperature-reduced hemodialysis

Many in the nephrology community have called for large-scale testing of temperature reduced dialysis.[8,9,77] Current trials of temperature-reduced hemodialysis registered on clinicaltrials.gov have fewer than 150 patients and none of the prior or current studies investigate major outcomes when a hemodialysis facility changes its protocol from a standard hemodialysis dialysate temperature of ≥36.5 °C to personalized temperature-reduced hemodialysis. To inform clinical practice change, we need evidence from at least one large, pragmatic, high-quality, multi-centre randomized controlled trial (that is generalizable to most hemodialysis centres) and has adequate statistical power to detect a meaningful change in the rates of major outcomes.

eFigure 1: Purified water (light blue) enters the hemodialysis machine where it passes through a passive heat exchanger. Spent dialysate (yellow) after leaving the dialyzer passively heats the purified water entering the hemodialysis machine (light red). The purified water is further heated by a heating element at a power that will raise the fresh dialysate to the desired programmed temperature (red). The heated water is combined with bicarbonate and acid to form the base of dialysate (green). A temperature sensor is used to measure the dialysate temperature to determine if it is equivalent to the programmed dialysate temperature. The temperature sensor will communicate with the heating element (by switching on or off) to achieve the programmed temperature.



eTable 1: Summary of systolic blood pressure measures in previous randomized controlled trials

Reference	N Patients	Dialysate temperature	Blood Pressure Measures ¥	
			Cooler dialysate temperature	Standard dialysate temperature
Beerenhout 2004 [51]	12	Fixed temperature 35.5 °C; duration: one session Vs Fixed temperature 36.0 °C; duration: one session	Change in SBP: -6 ± 2 mmHg	Change in SBP: -0.8 ± 22.7 mmHg
Beerenhout 2004 [52]	12	BTM (mean dialysate temperature 35.2 °C); duration: one session Vs Fixed temperature 37.5 °C; duration: one session	SBP pre-dialysis: 146 ± 5 mmHg SBP post-dialysis: 140 ± 6 mmHg	SBP pre-dialysis: 150 ± 5 mmHg SBP post-dialysis: 132 ± 4 mmHg
Chesterton 2009 [53]	10	Fixed temperature 35 °C; duration: one session Vs Fixed temperature 37 °C; duration: one session	Percent change in SBP: 2.71% above baseline ± 0.97%	Percent change SBP: 7.54% below baseline ± 1.92%
Cruz 1999 [54]	19	Fixed temperature 35.5 °C; duration: nine sessions	SBP pre-dialysis: 132 ± 3.3 mmHg Nadir SBP: 103 ± 2.9 mmHg	SBP pre-dialysis: 132.7 ± 3.4 mmHg Nadir SBP: 90.6 ± 2.5 mmHg

		Vs Fixed temperature 37 °C; duration: nine sessions	SBP post-dialysis: 118 ± 3.5 mmHg	SBP post-dialysis: 109.0 ± 2.1 mmHg
Maggiore 2002 [47]	95	BTM isothermic; duration: 12 sessions on average Vs BTM thermoneutral; duration: 12 sessions on average	Change in SBP between post- and pre-dialysis readings: -14 ± 17 mmHg * Post-dialysis SBP was 14 mmHg below pre-dialysis SBP	Change in SBP between post- and pre-dialysis readings: -21 ± 16 mmHg * Post-dialysis SBP was 21 mmHg below pre-dialysis SBP
Parker 2007 [55]	7	Fixed temperature 35 °C; duration: one session Vs Fixed temperature 37 °C; duration: one session	Intra-dialytic SBP: 137 ± 11.4 mmHg	Intra-dialytic SBP: 130.7 ± 11.4 mmHg
Selby 2006 [40]	10	Fixed temperature 35 °C; duration: one session Vs Fixed temperature 37 °C; duration: one session	Intra-dialytic SBP: 159 ± 14 mmHg	Intra-dialytic SBP: 142 ± 17 mmHg

van der Sande 1999 [56]	9	Fixed temperature 35.5 °C; duration: one session Vs Fixed temperature 37 °C; duration: one session	SBP pre-dialysis: 130 ± 22 mmHg Max ↓ in SBP: 21.8 ± 26.1 mmHg SBP post-dialysis: 132 ± 21 mmHg	SBP pre-dialysis: 144 ± 26 mmHg Max ↓ in SBP: 43 ± 20.6 mmHg SBP post-dialysis: 117 ± 26 mmHg
Kaufman 1998 [57]	17	BTM isothermic; BTM cooling 0.5 °C below body temperature; duration: 1.5 sessions on average Vs BTM thermoneutral; duration: 1.5 sessions on average	SBP pre-dialysis: 159 ± 35 mmHg Nadir SBP: 113 ± 30 mmHg SBP post-dialysis: 127 ± 39 mmHg	SBP pre-dialysis: 151 ± 27 mmHg Nadir SBP: 104 ± 27 mmHg SBP post-dialysis: 122 ± 28 mmHg
Zitt 2008 [58]	17	Fixed temperature 35 °C; duration: not clear Vs Fixed temperature 37 °C; duration: not clear	SBP pre-dialysis: 127 ± 6.4 mmHg SBP post-dialysis: 134 ± 3.9 mmHg	SBP pre-dialysis: 126 ± 4.6 mmHg SBP post-dialysis: 127 ± 2.1 mmHg

SBP=systolic blood pressure (mean ± standard deviation); Max ↓ in SBP: Maximum drop in intradialytic SBP (difference between pre-dialysis and nadir intra-dialytic SBP); Intra-dialytic SBP: Mean intradialytic SBP during the hemodialysis session;

¥ Information presented is Mean ± SD

eTable 2: Default temperature circuit specification for the Fresenius 5008 and Baxter Artis hemodialysis machines.

Machine	**Fresenius 5008**	**Baxter Artis**
Dialysate temperature range	+34 °C to +39 °C	+35 °C to +39.5 °C
Accuracy**	+0.2 °C/-0.5 °C of the set value	+0.5 °C/-1.8 °C of the set value
Resolution++	0.5 °C	0.5 °C (0.1 °C is possible)

**Accuracy of the delivered dialysate temperature compared to the programmed dialysate temperature.

++ The resolution (increments) at which the dialysate temperature can be programmed on the machine.

eTable 3: Change in body temperature by different levels of dialysate temperature using historic data from 4407 sessions. Patient body temperatures were measured using tympanic thermometers.

Dialysate is:	Dialysate Temperature	Arrival Temperature (Pre-dialysis)	Departure Temperature (Post-dialysis)	Change in Body Temperature**
At least 1 °C above body temperature	37 (36.5, 37.5)	35.8 (35.5, 35.9)	36.3 (36.1, 36.5)	0.7 (0.4, 1)
0.5 to 0.99 °C above body temperature	36.5 (36.5, 36.5)	36 (36, 36)	36.3 (36.1, 36.5)	0.3 (0.1, 0.6)
0.01 to 0.49 °C above body temperature	36.5 (36.5, 36.5)	36.3 (36.2, 36.4)	36.4 (36.3, 36.6)	0.2 (0, 0.4)
Equal to body temperature	36.5 (36.5, 36.5)	36.5 (36.5, 36.5)	36.5 (36.3, 36.7)	0.1 (-0.1, 0.2)
0.01 to 0.49 °C below body temperature	36.5 (36, 36.5)	36.6 (36.4, 36.7)	36.6 (36.4, 36.7)	0 (-0.2, 0.2)
0.5 to 0.99 °C below body temperature	36 (36, 36)	36.6 (36.6, 36.8)	36.5 (36.4, 36.7)	-0.1 (-0.3, 0.1)
At least 1 °C below temperature	35.5 (35.5, 36)	36.7 (36.6, 37)	36.5 (36.4, 36.7)	-0.2 (-0.5, 0)

** Change in Body Temperature refers to the difference in each patients' arrival from departure temperature. A positive number means the departure temperature greater (i.e., warmer) than the arrival temperature.

Columns are presented as median (25^{th}, 75^{th} percentile).

To convert from °C to °F, use the formula: (Temperature °C × 1.8) + 32;

Appendix 2: Patient Temperature and setting of the dialysate temperature for the intervention group. Centres that have dialysis machines able to change by increments of 0.1°C

Patient Temperature* (°C)	**Dialysate Temperature (°C)**
37.5 and greater	36.5 (or standard centre protocol)
37.4	36.5
37.3	36.5
37.2	36.5
37.1	36.5
37	36.5
36.9	36.4
36.8	36.3
36.7	36.2
36.6	36.1
36.5	36
36.4	35.9
36.3	35.8
36.2	35.7
36.1	35.6
36 and less	35.5 (or standard centre protocol)

When to measure patient temperature: before starting the dialysis session using your standard thermometer.

If temperature out of ordinary (e.g. patient consuming cool/warm beverage or just came from the cold outside in the winter), **then**: please start the patient on a reasonable dialysate temperature and re-check the body temperature in a few minutes.

Appendix 3: Patient Temperature and setting of the dialysate temperature for the intervention group. Centres that have hemodialysis machines able to change by increments of 0.5 °C

Patient Temperature* (°C)	**Dialysate Temperature (°C)**
37.5 and greater	36.5 (or standard centre protocol)
37.4	36.5
37.3	36.5
37.2	36.5
37.1	36.5
37	36.5
36.9	36
36.8	36
36.7	36
36.6	36
36.5	36
36.4	35.5
36.3	35.5
36.2	35.5
36.1	35.5
36 and less	35.5 (or standard centre protocol)

When to measure patient temperature: before starting the dialysis session using your standard thermometer.

If temperature out of ordinary (e.g. patient consuming cool/warm beverage or just came from the cold outside in the winter), **then**: please start the patient on a reasonable dialysate temperature and re-check the body temperature in a few minutes.

Appendix 4: Sampling accuracy for overall centre adherence

For eight centres, we had access to the full patient data on adherence to the allocated temperature protocol (5 centres in the control and 3 centres in the intervention arm). We sampled 15 patients 1000 times from each centre and compared the sampled adherence to the true adherence for all patients within the respective centre. The sampled adherence was within 10% of the true adherence approximately 50% to 90% of the time. The sampled adherence was within 20% of the true adherence over 80% of the time for all centres. We found as the true centre adherence increased towards 100%, so did the accuracy of our estimated sample adherence.

Appendix 5:

MyTEMP met the necessary criteria for alteration to the patient consent process as outlined in the TCPS-2 Statement: (i) the research poses a clear benefit to society and was unlikely to adversely affect patient welfare; (ii) the intervention was considered to be of minimal risk to patients (similar to a quality-control measure that could be implemented by a dialysis centre director); (iii) an informed consent model is impossible and impracticable given our research design and resources (e.g. a source of bias if patients in a hemodialysis centre randomly allocated to personalized temperature are less likely to consent to trial participation [a change compared to their historic dialysate prescription] compared to patients in a hemodialysis centre randomly allocated to control arm [where there is no change from what they have historically received]); and (iv) there is a plan to provide a debriefing which also offers patients the possibility of refusing the intervention.[78]

Appendix 6: Common data sources used for population-based studies

Database (Source)	Description	Key Data Variables
Health Services		
Discharge Abstract Database (CIHI)	Hospital discharge abstracts for acute, chronic and rehabilitative care (1988 onward)	Diagnoses; Procedures; Comorbidities; Length of Stay
National Ambulatory Care Reporting System (CIHI)	ED visits, same day surgery, outpatient clinics (e.g., dialysis, cancer clinics) (2002 onward)	Reason for visit; Triage level; Interventions; Mode of arrival
Ontario Drug Benefit Database (MOHLTC)	Claims for prescribed drugs covered by the Ontario Drug Formulary for adults aged 65+ and those receiving social assistance (1990 onward)	Drug ID number; Drug quantity; Cost
Ontario Health Insurance Plan (MOHLTC)	Reimbursement claims made by fee-for-service physicians and community-based labs (1991 onward)	Service provided; Diagnosis codes; Fee paid; Physician specialty
	Registry	
Canadian Organ Replacement Register (CIHI)	Collects and records the incidence, prevalence, treatment changes, and outcomes of all chronic dialysis and solid organ transplant patients in Canada. Data is collected by voluntary completion of survey forms for each patient at dialysis initiation and at yearly follow-up (2001 onward)	Hemodialysis start; vascular access use; nephrology referral; comorbid and baseline conditions
Ontario Renal Reporting System	Collects and records the incidence, prevalence, treatment changes, and outcomes of all chronic dialysis and solid organ transplant patients in Canada. Data is collected is mandated by the Ontario Renal Network for each patient at dialysis initiation and at yearly follow-up (2010 onward)	Hemodialysis start; vascular access use; nephrology referral; comorbid and baseline conditions
Population and Demographics		
Registered Persons Database (MOHLTC)	Basic demographic information about all Ontarians that ever had an Ontario Health Card Number. (1990 onward)	Date of birth; Date of death; Sex; Geographic information

Office of the Registrar General- Deaths (ORGD)	ORGD is an annual dataset containing information on all deaths registered in Ontario starting on January 1st, 1990.	Information on cause **Note**: Information on cause of death lags other variables by ~2 years.
Care Providers		
ICES Physicians Database	This data set contains yearly information about all physicians in Ontario (1992 onward)	Annual demographics; Specialization; Workload
Laboratory Datasets		
Ontario Laboratories Information System (pending linkage)	OLIS is a cornerstone information system that connects hospitals, community laboratories, public health laboratories and practitioners to facilitate the secure electronic exchange of laboratory test orders and results. ICES has signed and currently executing a Data Sharing Agreement to link Ontario-wide laboratory results to the Ontario-wide data holdings housed at ICES.	Creatinine levels, lipid panels, urine protein Outpatient, emergency room and inpatient values.

MOHTC: Ministry of Health and Long-term Care, CIHI – Canadian Institutes for Health Information

Appendix 7: List of 78 variables baseline variables

Medical history of the following		**Databases**
Demographic		
Age		RPDB
Sex		RPDB
Race (includes information about aboriginals)		ORRS
Rural living		RPDB
Socioeconomic status		RPDB
Primary Cause of ESRD		
Diabetes		ORRS
Drug Induced		ORRS
GN/Autoimmune disease		ORRS
Polycystic Kidney Disease		ORRS
Renal Vascular Disease		ORRS
Other		ORRS
Comorbid Factors		
Arrhythmia		OHIP/CIHI-DAD
Amputation		CIHI-DAD
Alcoholism		CIHI-DAD
Atrial Fibrillation/Flutter		CIHI-DAD
CABG/PCI		ORRS / CIHI-DAD/OHIP
Charlson Comorbidity Score		CIHI-DAD
Coronary Artery Disease (with angina)		ORRS/ CIHI-DAD/OHIP
Crash start with AKI		CIHI-DAD
Dementia		ORRS /CIHI-DAD/OHIP
Depression*		CIHI/ODB/OHIP
Diabetes mellitus		ORRS/CIHI-DAD/OHIP
Fracture		CIHI-DAD/OHIP
Heart failure ++		CIHI-DAD
Hemorrhage		OHIP/CIHI-DAD
Hypertension		ORRS/ CIHI-DAD/OHIP
Hypotension		CIHI-DAD
Ischemic Stroke ++		CIHI-DAD
Liver Disease		ORRS/ CIHI-DAD/OHIP

Lung disease (COPD)		ORRS/ CIHI-DAD/OHIP
Malignancy		ORRS /CIHI-DAD/OHIP
Myocardial infarction ++		ORRS/ CIHI-DAD
Other serious illness that would shorten life expectancy less than 5 years		ORRS
Peripheral vascular disease		ORRS/ CIHI-DAD/OHIP
Smoking		ORRS
Stroke/Transient ischemic attack		ORRS/CIHI-DAD
Subarachnoid Hemorrhage		CIHI-DAD
Syncope		CIHI-DAD
Drugs (for 65+ years)		
ACE Inhibitors		ODB
ARB		ODB
Anti-depressants		ODB
Anti-Psychotics		ODB
Benzodiazepine		ODB
Beta-Blockers		ODB
Healthcare Utilization		
Long term care facility utilization		ODB/OHIP/CCRS
Number of nephrology consults in the last 12 months		OHIP
Number of Family Doctor consults in the last 12 months		OHIP
Number of Hospitalizations in last 12 months		CIHII-DAD
Number of Visits to Emergency Department in last 12 months		NACRS
Total Healthcare Costs in last 12 months		Various sources at ICES [79]
Lab Data (Last measured)		
Hemoglobin		ORRS/OLIS
Urea		ORRS/OLIS
eGFR		ORRS/OLIS
Serum Albumin		ORRS/OLIS
Procedures / Monitoring		
Carotid endarterectomy		OHIP
Coronary angiogram		OHIP/CIHI-DAD
Coronary revascularization		OHIP/CIHI-DAD
Echocardiography		OHIP/CIHI-DAD
Holter monitoring		OHIP/CIHI-DAD

Other Variables		
Dialysate Temperature (baseline)		Case Report Forms**
Pre-dialysis systolic blood Pressure (baseline)		Case Report Forms**
Pre-dialysis diastolic blood pressure (baseline)		Case Report Forms**
Mean intra-dialytic nadir systolic blood pressure (baseline)		Case Report Forms**
Diastolic blood pressure accompanying the intra-dialytic nadir systolic blood pressure (baseline)		Case Report Forms**
Date of first nephrology visit		ORRS
Height		ORRS
Last measure weight		ORRS
Body Mass Index (BMI)		ORRS
History of Renal Transplant		ORRS /CIHI-DAD/OHIP
First Dialysis Modality		
Peritoneal Dialysis		ORRS/CORR
Hemodialysis		ORRS/CORR
Had a late nephrology referral		ORRS/CORR
Vascular access used at index date (April 01, 2017)		
Arteriovenous fistula		ORRS/CORR
Arteriovenous graft		ORRS/CORR
Central venous catheter		ORRS/CORR
Hemodialysis Characteristics at Index Date		
Patients Dialyzing in an Acute Care Hospital		ORRS
Patients Dialyzing in a Chronic or Community Hospital		ORRS
Duration of all dialysis modalities (Months)		ORRS
Centre Factors		
Number of patients at centre		ORRS
Centre Transplant Rate in previous 24 months		ORRS /CIHI-DAD/OHIP
Centre Death Rate in previous 24 months		ORRS/RPDB
Centre Transfer rate in previous 24 months		ORRS
Number of stations within centre		ORRS
Centre uses electronic dialysis run sheets		Case Report Forms**
Centre uses tympanic temperature measurement		Case Report Forms**
Centre uses heated chairs		Case Report Forms**

ODB= Ontario Drug Benefit database contains claims for prescription drugs received under the Ontario Drug Benefit program. Most are for those >=65 but from 1997 forward we also have data on other ODB program; OLIS=

Ontario Laboratories Information System; ORRS=Ontario Renal Reporting System has information is a database of all pre-dialysis, acute dialysis and chronic dialysis patients in Ontario since 2010; CIHI-DAD= Discharge Abstract Database records detailed diagnosis and procedural information on all hospitalizations in Ontario. Up to 25 unique diagnostic and 20 procedural codes can be assigned to each hospitalization.; OHIP= Ontario Health Insurance Plan database contains health claims for inpatient and outpatient physician services;

* Depression is defined as (1) having two events of OHIP diagnosis, hospitalizations, or ODB drug prescription; or (2) having at least one event in at least two of OHIP diagnosis, hospitalizations, or ODB drug prescription.[80]

**This information is captured on the dialysis run sheet that is completed with every dialysis treatment in Ontario (i.e. centres do not have to collect additional data outside standard of care).

++ History of components of primary or secondary outcomes

Appendix 8: Algorithm for capturing primary composite outcome

Outcome	Algorithm	Position of code	Performance
Cardiovascular-related death ~~Ѧ~~, ¥	ORGD: Leading Cause of Death LCD_33 = Chronic rheumatic heart disease LCD_34 = Hypertensive disease LCD_35 = Ischemic heart disease LCD_36 = Pulmonary heart disease and related LCD_37 = Nonrheumatic valve disorders LCD_38 = Cardiomyopathy LCD_39 = Cardiac arrest LCD_40 = Cardiac arrhythmias LCD_41 = Heart failure and complications, ill-defined heart disease LCD_42 = Cerebrovascular diseases LCD_43 = Atherosclerosis LCD_44 = Aortic aneurysm and dissection	N/A	Not available
Cardiovascular-related death	**ICD-10:** I00 - I78 AND Dischdisp="07" or death in Registered Persons Database during the hospital stay	Primary Diagnosis	RPDB has an accuracy of 99% for capturing death [81]
Hospital admission with ischemic stroke	***ICD-10:*** I63 (excl. I63.6), I64, H341	Primary Diagnosis	PPV= 85% [82,83]
Hospital admission with myocardial infarction	***ICD-10:*** I21, I22	Primary Diagnosis	Sn= 89%, PPV= 87% [84]
Hospital admission with heart failure	**ICD-10:** I50	Primary Diagnosis	Sn=61% , Sp=98%, PPV=66%[85]

Abbreviations: ICD = International Classification of Disease; OHIP = Ontario Health Insurance Plan; Dischdisp=Discharge disposition; Sn=Sensitivity; PPV= Positive Predictive Value; LCD=Leading Cause of Death; ORGD=Office of Registrar General – Deaths; RPDB = Registered Persons Database

~~Ѧ~~ Due to the time lag in data capture, deaths from ORGD will only capture events for the follow-up period between April 3rd, 2017 and December 31st, 2020. These events capture both in- and out-of-hospital cardiovascular-related deaths. For the remaining study period, we will only be able to capture in-hospital deaths using ICD-10 codes.

¥ Personal communication with Dr. Jack Tu who is part of a working group conducting a validation of this outcome using existing Ontario clinical trial data as the reference standard.

Appendix 9: Justification for using a composite primary endpoint

Our composite primary endpoint is composed of individual components that we believe will have a treatment effect in the same direction and magnitude and are clinically important – appreciating cardiovascular-related mortality is a more detrimental outcome than hospitalization. The outcome will provide an overall sense of the impact of the intervention on cardiovascular morbidity.

While there is some debate in the literature about including hospital admission with congestive heart failure as a component outcome of major cardiovascular events,[86] we chose to include it given that a personalized dialysate temperature may lead to fewer heart failure admissions if there is less cardiac ischemia or less left ventricular dysfunction over time. As well, patients who have a preserved blood pressure during dialysis may be less likely to stop their dialysis treatments early or may have more fluid removed on their dialysis treatments. In our analysis of historic Ontario data, the median stay for a hospital admission with congestive heart failure (ICD-10 code I50) in dialysis was 6 days (25th, 75th percentiles: 3, 10).

There is a strong relationship between intradialytic hypotension and myocardial stunning because of transient abnormalities in cardiac regional wall motion that occur in the presence of coronary hypoperfusion. Rapid reductions in blood pressure predispose to myocardial stunning because coronary flow is dependent on central arterial pressure. Hypotensive episodes also associate with aging of the arterial system, as well as extensive calcification and stiffening of the arterial walls.[87] The cumulative contribution of hypotensive events to cardiovascular events have been significant.[11,13,53] Reduction of dialysate temperature is one technique that has been shown to be effective in decreasing the of risk intradialytic hypotensive events and stabilizing blood pressure, reducing injury to the heart and brain as seen in magnetic imaging studies.[9]

In observational studies, compared to patients that did not experience intradialytic hypotension, patients that experienced intradialytic hypotension in more than 10% of their hemodialysis treatments had a hazard ratio of 1.22 (95% CI: 1.02 to 1.48) for cardiovascular-related mortality, 1.20 (95% CI: 1.00 to 1.45) for hospitalizations of non-fatal myocardial infarction, and 1.22 (95% CI: 1.11 to 1.34) for hospitalizations with heart failure or volume overload.[44] Similarly, compared to patients that did not experience intradialytic hypotension, those that experienced intradialytic hypotension in more than 10% of their treatments had a 1.23 (95% CI: 1.08 to 1.41) risk of experiencing a major cardiovascular event (defined as nonfatal myocardial infarction, nonfatal stroke, or cardiovascular-related mortality).[44] The study did not specifically provide the risk of experiencing an ischemic stroke.

The historic annual hazard rate of the components of the primary outcome in our data sources have similar baseline annual event rates: 0.031 for cardiovascular-related mortality, 0.030 for hospital admission with myocardial infarction, 0.032 for hospital admission with congestive heart failure, and 0.012 for hospital admission with ischemic stroke per person-year.

Appendix 10: Other important outcomes

Lower limb amputation: Patients on hemodialysis, especially those with diabetes, have a high hazard rate of amputation. The historic baseline hazard rate of lower extremity amputations over a 4-year period (from April 1, 2013 to March 31, 2017) for an open cohort was 0.026 events per person-year. For patients with diabetes, this historic hazard is 0.039 events per person-year. Amputations are associated with cardiovascular risk factors and likely linked to vascular injury caused by hemodialysis-induced ischemia, which complicates pre-existing arterial disease and diabetes related injury.

Major falls and fractures: Many patients on dialysis are frail and prone to falling, which may also predispose them to suffer a fracture. Bone fractures are an important outcome and can result in morbidity, high economic costs, and mortality. The three-year incidence of falls requiring a hospitalization ranges from 3% to 12% for patients on dialysis, with elderly females being the highest risk.[88] Major fractures (hip, forearm, pelvis, or proximal humerus) are also common occurring in nearly 6% of patients each year.[88] In our cohort, the historic hazard rate of major fractures over a 4-year period (from April 1, 2013 to March 31, 2017) for an open cohort was 0.037 events per person-year. Intra-dialytic hypotension might increase the rate and severity of falls after a hemodialysis session leading to additional fractures requiring hospitalizations.

Emergency department visits or hospitalizations (analyzed separately and as a composite): Patients on hemodialysis are frequently hospitalized and account for 5% to 7% of healthcare expenditures in developed countries despite comprising a very small percentage of the general adult population.[89–92] These patients have several characteristics that make them vulnerable to hospitalization and emergency department use, including multimorbidity, high rates cardiovascular complications, and complex

medication regimens. The historic hazard rate for emergency department visits was 1.05, all-cause hospitalizations was 0.65, and the composite all-cause emergency department visits or hospitalizations over a 4-year period (from April 1, 2013 to March 31, 2017) was 1.22 events per person-year.

Intradialytic hypotension:

In general, there is no consensus, evidence-based, medical definition for intradialytic hypotensive episodes.[93,94] Most definitions of intradialytic hypotension are made up of two or more components: 1) an absolute or relative decline in the intradialytic systolic blood pressure from the pre-dialysis systolic blood pressure reading; and 2) a nadir systolic blood pressure reading below a specific threshold.[94] Some definitions include an additional component of intradialytic symptoms (e.g., cramping, yawning,) and/or the need for an intradialytic intervention (e.g., Trendelenburg position, fluid administration,). In our trial, we will not have information on patient symptoms of hypotension or interventions used to treat these episodes. It has been previously shown that adding symptom or intervention criteria to intradialytic hypotension definitions did not change the strength of association with mortality.[10]

In MyTEMP, in post-hoc analysis, we will define intradialytic hypotension if the patient experiences any of the following: **i)** nadir systolic blood pressure < 90 mmHg anytime during the hemodialysis session (regardless if patients begin the hemodialysis session with systolic blood pressure below 90 mmHg); or **ii)** drop in systolic blood pressure by ≥ 30 mmHg from the pre-dialysis systolic blood pressure reading.[95,96] We will also consider alternate definitions of intradialytic hypotension:

a) Systolic blood pressure < 90 mmHg alone. A nadir systolic blood pressure of < 90 mmHg was strongly associated with all-cause mortality in a previous observational study.[10,94]

b) At least a 25% relative reduction in nadir systolic blood pressure from pre-dialysis systolic blood pressure or nadir ≤ 90 mmHg.[53,94,97]

c) At least a 25% relative reduction in nadir systolic blood pressure from pre-dialysis systolic blood pressure.[53,94,97]

d) A drop in nadir systolic blood pressure by ≥ 35 mmHg from pre-dialysis systolic blood pressure.[94,98]

Appendix 11a: Statistical power estimates for different hazard ratios of the treatment effect different coefficients of variation, and different rates of the primary composite outcome. A statistical power estimate of 0.8 means the trial has 80% power to detect the specified hazard ratio with the intervention vs. control, if the effect in truth exists.

Different Hazard Ratios of the Treatment Effect	Different rates of the primary composite outcome (per person-year)			
	0.08	**0.09**	**0.1**	**0.11**
CV=0.19				
0.75	95%	96%	97%	98%
0.8	80%	83%	85%	88%
0.85	53%	56%	59%	62%
0.9	25%	27%	29%	31%
CV=0.20				
0.75	94%	96%	97%	97%
0.8	78%	82%	84%	86%
0.85	52%	55%	58%	60%
0.9	25%	26%	28%	30%
CV=0.21				
0.75	93%	95%	96%	97%
0.8	77%	80%	83%	85%
0.85	50%	53%	56%	59%
0.9	24%	26%	27%	28%
CV=0.22				
0.75	93%	94%	95%	96%
0.8	76%	79%	81%	83%
0.85	49%	52%	54%	57%
0.9	23%	25%	26%	27%
CV=0.23				
0.75	92%	93%	95%	96%
0.8	74%	77%	80%	82%
0.85	47%	50%	53%	55%
0.9	23%	24%	25%	27%
CV=0.24				
0.75	91%	93%	94%	95%
0.8	73%	76%	78%	80%
0.85	46%	49%	51%	53%
0.9	22%	23%	24%	26%

CV=0.25				
0.75	90%	92%	93%	94%
0.8	71%	74%	76%	79%
0.85	45%	47%	50%	52%
0.9	21%	23%	24%	25%

CV = Coefficient of variation. We assumed a total follow-up of 4 years, a cluster harmonic average of 163 person-years, alpha of 0.04, and 42 clusters per arm. Starred values (*)highlights conditions where we have at least 80% power to detect a difference, if a difference truly exists.

Appendix 11b: Details of power estimates using computer simulations.

In addition to the closed form sample size estimation, we also confirmed our power calculations using simulation studies. This method allowed us to account for the complexity of our study design, variable cluster (HD centre) sizes, different follow-up periods among patients in participating centres, clustering, and censoring events during follow-up.[99–102] We generated 1000 simulated data sets based on the correlation structure observed for the prevalent HD cohort from April 1st, 2013 to March 31st, 2017. For each simulated dataset, 84 observations (i.e., HD centres) were generated and included information on the following: 1) number of outcome events that occurred within a 4-year period, 2) number of days of follow-up, and 3) a randomly allocated indicator representing the control or intervention arm. Assuming a two-tailed alpha 0.04, we have 56%, 81%, and 96% power to detect a 15%, 20%, and 25% hazard rate reduction in the primary composite endpoint, respectively.

Appendix 11c: Power estimates for the key secondary endpoint of between group difference in the mean drop of systolic blood pressure (mmHg).

	Standard deviation of the cluster-period means				
Between group difference (mmHg)**	**2**	**4**	**5**	**6**	**7**
1	54%	16%	12%	6%	5%
2	100%	71%	57%	31%	22%
3	100%	98%	94%	71%	55%
4	100%	100%	100%	94%	85%
5	100%	100%	100%	100%	97%
6	100%	100%	100%	100%	100%
7	100%	100%	100%	100%	100%
8	100%	100%	100%	100%	100%
9	100%	100%	100%	100%	100%
10	100%	100%	100%	100%	100%

**Between-group difference in the mean drop of systolic blood pressure.

The above data assumed there are 84 clusters with at least 6 repeated observations and a constant intraclass correlation coefficient (ICC) of 0.4 and an average drop across all sites/periods of 28 mmHg with an alpha of 0.01.

Shaded area highlights conditions where we have at least 80% power to detect a difference, if a difference truly exists.

Appendix 12: Bayesian analysis

As a first step, we will use a minimally informative reference prior (which regards all possible log-hazard ratio values to be equally likely and will produce results largely dependent on observed data from MyTEMP). Sources of prior information will include: 1) results from published literature that compare temperature-reduced hemodialysis to standard hemodialysis temperature;[66–68] and 2) historic data from our administrative data sources. At the analytic stage, we will update **Table 3** based on current data from the literature.

We will use PROC PHREG (SAS 9.4, NC Cary) – in a similar manner as conducted for the primary analysis – and invoke the BAYES statement to request that the parameters of the model be estimated by using Gibbs sampling techniques.[103] This approach enables the specification of prior information, control the sampling, as well as obtain posterior summary statistics and convergence diagnostics. Convergence of the generated Markov chain will be assessed by examining the trace plot, autocorrelation function plot, and posterior density plot.

Appendix 13: Planned additional analyses

We will conduct several analyses to assess the robustness of the results from the primary analysis. These additional analyses will include:

1. Adjusted Cox model to test the effect of the intervention vs. control on the primary composite outcome.

2. Treating kidney transplants, switching to a home dialysis modality, and switching to a non-participating hemodialysis centre as a censoring event.

3. Assuming a closed cohort, where we will include only a subset of our cohort who were on hemodialysis prior to April 3rd, 2017. Using historic data, we estimate there will be ~7500 patients included in this cohort.

4. In our historic data, over a 4-year follow-up period we found 19% of patients experienced at least one event in our primary composite outcome and 4% of all patients had 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, it will be important to understand repeated events (i.e. one patient may contribute multiple events) that may occur during the study period.

   At first, we will explore these repeated events descriptively to estimate differences across the two arms. We will also conduct a Cox regression analysis that accounts for multiple events per patient. We will define a hospitalization episode of care as either a direct admission to an acute care hospital from which the patient is subsequently discharged home, or a continuous sequence of hospitalizations (i.e., a hospital discharge and admission within the same day is

considered to all be part of the same episode of care). Unless the same event is within the episode of care, patients can contribute multiple events from the time they enter the study and until a censoring event.

5. Patients on hemodialysis are at high risk of non-cardiovascular causes of death (e.g., sepsis, malignancy), may receive a kidney transplant, or switch to home dialysis. The extent to which these events impact the probability of observing the event of interest can be explored through competing risks. Ideally, we will see comparable results with the Cox model, however in absence of agreement, we will assume that the bias of results in the Cox model occurs due to the number, type, and distribution of competing events. In this analysis, we will censor follow-up when patients switch to another centre not in the same group allocation.

6. For the as-treated analysis, patients will be coded as receiving the intervention depending on the centre where they are being treated. For patients that experience an outcome of interest within 30-days of switching to another centre, the outcome will be attributed to the previous centre.

Appendix 14: Main responsibilities of the data safety monitoring board

1. Consider factors external to this trial when relevant information becomes available. This includes any scientific or therapeutic developments that may have an impact on the safety of the participants or the ethics of this trial.
2. Review the conduct of the trial, including protocol violations.
3. Review data on hemodialysis centre recruitment, accrual, and retention, as well as assessments of data quality, completeness, and timeliness.
4. Protect the confidentiality of the trial data and the DSMB discussions.
5. Approve the statistical analysis plan prior to trial analysis.
6. Make recommendations to continue, modify, or stop the trial if necessary.

To date, with the information available about the safety of temperature-reduced dialysis, the DSMB is not planning to perform any between-group interim analyses during the trial period.

References

1. Liyanage T, Ninomiya T, Jha V, et al. Worldwide access to treatment for end-stage kidney disease: a systematic review. *Lancet*. 2015;385(9981):1975-1982. doi:10.1016/S0140-6736(14)61601-9

2. CIHI. CORR Annual Statistics 2017. https://www.cihi.ca/en/canadian-organ-replacement-register-2016. Accessed January 2, 2018.

3. Foley RN, Collins AJ. End-stage renal disease in the United States: an update from the United States Renal Data System. *J Am Soc Nephrol*. 2007;18(10):2644-2648. doi:10.1681/ASN.2007020220

4. Foote C, Ninomiya T, Gallagher M, et al. Survival of elderly dialysis patients is predicted by both patient and practice characteristics. *Nephrol Dial Transplant*. 2012;27(9):3581-3587. doi:10.1093/ndt/gfs096

5. Jassal SVS, Trpeski L, Zhu N, et al. Changes in survival among elderly patients initiating dialysis from 1990 to 1999. *CMAJ*. 2007;177(9):1033-1038. doi:10.1503/cmaj.061765

6. Larkin JW, Reviriego-Mendoza MM, Usvyat LA, Kotanko P, Maddux FW. To cool, or too cool: Is reducing dialysate temperature the optimal approach to preventing intradialytic hypotension? *Semin Dial*. 2017;30(6):501-508. doi:10.1111/sdi.12628

7. Toth-Manikowski SM, Sozio SM. Cooling dialysate during in-center hemodialysis: Beneficial and deleterious effects. *World J Nephrol*. 2016;5(2). doi:10.5527/wjn.v5.i2.166

8. Sakkas GK, Krase AA, Giannaki CD, Karatzaferi C. Cold dialysis and its impact on renal patients' health: An evidence-based mini review. *World J Nephrol*. 2017;6(3):119-122. doi:10.5527/wjn.v6.i3.119

9. Mustafa RA, Bdair F, Akl EA, et al. Effect of Lowering the Dialysate Temperature in Chronic Hemodialysis: A Systematic Review and Meta-Analysis. *Clin J Am Soc Nephrol*. 2016;11(3):442-457. doi:10.2215/CJN.04580415

10. Flythe JE, Xue H, Lynch KE, Curhan GC, Brunelli SM. Association of mortality risk with various definitions of intradialytic hypotension. *J Am Soc Nephrol*. 2015;26(3):724-734. doi:10.1681/ASN.2014020222

11. Burton JO, Jefferies HJ, Selby NM, McIntyre CW. Hemodialysis-induced cardiac injury: determinants and associated outcomes. *Clin J Am Soc Nephrol*. 2009;4(5):914-920. doi:10.2215/CJN.03900808

12. Burton JO, Jefferies HJ, Selby NM, McIntyre CW. Hemodialysis-induced repetitive myocardial injury results in global and segmental reduction in systolic cardiac function. *Clin J Am Soc Nephrol*. 2009;4(12):1925-1931. doi:10.2215/CJN.04470709

13. Eldehni MT, Odudu A, McIntyre CW. Randomized Clinical Trial of Dialysate Cooling and Effects on Brain White Matter. *J Am Soc Nephrol*. 2015;26(4):957-965. doi:10.1681/ASN.2013101086

14. McIntyre CW. Effects of hemodialysis on cardiac function. *Kidney Int*. 2009;76(4):371-375. doi:10.1038/ki.2009.207

15. Odudu A, Eldehni MT, McCann GP, McIntyre CW. Randomized Controlled Trial of Individualized Dialysate Cooling for Cardiac Protection in Hemodialysis Patients. *Clin J Am Soc Nephrol*. May

2015. doi:10.2215/CJN.00200115

16. Santoro A, Mancini E, Paolini F, Cavicchioli G, Bosetto A, Zucchelli P. Blood Volume Regulation During Hemodialysis. *Am J Kidney Dis*. 1998;32(5):739-748. doi:10.1016/S0272-6386(98)70128-3

17. Veljančic L, Popović J, Radović M, et al. Simultaneous blood temperature control and blood volume control reduces intradialytic symptoms. *Int J Artif Organs*. 2011;34(4):357-364. doi:10.5301/IJAO.2011.7746

18. Daugirdas JT. Pathophysiology of dialysis hypotension: An update. *Am J Kidney Dis*. 2001;38((4 Suppl 4)):S11-7.

19. National Kidney Foundation. K/DOQI Clinical Practice Guidelines for Cardiovascular Disease in Dialysis Patients. *Am J Kidney Dis*. 2005;45(4):16-153. doi:10.1053/j.ajkd.2005.01.019

20. Meinke L, Lighthall GK. Fluid management in hospitalized patients. *Compr Ther*. 2005;31(3):209-223.

21. Baskett PJ. ABC of major trauma. Management of hypovolaemic shock. *BMJ*. 1990;300(6737):1453-1457.

22. Barth C, Boer W, Garzoni D, et al. Characteristics of hypotension-prone haemodialysis patients: is there a critical relative blood volume? *Nephrol Dial Transpl*. 2003;18(7):1353-1360.

23. Poldermans D, Man In 't Veld AJ, Rambaldi R, et al. Cardiac evaluation in hypotension-prone and hypotension-resistant hemodialysis patients. *Kidney Int*. 1999;56(5):1905-1911. doi:10.1046/j.1523-1755.1999.00737.x

24. Owen PJ, Priestman WS, Sigrist MK, et al. Myocardial contractile function and intradialytic hypotension. *Hemodial Int*. 2009;13(3):293-300. doi:10.1111/j.1542-4758.2009.00365.x

25. Pelosi G, Emdin M, Carpeggiani C, et al. Impaired sympathetic response before intradialytic hypotension: a study based on spectral analysis of heart rate and pressure variability. *Clin Sci (Lond)*. 1999;96(1):23-31.

26. London GM, Guerin AP, Marchais SJ. Pathophysiology of left ventricular hypertrophy in dialysis patients. *Blood Purif*. 1994;12(4-5):277-283.

27. London GM. Left ventricular alterations and end-stage renal disease. *Nephrol Dial Transplant*. 2002;17 Suppl 1:29-36.

28. Tislér A, Akócsi K, Hárshegyi I, et al. Comparison of dialysis and clinical characteristics of patients with frequent and occasional hemodialysis-associated hypotension. *Kidney Blood Press Res*. 2002;25(2):97-102. doi:10.1159/000063515

29. Chang TI. Impact of drugs on intradialytic hypotension: Antihypertensives and vasoconstrictors. *Semin Dial*. 2017;30(6):532-536. doi:10.1111/sdi.12633

30. Maggiore Q, Pizzarelli F, Sisca S, et al. Blood temperature and vascular stability during hemodialysis and hemofiltration. *Trans Am Soc Artif Intern Organs*. 1982;28:523-527.

31. van der Sande FM, Gladziwa U, Kooman JP, Böcker G, Leunissen KM. Energy transfer is the single most important factor for the difference in vascular response between isolated ultrafiltration and hemodialysis. *J Am Soc Nephrol*. 2000;11(8):1512-1517.

32. Pizzarelli F, Sisca S, Zoccali C, et al. Blood temperature and cardiovascular stability in hemofiltration. *Int J Artif Organs*. 1983;6(1):37-41.

33. Raj DSC, Vincent B, Simpson K, et al. Hemodynamic changes during hemodialysis: Role of nitric oxide and endothelin. *Kidney Int*. 2002;61(2):697-704. doi:10.1046/j.1523-1755.2002.00150.x

34. Erkan E, Devarajan P, Kaskel F. Role of nitric oxide, endothelin-1, and inflammatory cytokines in blood pressure regulation in hemodialysis patients. *Am J Kidney Dis*. 2002;40(1):76-81. doi:10.1053/ajkd.2002.33915

35. Song JH, Park GH, Lee SY, Lee SW, Lee SW, Kim M-J. Effect of Sodium Balance and the Combination of Ultrafiltration Profile during Sodium Profiling Hemodialysis on the Maintenance of the Quality of Dialysis and Sodium and Fluid Balances. *J Am Soc Nephrol*. 2004;16(1):237-246. doi:10.1681/ASN.2004070581

36. Kim M, Song J ho, Kim G a, Lim H jung, Lee S woo. Optimization of dialysate sodium in sodium profiling haemodialysis. *Nephrology (Carlton)*. 2003;8 Suppl:S16-22.

37. Zhou YL, Liu HL, Duan XF, Yao Y, Sun Y, Liu Q. Impact of sodium and ultrafiltration profiling on haemodialysis-related hypotension. *Nephrol Dial Transplant*. 2006;21(11):3231-3237. doi:10.1093/ndt/gfl375

38. Henrich WL, Woodard TD, Blachley JD, Gomez-Sanchez C, Pettinger W, Cronin RE. Role of osmolality in blood pressure stability after dialysis and ultrafiltration. *Kidney Int*. 1980;18(4):480-488.

39. McIntyre CW, Burton JO, Selby NM, et al. Hemodialysis-Induced Cardiac Dysfunction Is Associated with an Acute Reduction in Global and Segmental Myocardial Blood Flow. *Clin J Am Soc Nephrol*. 2008;3(1):19-26. doi:10.2215/CJN.03170707

40. Selby NM, Burton JO, Chesterton LJ, McIntyre CW. Dialysis-induced regional left ventricular dysfunction is ameliorated by cooling the dialysate. *Clin J Am Soc Nephrol*. 2006;1(6):1216-1225. doi:10.2215/CJN.02010606

41. Singh N, Langer A, Freeman MR, Goldstein MB. Myocardial alterations during hemodialysis: insights from new noninvasive technology. *Am J Nephrol*. 1994;14(3):173-181.

42. Galetta F, Cupisti A, Franzoni F, Carpi A, Barsotti G, Santoro G. Acute effects of hemodialysis on left ventricular function evaluated by tissue Doppler imaging. *Biomed Pharmacother*. 2006;60(2):66-70. doi:10.1016/j.biopha.2005.10.008

43. Selby NM, Lambie SH, Camici PG, Baker CS, McIntyre CW. Occurrence of Regional Left Ventricular Dysfunction in Patients Undergoing Standard and Biofeedback Dialysis. *Am J Kidney Dis*. 2006;47(5):830-841. doi:10.1053/j.ajkd.2006.01.012

44. Stefánsson B V., Brunelli SM, Cabrera C, et al. Intradialytic hypotension and risk of cardiovascular disease. *Clin J Am Soc Nephrol*. 2014;9(12):2124-2132. doi:10.2215/CJN.02680314

45. Maggiore Q, Pizzarelli F, Zoccali C, Sisca S, Nicolò F, Parlongo S. Effect of extracorporeal blood cooling on dialytic arterial hypotension. *Proc Eur Dial Transplant Assoc*. 1981;18:597-602.

46. Jefferies HJ, Burton JO, McIntyre CW. Individualised dialysate temperature improves intradialytic haemodynamics and abrogates haemodialysis-induced myocardial stunning, without

compromising tolerability. *Blood Purif*. 2011;32(1):63-68. doi:10.1159/000324199

47. Maggiore Q, Pizzarelli F, Santoro A, et al. The effects of control of thermal balance on vascular stability in hemodialysis patients: results of the European randomized clinical trial. *Am J Kidney Dis*. 2002;40(2):280-290. doi:10.1053/ajkd.2002.34506

48. Maggiore Q. Isothermic dialysis for hypotension-prone patients. *Semin Dial*. 15(3):187-190.

49. Maggiore Q, Dattolo P, Piacenti M, et al. Thermal balance and dialysis hypotension. *Int J Artif Organs*. 1995;18(9):518-525.

50. Enia G, Catalano C, Pizzarelli F, et al. The effect of dialysate temperature on haemodialysis leucopenia. *Proc Eur Dial Transplant Assoc Eur Ren Assoc*. 1985;21:167-172.

51. Beerenhout C, Dejagere T, van der Sande FM, Bekers O, Leunissen KM, Kooman JP. Haemodynamics and electrolyte balance: a comparison between on-line pre-dilution haemofiltration and haemodialysis. *Nephrol Dial Transplant*. 2004;19(9):2354-2359. doi:10.1093/ndt/gfh315

52. Beerenhout CH, Noris M, Kooman JP, et al. Nitric Oxide Synthetic Capacity in Relation to Dialysate Temperature. 2004;22(2):203-209. doi:10.1159/000076854

53. Chesterton LJ, Selby NM, Burton JO, McIntyre CW. Cool dialysate reduces asymptomatic intradialytic hypotension and increases baroreflex variability. *Hemodial Int*. 2009;13(2):189-196. doi:10.1111/j.1542-4758.2009.00355.x

54. Cruz DN, Mahnensmith RL, Brickel HM, Perazella MA. Midodrine and cool dialysate are effective therapies for symptomatic intradialytic hypotension. *Am J Kidney Dis*. 1999;33(5):920-926. doi:10.1016/s0272-6386(99)70427-0

55. Parker KP, Bailey JL, Rye DB, Bliwise DL, Van Someren EJW. Lowering dialysate temperature improves sleep and alters nocturnal skin temperature in patients on chronic hemodialysis. *J Sleep Res*. 2007;16(1):42-50. doi:10.1111/j.1365-2869.2007.00568.x

56. van der Sande FM, Kooman JP, Burema JH, et al. Effect of dialysate temperature on energy balance during hemodialysis: quantification of extracorporeal energy transfer. *Am J Kidney Dis*. 1999;33(6):1115-1121. doi:10.1016/S0272-6386(99)70149-6

57. Kaufman AM, Morris AT, Lavarias VA, et al. Effects of controlled blood cooling on hemodynamic stability and urea kinetics during high-efficiency hemodialysis. *J Am Soc Nephrol*. 1998;9(5):877-883.

58. Zitt E, Neyer U, Meusburger E, et al. Effect of Dialysate Temperature and Diabetes on Autonomic Cardiovascular Regulation During Hemodialysis. *Kidney Blood Press Res*. 2008;31(4). doi:10.1159/000141926

59. Hoeben H, Abu-Alfa AK, Mahnensmith R, Perazella MA. Hemodynamics in patients with intradialytic hypotension treated with cool dialysate or midodrine. *Am J Kidney Dis*. 2002;39(1):102-107. doi:10.1053/ajkd.2002.29887

60. Zhao H, Steinberg GK, Sapolsky RM. General versus specific actions of mild-moderate hypothermia in attenuating cerebral ischemic damage. *J Cereb Blood Flow Metab*. 2007;27(12):1879-1894. doi:10.1038/sj.jcbfm.9600540

61. Kooman J, Basci A, Pizzarelli F, et al. EBPG guideline on haemodynamic instability. *Nephrol Dial Transpl*. 2007;22(Suppl 2):ii22-44. doi:10.1093/ndt/gfm019

62. Sajadi M, Gholami Z, Hekmatpou D, Soltani P, Haghverdi F. Cold Dialysis Solution for Hemodialysis Patients With Fatigue: a Cross-over Study. *Iran J Kidney Dis*. 2016;10(5):319-324.

63. Fine A, Penner B. The protective effect of cool dialysate is dependent on patients' predialysis temperature. *Am J Kidney Dis*. 1996;28(2):262-265.

64. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*. 2008;336(7650):924-926. doi:10.1136/bmj.39489.470347.AD

65. Guyatt GHG, Oxman AD, Akl EAEA, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol*. 2011;64(4):383-394. doi:10.1016/j.jclinepi.2010.04.026

66. Hsu H-J, Yen C-H, Hsu K-H, et al. Association between cold dialysis and cardiovascular survival in hemodialysis patients. *Nephrol Dial Transpl*. 2012;27(6):2457-2464. doi:10.1093/ndt/gfr615

67. Dasgupta I, Thomas GN, Clarke J, et al. Associations between Hemodialysis Facility Practices to Manage Fluid Volume and Intradialytic Hypotension and Patient Outcomes. *Clin J Am Soc Nephrol*. 2019;14(3):385-393. doi:10.2215/CJN.08240718

68. Gray KS, Cohen DE, Brunelli SM. Dialysate temperature of 36 °C: association with clinical outcomes. *J Nephrol*. December 2016. doi:10.1007/s40620-016-0369-3

69. Levin NW, Morris AT, Lavarias VA, et al. Effects of body core temperature reduction on haemodynamic stability and haemodialysis efficacy at constant ultrafiltration. *Nephrol Dial Transplant*. 1996;11 Suppl 2:31-34.

70. Yu AW, Ing TS, Zabaneh RI, Daugirdas JT. Effect of dialysate temperature on central hemodynamics and urea kinetics. *Kidney Int*. 1995;48(1):237-243.

71. Maheshwari V, Lau T, Samavedham L, Rangaiah GP. Effect of cool vs. warm dialysate on toxin removal: rationale and study design. *BMC Nephrol*. 2015;16:25. doi:10.1186/s12882-015-0017-5

72. Ye X, Usvyat LA, Jiao Y, Kotanko P, Maddux FW. Patient and Dialysate Temperature Characteristics in Incident Hemodialysis Patients: Results from a Large U.S. Population. In: *J Am Soc Nephrol*. ; 2015:26:281A–282A.

73. Pérgola PE, Habiba NM, Johnson JM. Body temperature regulation during hemodialysis in long-term patients: is it time to change dialysate temperature prescription? *Am J Kidney Dis*. 2004;44(1):155-165. doi:10.1053/j.ajkd.2004.03.036

74. Ayoub A, Finlayson M. Effect of cool temperature dialysate on the quality and patients' perception of haemodialysis. *Nephrol Dial Transplant*. 2004;19(1):190-194. doi:10.1093/ndt/gfg512

75. Azar AT. Effect of dialysate temperature on hemodynamic stability among hemodialysis patients. *Saudi J Kidney Dis Transpl*. 2009;20(4):596-603.

76. Selby NM, McIntyre CW. A systematic review of the clinical effects of reducing dialysate fluid temperature. *Nephrol Dial Transpl*. 2006;21(7):1883-1898. doi:10.1093/ndt/gfl126

77. Roumelioti M-E, Unruh ML. Lower Dialysate Temperature in Hemodialysis: Is It a Cool Idea? *Clin J Am Soc Nephrol*. 2015;10(8):1318-1320. doi:10.2215/CJN.06920615

78. Canadian Institutes for Health Research, Natural Sciences and Engineering Research Council of Canada, Social Sciences and Humanities Research Council of Canada, Canadian Institutes for Health Research the Natural Sciences, Natural Sciences and Engineering Research Council of Canada, Social Sciences and Humanities Research Council of Canada. *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans. 2014.* Ottawa; 2014.

79. Wodchis WP, Bushmeneva K, Nikitovic M, McKillop I. Guidelines on Person-Level Costing Using Administrative Databases in Ontario. Working Paper Series. http://www.hsprn.ca/uploads/files/Guidelines_on_PersonLevel_Costing_May_2013.pdf. Published 2013. Accessed April 15, 2016.

80. Fiest KM, Jette N, Quan H, et al. Systematic review and assessment of validated case definitions for depression in administrative data. *BMC Psychiatry*. 2014;14:289. doi:10.1186/s12888-014-0289-5

81. Quinn RR, Laupacis A, Austin PPC, et al. Using administrative datasets to study outcomes in dialysis patients: a validation study. *Med Care*. 2010;48(8):745-750. doi:10.1097/MLR.0b013e3181e419fd

82. Kokotailo R a, Hill MD. Coding of stroke and stroke risk factors using international classification of diseases, revisions 9 and 10. *Stroke*. 2005;36(8):1776-1781. doi:10.1161/01.STR.0000174293.17959.a1

83. Andrade SE, Harrold LR, Tjia J, et al. A systematic review of validated methods for identifying cerebrovascular accident or transient ischemic attack using administrative data. *Pharmacoepidemiol Drug Saf*. 2012;21 Suppl 1:100-128. doi:10.1002/pds.2312

84. Juurlink D, Preyra C, Croxford R, et al. *Canadian Institute for Health Information Discharge Abstract Database : A Validation Study*. Toronto, Ontario; 2006.

85. Schultz SE, Rothwell DM, Chen ; Z, Tu ; K, Chen Z, Tu K. Identifying cases of congestive heart failure from administrative data: a validation study using primary care patient records. *Chronic Dis Inj Can*. 2013;33(3):160-166.

86. Kip KE, Hollabaugh K, Marroquin OC, Williams DO. The Problem With Composite End Points in Cardiovascular Studies. *J Am Coll Cardiol*. 2008;51(7):701-707. doi:10.1016/j.jacc.2007.10.034

87. Rocha A, Sousa C, Teles P, Coelho A, Xavier E. Effect of Dialysis Day on Intradialytic Hypotension Risk. *Kidney Blood Press Res*. 2016;41(2):168-174. doi:10.1159/000443418

88. Naylor KL, McArthur E, Leslie WD, et al. The three-year incidence of fracture in chronic kidney disease. *Kidney Int*. 2014;86(4):810-818. doi:10.1038/ki.2013.547

89. Manns BJ, Mendelssohn DC, Taub KJ. The economics of end-stage renal disease care in Canada: incentives and impact on delivery of care. *Int J Heal Care Financ Econ*. 2007;7(2-3):149-169. doi:10.1007/s10754-007-9022-y

90. De Vecchi AF, Dratwa M, Wiedemann ME. Healthcare systems and end-stage renal disease (ESRD) therapies--an international review: costs and reimbursement/funding of ESRD therapies. *Nephrol Dial Transplant*. 1999;14 Suppl 6:31-41.

91. Saran R, Robinson B, Abbott KC, et al. US Renal Data System 2017 Annual Data Report: Epidemiology of Kidney Disease in the United States. *Am J Kidney Dis*. 2018;71(3):A7. doi:10.1053/j.ajkd.2018.01.002

92. United States Renal Data System. *2018 USRDS Annual Data Report: Epidemiology of Kidney Disease in the United States.* Bethesda, MD; 2018.

93. Tsujimoto Y, Tsujimoto H, Nakata Y, et al. Dialysate temperature reduction for intradialytic hypotension for people with chronic kidney disease requiring haemodialysis. *Cochrane Database Syst Rev*. 2019;7:CD012598.

94. Assimon MM, Flythe JE. Definitions of intradialytic hypotension. *Semin Dial*. 2017;30(6):464-472. doi:10.1111/sdi.12626

95. Tislér A, Akócsi K, Borbás B, et al. The effect of frequent or occasional dialysis-associated hypotension on survival of patients on maintenance haemodialysis. *Nephrol Dial Transplant*. 2003;18(12):2601-2605.

96. Sands JJ, Usvyat LA, Sullivan T, et al. Intradialytic hypotension: frequency, sources of variation and correlation with clinical outcome. *Hemodial Int*. 2014;18(2):415-422. doi:10.1111/hdi.12138

97. Zhang M, Wang M, Li H, et al. Association of initial twice-weekly hemodialysis treatment with preservation of residual kidney function in ESRD patients. *Am J Nephrol*. 2014;40(2):140-150. doi:10.1159/000365819

98. Mc Causland FR, Waikar SS. Association of Predialysis Calculated Plasma Osmolarity With Intradialytic Blood Pressure Decline. *Am J Kidney Dis*. 2015;66(3):499-506. doi:10.1053/j.ajkd.2015.03.028

99. Reich NG, Myers JA, Obeng D, Milstone AM, Perl TM. Empirical Power and Sample Size Calculations for Cluster-Randomized and Cluster-Randomized Crossover Studies. Vermund SH, ed. *PLoS One*. 2012;7(4):e35564. doi:10.1371/journal.pone.0035564

100. Arnold BF, Hogan DR, Colford JM, Hubbard AE, Hubbard AE. Simulation methods to estimate design power: an overview for applied research. *BMC Med Res Methodol*. 2011;11:94. doi:10.1186/1471-2288-11-94

101. Wicklin R. *Simulating Data with SAS ®*. Cary, NC: SAS Institute Inc. ; 2013.

102. Gelman A, Hill J. Causal inference using regression on the treatment variable. In: Alvaerz M, Beck N, Wu L, eds. *Data Analysis Using Regression and Multilevel/Hierarchical Models*. New York, NY: Cambridge University Press; 2006:167-194.

103. SAS Institute Inc. *SAS/STAT® 15.1 User's Guide The PHREG Procedure*. Cary, NC; 2018.

Table of Changes to Protocol

Note: This table was posted publicly on ClinicalTrial.Gov on August 14, 2020

Protocol Updates

**** All Protocol updates below were made without any viewing of any outcome data (viewing and analysis will only occur after the trial period is over) and were done after the start of the MyTEMP Trial period (April 3rd, 2017). Please note that a revision date of Dec 2, 2019 indicates when protocol updates were posted to clinicaltrials.gov, however, these changes are reflected in the final published version of the MyTEMP protocol. Any changes to the protocol that occurred after the protocol was published were deemed to be minor. ****

Revision	Date of revision	Details of Revision	Rationale
Title Change	March 05, 2019	**Changed from**: Major cardiovascular and other patient important outcomes with personalized dialYsate TEMPerature (MY TEMP): A registry-based cluster randomized controlled trial. **Changed to**: Major outcomes with personalized dialysate TEMPerature (MyTEMP): A pragmatic, registry-based, cluster randomized controlled trial	Our updated title is more reflective of the trial.
Study follow-up period	March 05, 2019	**Changed from**: Two-year follow-up **Change to**: Four-year follow-up	To increase statistical power, the trial was extended from a two- to a four-year follow-up period (see *Statistical Power* below).
Objective	March 05, 2019	**Changed from**: To test for differences in the rate of the composite outcome of all-cause mortality and major cardiovascular events among centres that provide temperature-reduced personalized hemodialysis compared with centres that provide standard-temperature hemodialysis. **Changed to**: To test the effect of randomizing hemodialysis centres to provide (i) a personalized temperature-reduced dialysate protocol of 0.5 to 0.9 °C below the patient's pre-dialysis body temperature measured before each dialysis session, to a minimum dialysate temperature of 35.5 °C, vs. (ii) a standard-temperature dialysate protocol of 36.5 °C, for a period of four years, on a composite outcome of cardiovascular-related death or hospitalization for major cardiovascular events in outpatients receiving maintenance hemodialysis.	After undergoing peer-review at the Heart and Stroke Foundation, peer-reviewers strongly recommended using CV-mortality as opposed to all-cause mortality. With regards to the follow-up time, please see rationale in the "Power Estimates" section. We also added additional details to the objective to improve clarity.

Primary Outcome	March 05, 2019	**Changed from**: Composite outcome of all-cause mortality or a hospitalization for a major cardiovascular event. CV-related hospitalizations included: • Hospital admission with Ischemic Stroke • Hospital admission with Myocardial infarction • Coronary revascularization (includes CABG/PCI) **Changed to**: Composite outcome of time to first cardiovascular-related mortality or hospitalization. CV-related hospitalizations included: • Hospital admission with ischemic stroke • Hospital admission with myocardial infarction Hospital admission with heart failure	After undergoing peer-review at the Heart and Stroke Foundation, peer-reviewers strongly recommended using CV-mortality as opposed to all-cause mortality. We chose a cause-specific death (i.e. cardiovascular) in our endpoint, in contrast to all-cause mortality, because non-cardiovascular causes of death are common in the hemodialysis population and the intervention is less likely to reduce the rate of such deaths. Since submitting the grant for peer-review, a validation study of CV mortality database codes against clinical trial adjudicated outcomes has been done in our province, which shows the CV mortality codes operate well. As a secondary outcome, we will also test the effect of personalized temperature-reduced dialysate temperature on all-cause mortality. 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 (i.e., 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. The removal of "Coronary revascularization" was related to the wide variation in practice across hospitals and individual physicians. In previous research, the physician performing the diagnostic catheterization and the treating hospital were strong independent predictors of the mode of revascularization. As such, we removed this outcome because differences between the two groups may have been related to varying hospital practices rather than the intervention itself.

Primary Outcome	July 06, 2022	**Changed from:** 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. Deaths that occur in the last 3 months of follow-up will be captured using the Registered Persons Database 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. Hospital encounters for cardiovascular events will be ascertained using the 10th version of the International Classification of Diseases (ICD-10) codes. **Changed to:** Data on cardiovascular-related causes of death will primarily be captured using the following definition: (a) in-hospital (or emergency department) death with a cardiovascular disease diagnosis in the primary/most responsible diagnosis position or (b) out-of-hospital death (including death in an emergency department) without documentation of cancer in the 365 days before and including the date of death and without documentation of trauma in the 30 days before and including the date of death. A death in the emergency department with a cardiovascular event as the primary diagnosis will be defined as "in-hospital" cardiovascular-related death, regardless of whether they had cancer or trauma code.	We were recently notified of unanticipated delays in the linkage of the Office of the Register General deaths database at ICES, which will now take several more years to cover the entire trial period. As a result, we will use an alternate method of ascertaining cardiovascular-related deaths, validated by Lix et al. (2021)[1]. 1. Lix LM, Sobhan S, St-Jean A, et al. Validity of an algorithm to identify cardiovascular deaths from administrative health records: a multi-database population-based cohort study. BMC Health Serv Res. 2021;21(1). doi:10.1186/S12913-021-06762-0

Key Secondary Outcome	March 05, 2019	**Added**: proportion of sampled hemodialysis sessions complicated by intradialytic hypotension.	While there are complex physiologic mechanisms by which a personalized dialysis temperature may have beneficial effects compared to standard dialysis temperature, a reduction in the risk of intradialytic hypotension is a key consideration.
	December 02, 2019	**Changed from**: Proportion of sampled hemodialysis sessions complicated by intradialytic hypotension **Changed to**: Between-group mean difference in the intradialytic drop of systolic blood pressure.	Given the change in alpha level (see *Statistical Significance*, below) we have modified the key secondary outcome due to a lack of statistical power.
Other Important Outcomes	March 05, 2019	**Changed from**: *(i)* Ability to live independently *(ii)* Amputation rate *(iii)* Rate of major falls and fractures **Changed to**: *(i)* We now focus on "Lower Limb Amputation". *(ii)* We now include composite outcome of hospital encounter of either falls and fractures, rather than fractures alone. *(iii)* We added the following outcomes ▪ Emergency department visits or hospital admissions ▪ Intensity use of blood pressure medications ▪ Intradialytic hypotension	We are reporting on several patient-important outcomes that may be: *(i)* responsive to our intervention; and reliably assessed using the administrative data sources.
	December 02, 2019	**Removed**: Intensity use of blood pressure medication.	Given our data administrative data sources, we will not have drug prescription data on all patients included in the trial. We are also not confident we can accurately capture this outcome in our data sets.
Statistical Significance	December 02, 2019	**Added**: The first family of hypotheses includes both the primary and key secondary hypotheses (composite primary outcome and drop in intra-dialytic systolic blood pressure), with weights of 0.8 and 0.2, respectively. If the intervention improves at least one of the two outcomes in the first family of hypotheses,	In keeping with recommended practice [2, 3, 4] our aim is to avoid Type I errors due to multiple comparisons. We will use the parallel gatekeeping procedure to control the overall familywise error rate at 0.05. The first family of hypotheses includes both the primary and key secondary 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 0.05: all-cause mortality or cardiovascular-related hospitalization, all-cause mortality, hospital admission with myocardial infarction, hospital admission with congestive heart failure, hospital admission with ischemic stroke. Any reported confidence intervals that maintain the familywise error rate at 0.05 will be adjusted for the tested level of significance. **Added:** Cardiovascular death was added as the last secondary outcome that will be tested at a level of significance that maintains the overall error rate across all prior testing at 0.05.	(composite primary outcome and drop in intra-dialytic systolic blood pressure), with weights of 0.8 and 0.2, respectively. 2. Harrington D, D'Agostino RB, Gatsonis C, et al. New Guidelines for Statistical Reporting in the Journal. N Engl J Med. 2019;381(3):285-286. doi:10.1056/NEJMe1906559 3. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER). Multiple Endpoints in Clinical Trials: Guidance for Industry. Silver Spring, MD; 2017. 4. Massachusetts Medical Society. Submitting to NEJM - Statistical Reporting Guidelines. https://www.nejm.org/author-center/new-manuscripts. Accessed September 4, 2019.
Power Estimates	December 02, 2019	**Changed from**: More than 80% power to detect a 15% relative-rate reduction in all-cause mortality. **Changed to**: Our trial will have at least 80% power to detect a hazard rate reduction of 20% or more (corresponding to a hazard ratio of 0.80; 2-sided α=0.04; 0.04 chosen to control the familywise error rate, see *Statistical significance*). We assumed a hazard rate for the composite outcome of cardiovascular-related death or hospitalization of 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.	See Primary Outcome (above) for explanation of change in the outcome.
Cohort Selection	March 05, 2019	**Changed from**: Closed cohort - prevalent patients who were alive on maintenance in-centre hemodialysis April 3rd, 2017. Additional analyses - open cohort, where only patients that remain on HD during the trial period for at least 30 days.	To minimize the inclusion of patients who leave the study or switch centres soon after starting in-centre hemodialysis, we will restrict the cohort to patients who received treatment at the same participating study centre 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).

		Changed to: At the time of the analysis, we will restrict the study cohort to outpatients who received in-centre maintenance hemodialysis at a participating study centre between April 3rd, 2017 and March 31st, 2021.	This added restriction would exclude (*i)* patients who quickly recover renal function (e.g., patients with acute kidney injury) (*ii)* early scheduled transfers to home dialysis or those receiving kidney transplants; and (*iii)* those with arranged dialysis treatments away from home (transient dialysis).
Analysis	December 02, 2019	**Changed from**: Using a modified Poisson regression model for patient level data and account for the effect of clustering at the centre level. **Changed to**: 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 centres. 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 centre 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.	This statistical method is more appropriate given our data structure and our updated primary outcome.
	April 20, 2022	**Changed from:** Patients will be censored at end of study follow-up or earlier if they die due to a non-cardiovascular–related cause **Changed to:** In the analysis of the primary composite outcome, patients will be censored at end of study follow-up, upon emigration or experiencing the	

		primary composite outcome. Non-cardiovascular death will be treated as a competing risk event.	
	August 27, 2021	**Changed from:** 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 ≥25% lower than their pre-dialysis 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 ≥25% lower than their pre-dialysis level; and (4) nadir intradialytic systolic blood pressure was ≥35 mm Hg lower than their pre-dialysis level. **Changed to:** We will examine the center's proportion of patients whose (1) nadir systolic blood pressure is < 90 mmHg anytime during a dialysis session when the value before the session was ≥ 90 mmHg, or drop in systolic blood pressure ≥ 30 mmHg anytime during session from value before session; (2) systolic blood pressure dropped from ≥90 mm Hg before dialysis to <90 mm Hg during dialysis; (3) nadir intradialytic systolic blood pressure was ≥25% lower than their pre-dialysis level or whose systolic blood pressure dropped from ≥90 mm Hg before dialysis to <90 mm Hg during dialysis; (4) nadir intradialytic systolic blood pressure was ≥25% lower than their pre-dialysis level; and (5) nadir intradialytic systolic blood pressure was ≥35 mm Hg lower than their pre-dialysis level.	Clarification regarding weighting: 1)We are analyzing intradialytic hypotension in a similar manner to out "key secondary outcome." 2)Weights are estimated using the cluster size based on the measured monthly observations, which is the standard approach (cluster size or the sample size selected in each cluster if subsampling is carried out). In our trial, this results in constant cluster sizes because each cluster contributes 15 randomly selected individuals to provide pre-dialysis systolic blood pressure and the nadir intradialytic systolic blood pressure. As such, the weighted and unweighted analysis will align since the same weight would be applied to all clusters. After some data cleaning, there may be slight variations in the number of contributing patients per cluster (i.e., 13-15). However, this likely will not impact the overall point estimate.
Bayesian analysis of the primary outcome	March 05, 2019	**Added**: 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	We will have limited statistical power to detect a risk reduction below 20%, yet a risk reduction of even 5% (i.e., 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 pre-specified Bayesian analysis to

		supplement, we will conduct and report a Bayesian analysis based on existing guidelines.	examine the probability that the intervention is effective under differing thresholds that could be clinically relevant, in keeping with advice that investigators should pre-specify both frequentist and Bayesian analyses as part of their statistical analysis plan for randomized clinical trials [5]. 5. Food and Drug Administration. Guidance for Industry and FDA Staff: Guidance for the Use of Bayesian Statistics in Medical Device Clinical Trials. http://www.rkstatistics.com/files/public/Knowledge_Bank/FDA-Bayesian_Stats_in_Medical_Device_Trials.pdf. Published 2010. Accessed January 11, 2019.
Analysis – Key Secondary Outcome	December 02, 2019	**Added**: Between-group mean differences in the drop of mean systolic blood pressure, analyzed at the centre level using a repeated measures random-effects linear mixed model.	This statistical method is more appropriate given our data structure and updated secondary outcome.
Analysis - Sub Group	March 05, 2019	**Changed from**: No pre specified subgroup analyses. **Changed to**: Pre specified subgroups: *(i)* patients with a history of prior hospital admission for myocardial infarction, ischemic stroke, or congestive heart failure; and *(ii)* patients with diabetes.	These are two subgroups of interest, where a personalized dialysis temperature may have a larger treatment effect.
	December 02, 2019	**Changed to**: Estimate of the hazard ratio for the primary outcome with its accompanying 95% confidence intervals across subgroups for consistency of the effect. Pre-specified subgroups: *(i)* Patients with a baselines hospital admission for myocardial infarction, ischemic stroke, or conestive heart failure, and *(ii)* Incident patients, defined as new patients starting in-centre hemodialysis during follow-up	

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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 clincaltrials.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 clincaltrials.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 procedure[9] 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 patent's observation time. Based on our analysis of historical records, we expect ≥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 ≥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 ≥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-in-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 model[39] 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.

References

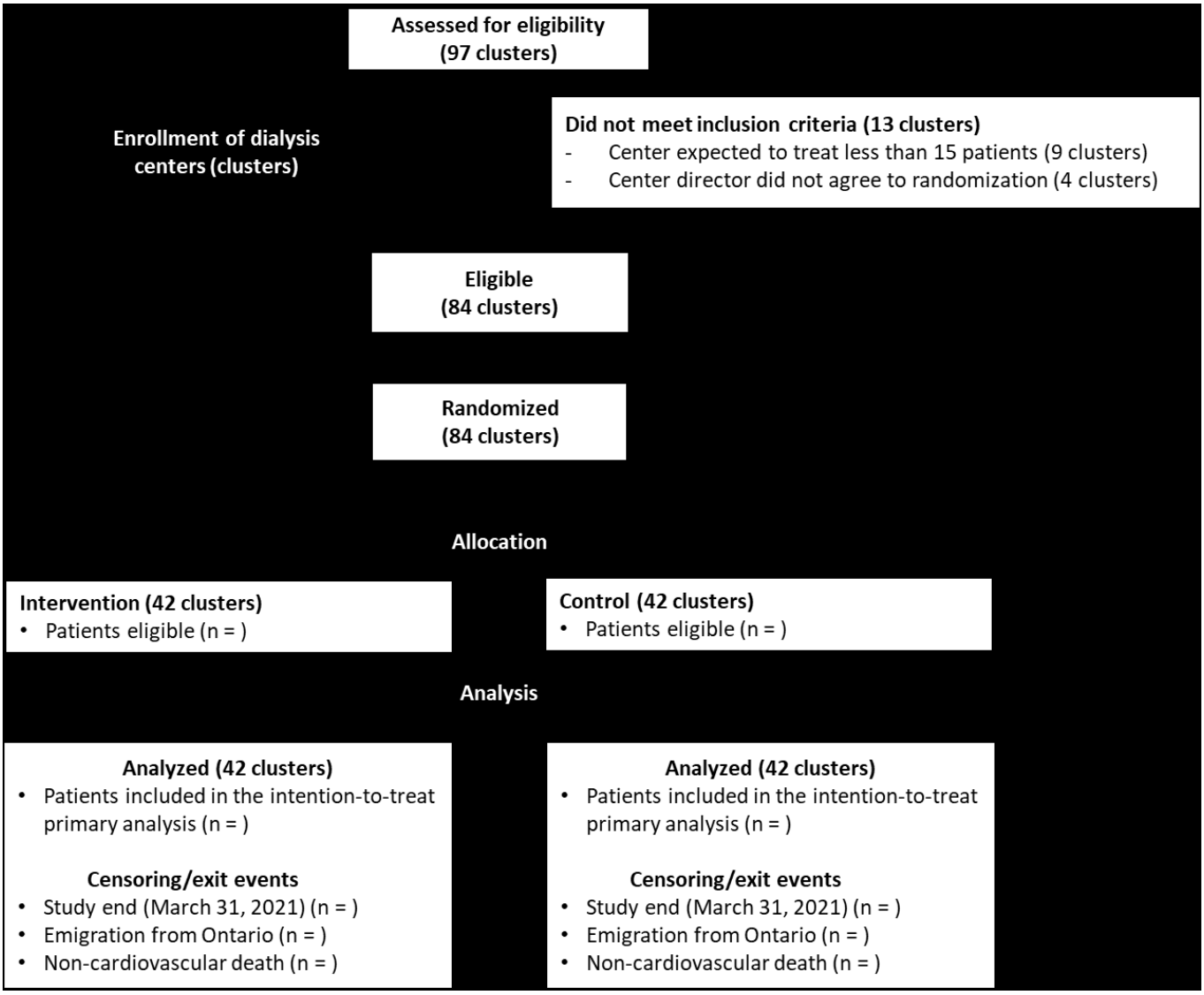
1. Al-Jaishi AA, McIntyre CW, Sontrop JM, et al. Major Outcomes With Personalized Dialysate TEMPerature (MyTEMP): rationale and design of a pragmatic, registry-based, cluster randomized controlled trial. *Can J Kidney Health Dis*. 2020;7:1-18. doi:10.1177/2054358119887988.
2. Campbell MK, Piaggio G, Elbourne DR, Altman DG. Consort 2010 statement: extension to cluster randomised trials. *BMJ*. 2012;345(7881):e5661. doi:10.1136/bmj.e5661.
3. Kwakkenbos L, Juszczak E, Hemkens LG, et al. Protocol for the development of a CONSORT extension for RCTs using cohorts and routinely collected health data. *Res Integr Peer Rev*. 2018;3:9. doi:10.1186/s41073-018-0053-3.
4. Gamble C, Krishan A, Stocken D, et al. Guidelines for the content of statistical analysis plans in clinical trials. *J Am Med Assoc*. 2017;318(23):2337-2343. doi:10.1001/jama.2017.18556.
5. Ontario Health. Ontario renal reporting system—datasets—Ontario data catalogue. https://data.ontario.ca/dataset/ontario-renal-reporting-system. Accessed March 23, 2021.
6. Raab GM, Butcher I. Randomization inference for balanced cluster-randomized trials. *Clin Trials*. 2005;2(2):130-140. doi:10.1191/1740774505cn075oa.
7. Moulton L. Covariate-based constrained randomization of group-randomized trials. *Clin Trials*. 2004;1(3):297-305. doi:10.1191/1740774504cn024oa.
8. Ivers NM, Halperin IJ, Barnsley J, et al. Allocation techniques for balance at baseline in cluster randomized trials: a methodological review. *Trials*. 2012;13:120. doi:10.1186/1745-6215-13-120.
9. Dmitrienko A, Offen WW, Westfall PH. Gatekeeping strategies for clinical trials that do not require all primary effects to be significant. *Stat Med*. 2003;22(15):2387-2400. doi:10.1002/sim.1526.
10. Harrington D, D'Agostino RB, Gatsonis C, et al. New guidelines for statistical reporting in the journal. *N Engl J Med*. 2019;381(3):285-286. doi:10.1056/nejme1906559.

11. Ranganathan P, Pramesh C, Aggarwal R. Common pitfalls in statistical analysis: intention-to-treat versus per-protocol analysis. *Perspect Clin Res*. 2016;7(3):144-146. doi:10.4103/2229-3485.184823.
12. Statistics Canada. Population estimates on July 1st, by age and sex. Table: 17-10-0005-01 (formerly CANSIM 051-0001). https://www150.statcan.gc.ca/t1/tbl1/en/tv.action?pid=1710000501. Accessed March 23, 2021.
13. Lipscombe LL, Hwee J, Webster L, Shah BR, Booth GL, Tu K. Identifying diabetes cases from administrative data: a population-based validation study. *BMC Health Serv Res*. 2018;18(1):316. doi:10.1186/s12913-018-3148-0.
14. Schultz SE, Rothwell DM, Chen Z, Tu K. Identifying cases of congestive heart failure from administrative data: a validation study using primary care patient records. *Chronic Dis Inj Can*. 2013;33(3):160-166.
15. Tu K, Campbell NR, Chen Z-L, Cauch-Dudek KJ, McAlister FA. Accuracy of administrative databases in identifying patients with hypertension. *Open Med*. 2007;1(1):e18-e26. http://www.ncbi.nlm.nih.gov/pubmed/20101286. Accessed March 23, 2021.
16. Tu K, Chen Z, Lipscombe LL. Prevalence and incidence of hypertension from1995 to 2005: a population-based study. *CMAJ*. 2008;178(11):1429-1435. doi:10.1503/cmaj.071283.
17. Gershon AS, Wang C, Guan J, Vasilevska-Ristovska J, Cicutto L, To T. Identifying individuals with physcian diagnosed COPD in health administrative databases. *COPD*. 2009;6(5):388-394. doi:10.1080/15412550903140865.
18. Juurlink D, Preyra C, Croxford R, et al. *Canadian Institute for Health Information Discharge Abstract Database : A Validation Study*. Toronto, ON, Canada: Institute for Clinical Evaluative; 2006.
19. Kokotailo RA, Hill MD. Coding of stroke and stroke risk factors using International Classification of Diseases, revisions 9 and 10. *Stroke*. 2005;36(8):1776-1781. doi:10.1161/01.STR.0000174293.17959.a1.
20. Andrade SE, Harrold LR, Tjia J, et al. A systematic review of validated methods for identifying cerebrovascular accident or transient ischemic attack using administrative data. *Pharmacoepidemiol Drug Saf*. 2012;21(suppl 1):100-128. doi:10.1002/pds.2312.
21. Becker R, Silvi J, Ma Fat D, L'Hours A, Laurenti R. A method for deriving leading causes of death. *Bull World Health Organ*. 2006;84(4):297-304. doi:10.2471/BLT.05.028670.
22. O'Donnell S, Canadian Chronic Disease Surveillance System (CCDSS) Osteoporosis Working Group. Use of administrative data for national surveillance of osteoporosis and related fractures in Canada: results from a feasibility study. *Arch Osteoporos*. 2013;8:143. doi:10.1007/s11657-013-0143-2.
23. Papaioannou A, Kennedy CC, Ioannidis G, et al. Comparative trends in incident fracture rates for all long-term care and community-dwelling seniors in Ontario, Canada, 2002–2012. *Osteoporos Int*. 2016;27(3):887-897. doi:10.1007/s00198-015-3477-3.
24. Jaglal S, Cameron C, Croxford R, Mackay C, Yasmin F. Ontario osteoporosis strategy-provincial performance data for osteoporosis management: technical report; 2020. https://osteostrategy.on.ca/wp-content/uploads/Final-OOS-Provincial-Performance-Data-Technical-Report-Nov-18-20.pdf. Accessed March 23, 2021.
25. Pocock SJ, Clayton TC, Altman DG. Survival plots of time-to-event outcomes in clinical trials: good practice and pitfalls. *Lancet*. 2002;359(9318):1686-1689. doi:10.1016/S0140-6736(02)08594-X.
26. Lau B, Cole SR, Gange SJ. Competing risk regression models for epidemiologic data. *Am J Epidemiol*. 2009;170(2):244-256. doi:10.1093/aje/kwp107.
27. Lin DY, Wei LJ. The robust inference for the cox proportional hazards model. *J Am Stat Assoc*. 1989;84(408):1074-1078. doi:10.1080/01621459.1989.10478874.
28. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc*. 1999;94(446):496-509. doi:10.1080/01621459.1999.10474144.
29. Varadhan R, Weiss CO, Segal JB, Wu AW, Scharfstein D, Boyd C. Evaluating health outcomes in the presence of competing risks: a review of statistical methods and clinical applications. *Med Care*. 2010;48(6)(suppl):S96-S105. doi:10.1097/MLR.0b013e3181d99107.
30. Troendle JF, Leifer ES, Kunz L. Dealing with competing risks in clinical trials: how to choose the primary efficacy analysis? *Stat Med*. 2018;37(19):2787-2796. doi:10.1002/sim.7800.
31. Austin PC, Fine JP. Accounting for competing risks in randomized controlled trials: a review and recommendations for improvement. *Stat Med*. 2017;36(8):1203-1209. doi:10.1002/sim.7215.
32. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987;40(5):373-383. doi:10.1016/0021-9681(87)90171-8.
33. Quan H, Sundararajan V, Halfon P, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Med Care*. 2005;43(11):1130-1139. doi:10.1097/01.mlr.0000182534.19832.83.
34. Goligher EC, Tomlinson G, Hajage D, et al. Extracorporeal membrane oxygenation for severe acute respiratory distress syndrome and posterior probability of mortality benefit in a post hoc Bayesian analysis of a randomized clinical trial. *J Am Med Assoc*. 2018;320(21):2251-2259. doi:10.1001/jama.2018.14276.
35. Lewis RJ, Angus DC. Time for clinicians to embrace their inner Bayesian? *J Am Med Assoc*. 2018;320(21):2208-2210. doi:10.1001/jama.2018.16916.
36. van Doorn J, van den Bergh D, Böhm U, et al. The JASP guidelines for conducting and reporting a Bayesian analysis. *Psychon Bull Rev*. 2021;28:813-826. doi:10.3758/s13423-020-01798-5.
37. Hussey MA, Hughes JP. Design and analysis of stepped wedge cluster randomized trials. *Contemp Clin Trials*. 2007;28(2):182-191. doi:10.1016/j.cct.2006.05.007.
38. Austin PC, Fine JP. Practical recommendations for reporting Fine-Gray model analyses for Practical recommendations for competing risk data. *Stat Med*. 2017;36(27):4391-4400. doi:10.1002/sim.7501.
39. Lin DY, Wei LJ, Yang I, Ying Z. Semiparametric regression for the mean and rate functions of recurrent events. *J R Stat Soc Ser B (Statistical Methodol)*. 2000;62(4):711-730. doi:10.1111/1467-9868.00259.
40. Schaubel DE. Analysis of clustered recurrent event data with application to hospitalization rates among renal failure patients. *Biostatistics*. 2005;6(3):404-419. doi:10.1093/biostatistics/kxi018.
41. Hemmelgarn BR, Manns BJ, Quan H, Ghali WA. Adapting the Charlson comorbidity index for use in patients with ESRD. *Am J Kidney Dis*. 2003;42(1):125-132. doi:10.1016/S0272-6386(03)00415-3.

SUPPLEMENT

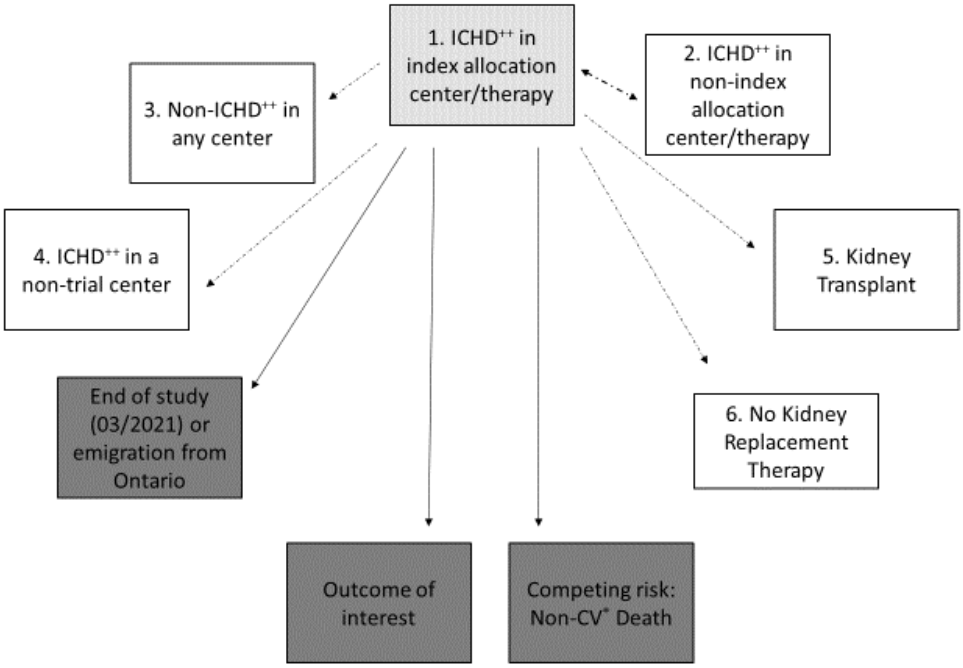
Supplementary content for Dixon SN, Sontrop JM, Al-Jaishi A, et al. Major Outcomes With Personalized Dialysate TEMPerature (MyTEMP) Trial: Statistical Analysis Plan of a Registry-Based, Cluster-Randomized Clinical Trial. *Can J Kid Health Dis.* 20xx: doi

Figure 1. Flow of hemodialysis centers (clusters) and patients in the Major Outcomes with Personalized Dialysate TEMPerature (MyTEMP) Trial[a]



[a] No loss to follow-up is expected other than if a patient emigrates from Ontario (expected in less 0.5% of patients).

Figure 2. Potential patient transitions during their observation time in the MyTEMP trial



Abbreviations: *CV, cardiovascular; ++ ICHD, in-center hemodialysis.

Patients can only enter states 2, 3 and 4 (i.e., change in modality and/or change in dialysis center) after they have remained in the new modality or center for at least 30 days. Their time in this state begins to accrue once they have met the 30-day rule.

Patients can only enter the "6. No kidney replacement therapy" state after they have remained off kidney replacement for at least 90 days. Their time in this state begins to accrue once they have met the 90-day rule.

LEGEND

Black arrows: Patient transitions to terminating events (i.e., where a patient's follow-up ends).

Dash arrow: Patient crossovers between the intervention and control arms (this transition will be ignored in the intent-to-treat analysis and treated as a time-varying exposure variable in the as-treated analysis).

Dotted arrows: Patient transitions away from the allocated therapy (i.e., to dialysis centers not participating in the trial, to other types of treatments for kidney failure, and to no kidney replacement therapy). These transitions will be ignored in the intent-to-treat analysis and treated as competing-risk events in the as-treated analysis, where a patient's observation time will end when they experience any of these events.

Light grey-shaded box: The index center where a patient's observation time begins.

Dark grey-shaded boxes: Terminating events (i.e., the outcome of interest [e.g., the primary outcome or another study outcome], non-cardiovascular death [which will be treated as a competing-risk event in the primary analysis], the study end date (March 31, 2021), or emigration from Ontario.

Non-shaded boxes: Transient events (i.e., changes in treatment modality or center), where patients may move back and forth between different treatment modalities or hemodialysis centers.

The care of patients receiving hemodialysis can be complex. Patients may transition to different hemodialysis centers or to different types of treatment for kidney failure. For both the intervention and control groups, we will report the proportion of the 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 non-study center in Ontario;
4. Other types of dialysis (i.e., home hemodialysis, peritoneal dialysis, in-center nocturnal hemodialysis, or in-center self-care hemodialysis);
5. No dialysis due to receiving a kidney transplant; and
6. No dialysis for at least 90 days which could represent recovered kidney function.

The proportions will be weighted by patient's observation time on study. Based on historical data (over a 4-year follow-up period pre-dating the trial), we expect 86.7% of the patients' observation time will be spent receiving in-center hemodialysis using the originally allocated temperature protocol. We expect 2.4% of patients' observation time will be spent receiving other forms of dialysis (i.e., home hemodialysis, peritoneal dialysis, in-center nocturnal hemodialysis, or in-center self-care hemodialysis), 3.2% will be spent receiving hemodialysis at a center providing the other allocated therapy (or a center not participating in the trial), 2.6% will be spent not receiving kidney replacement (due to withdrawal or recovered kidney function), 0.5% will be spent outside of Ontario, and 4.6% will be spent living with a transplant. We expect < 1% of patients in the trial population to emigrate from Ontario during the trial period (we can ascertain any outcomes that occur before emigration), 21% to experience the

primary composite outcome, 23% to die of non-cardiovascular causes, and the remaining 55% to reach the end of the trial period.

Appendix 1: Bayesian analysis: Prior beliefs

We will conduct and report a Bayesian analysis based on existing guidelines.[1] 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%, 10%, and 15%, given the observed data. We considered a minimum 5% hazard rate reduction (i.e., 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 several prior distributions (**Table 1**, below) that can condition the posterior distribution and provide insight into the primary results' sensitivity. 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.

We will conduct the Bayesian analysis similar to the primary analysis. However, the parameters of the model will be estimated by using Gibbs sampling techniques. 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.

References

1. van Doorn J, van den Bergh D, Böhm U, et al. The JASP guidelines for conducting and reporting a Bayesian analysis. *Psychon Bull Rev*. 2020. doi:10.3758/s13423-020-01798-5

Table 1. Characteristics of Reference Prior Probability Distributions Representing Prior Beliefs About Primary Composite Endpoint Benefit

Prior Belief	**Assumed HR**	**Assumed SD of log HR**	**Probability of treatment effect ≤ than the specified threshold**						**Rationale for Specifying Distribution Characteristics**
			< 1.00	**< 0.95**	**< 0.90**	**< 0.85**	**< 0.80**	**< 0.7**	-
Non-informative	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 historical data from our data sources, the standard deviation is generally less than 0.1, and published observational studies have shown the intervention can have less than an HR of 0.8.
Moderately Enthusiastic	0.8	0.135	95%	90%	81%	67%	50%	16%	Probability of observing a treatment effect greater than that assumed in the MyTEMP trial design (HR = 0.8) is 50%; the 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%; the 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 the MyTEMP trial design (HR = 0.8) is 5%; the 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 the MyTEMP trial design (HR = 0.8) is 5%; the probability of any benefit or harm is equivalent.

Canadian Society of Nephrology/ Société canadienne de néphrologie CSN/SCN

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Corrigendum

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Dixon, Stephanie N., et al. "MyTEMP: Statistical Analysis Plan of a Registry-Based, Cluster-Randomized Clinical Trial." *Canadian journal of kidney health and disease* 8 (2021): 20543581211041182.

In the published version of the above article, there are three corrections or updates the authors want to make as stated below:

1) **Correction:** One definition of intradialytic hypotension, which was reported in the study protocol, was accidentally missed in the statistical analysis plan.
The published statistical plan stated: Finally, we will examine four definitions of intradialytic hypotension using the same blood pressure data as 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 ≥ 25% lower than their pre-dialysis 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 ≥ 25% lower than their pre-dialysis level; and (4) nadir intradialytic systolic blood pressure was ≥ 35 mm Hg lower than their pre-dialysis level.
However, it should have stated: Finally, we will examine five definitions of intradialytic hypotension using the same blood pressure data as the key secondary outcome at the cluster level. We will examine the center's proportion of patients whose (1) nadir systolic blood pressure is < 90 mmHg anytime during a dialysis session when the value before the session was ≥ 90 mmHg, or drop in systolic blood pressure ≥ 30 mmHg anytime during the session from value before session; (2) systolic blood pressure dropped from ≥ 90 mm Hg before dialysis to < 90 mm Hg during dialysis; (3) nadir intradialytic systolic blood pressure was ≥ 25% lower than their pre-dialysis level or whose systolic blood pressure dropped from ≥ 90 mm Hg before dialysis to < 90 mm Hg during dialysis; (4) nadir intradialytic systolic blood pressure was ≥ 25% lower than their pre-dialysis level; and (5) nadir intradialytic systolic blood pressure was ≥ 35 mm Hg lower than their pre-dialysis level."

2) *The published statistical plan stated*: 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).
Update: All analyses described in the statistical analysis plan 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 in 2022.
3) *The published statistical plan stated*: 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.
Update: Data on cardiovascular-related causes of death will primarily be captured using the following definition: (a) in-hospital (or emergency department) death with a cardiovascular disease diagnosis in the primary/most responsible diagnosis position or (b) out-of-hospital death (including death in an emergency department) without documentation of cancer in the 365 days before and including the date of death and without documentation of trauma in the 30 days before and including the date of death.[2] A death in the emergency department with a cardiovascular event as the primary diagnosis will be defined as "in-hospital" cardiovascular-related death, regardless of whether they had cancer or trauma code.
Justification: We were recently notified of unanticipated delays in the linkage of the Office of the Register General deaths database at ICES, which will now take several more years to cover the entire trial period. As a result, we will use an alternate method of ascertaining cardiovascular-related deaths, validated by Lix et al.[2] (2021).

References

1. Dixon S, Sontrop J, Al-Jaishi A, et al. MyTEMP: Statistical Analysis Plan of a Registry-Based, Cluster-Randomized Clinical Trial. *Can J kidney Heal Dis*. 2021;8:205435812110411. doi:10.1177/20543581211041182
2. Lix LM, Sobhan S, St-Jean A, et al. Validity of an algorithm to identify cardiovascular deaths from administrative health records: a multi-database population-based cohort study. *BMC Health Serv Res*. 2021;21(1). doi:10.1186/S12913-021-06762-0

MyTEMP sub-study investigating **P**atient **R**eported **O**utcomes **(MyTEMP PRO)** of patients receiving personalized or standard dialysate temperatures

Protocol Version: 3.0

Funding:

MyTEMP is funded from partnering organizations including the Ontario Strategy for Patient-Oriented Research (SPOR) Support Unit, Lawson Health Research Institute, Ontario Renal Network, Dialysis Clinic Inc., Heart and Stroke Foundation of Canada, and Canadian Institutes of Health Research (CIHR).

Roles and Responsibilities

Principle Investigator:

- Dr. Amit Garg

Research Coordinator:

- Sierra Anderson
    - Assisting with study coordination

Table of Contents

Protocol Summary

Objective: To report descriptive symptomology statistics of a group of patients receiving personalized dialysate temperatures (0.5°C-0.9°C below patients' body temperature) and a group of patients receiving usual dialysate temperature of 36.5°C.

Settings: Ten hemodialysis centres across the London Health Sciences Centre renal program that are participating in the MyTEMP clinical trial. Five centres are allocated to personalized reduced dialysate temperature and five centres are allocated to control dialysate temperature.

Patients: Consenting adults at least 18 years old, with no communication impairment (blind/deaf), and reasonable ability to speak and understand English.

Interventions: MyTEMP PRO will be utilizing treatment allocations from the MyTEMP parent randomized trial.

Measurements: Patients will be asked to: 1) complete the Edmonton Symptom Assessment System (revised) Renal (ESASr: Renal) questionnaire using a visual analog scale; 2) how cold they feel while on dialysis; 3) severity of muscle cramps; 4) headaches while on hemodialysis; 5) record their self-rated health; 6) record if they have missed a session in the last month; and 7) record their average amount of time required to recover from their dialysis session (i.e. return to normal duties). We will capture this information electronically using a website accessed on a tablet.

Outcomes: ESASr: Renal item scores, self-rated temperature, self-rated cramp severity, self-rated health, missed sessions, and time to recover following dialysis.

Planned analysis: Descriptive statistics will be reported.

Background

For persons whose kidneys have permanently failed (~ 3 million worldwide and ~23,000 in Canada), maintenance hemodialysis provides a life-saving treatment option (1,2). However, over 500,000 individuals receiving hemodialysis worldwide and 2,500 in Canada are admitted to hospital or die from a major cardiovascular event each year (1–3). We are currently conducting a pragmatic cluster randomized controlled trial in Ontario (known as the MyTEMP clinical trial) that is investigating if personalized dialysate temperature (0.5°C-0.9°C below patients' body temperature) reduces the risk of cardiovascular death and cardiovascular events compared to usual dialysate temperature of 36.5°C. The MyTEMP trial involves 84 hemodialysis centres that care for more than 7000 patients across Ontario. This current sub-study will capture patient reported outcomes for 10 of the 84 centres participating in MyTEMP; we call this sub-study MyTEMP PRO. MyTEMP PRO aims to assess the symptomology of patients receiving personalized dialysate and usual dialysate temperature of 36.5°C.

The outcomes that are most important to patients are often different than what healthcare professional might perceive as important (4). Patients have routinely placed an emphasis on trying to ameliorate the symptoms experienced on hemodialysis, such as itching, cramping and poor energy (4,5). Physicians on the other hand focus more on dialysis care, and outcomes such as all-cause mortality (4). The current pan-provincial primary outcomes of MyTEMP relate to cardiovascular mortality and hospitalizations with major cardiovascular events (defined as hospitalization for myocardial infarction, ischemic stroke, and congestive heart failure). Further evaluation of the dialysate temperature intervention on patient priorities (e.g. symptoms) is warranted and is the focus of the current study protocol.

What symptoms and outcomes will be measured?

Patients on maintenance hemodialysis are characterized by an extreme reduction in quality of life (6). Patients on hemodialysis often require three visits per week to adequately remove toxins from the blood, where each session is commonly up to four hours in duration. The most frequently reported symptoms include fatigue, headaches, shortness of breath, insomnia, nausea and vomiting, and loss of appetite (7). The modified Edmonton Symptom Assessment Scale (ESASr: Renal) can be used in the hemodialysis population to assess symptom frequency and burden, with proven cross-sectional validity, as it shown to be highly correlated scores with the Kidney Disease Quality of Life Short Form (KDQOL-SF) subscales of symptom/problem list, and the lower RAND-12 physical health and mental health composites (8). The symptoms measured by ESASr: Renal include pain, tiredness, drowsiness, nausea, appetite, shortness of breath, depression, anxiety, well-being, itchiness, problems sleeping, and restless legs. This is included in MyTEMP PRO for symptomology assessment.

With these symptoms, the quality of life of many patients is drastically reduced, as it can often take an extended amount of time to recover from a dialysis session (6). In addition to the ESASr: Renal items, MyTEMP PRO also aims to investigate feeling of coldness of dialysis, severity of muscle cramps, general overall health, missed dialysis sessions, self-rated overall health and time to recover following dialysis.

Dialysate Temperature and Outcomes

Pain

In a prospective cohort study of 205 Canadians on hemodialysis treatment, 50% of patients reported chronic pain as a problem, with 55% of these patients reporting the chronic pain

as severe (9) compared with 1% to 14% in the general population (10,11). The cause of pain has been reported to be highly diverse in the hemodialysis population; however, 63% of hemodialysis patients have reported musculoskeletal pain as the most common cause of pain (attributable to osteoarthritis and undiagnosed musculoskeletal pain). This study also reported suboptimal pain management in patients undergoing long-term hemodialysis therapy. A previous study showed 46% of patients with moderate to severe pain considered withdrawing from hemodialysis, compared to 16.7% of patients with no to mild pain (12). These findings suggest a need to further develop treatment options that can reduce the severity of pain in this population.

A reduction in dialysate temperature may reduce pain. Patients receiving a lowered dialysate temperature may be less likely to stop their treatment due to hypotension, and so may also experience less frequent muscl cramps and associated pains from trying to take off too much fluid after a patient misses a dialysis session.

Tiredness, Drowsiness and Problems Sleeping

Tiredness has routinely been reported to be the most frequent symptom for patients on hemodialysis. Previous reports suggest 92% of patients report tiredness, with 73% of the patients considering it to be moderate or severe problem (13). Sleep disturbance has been reported alongside tiredness where 70% of patients on hemodialysis report sleep disturbance 1-2 times per week (14). Fatigue and tiredness is multidimensional that can be attributed to a variety of mechanisms, such as: physiology, psychology, social, and hemodialysis treatment itself (15).

Patients on hemodialysis consider fatigue a key symptom that requires further investigation. Prior evidence suggests that cooler dialysate temperatures of 35.5°C reduces

fatigue scores by 31% on the Piper Fatigue Scale when compared to patients using a dialysate temperature of 37°C (16).

The reduction in fatigue scores may be linked to a reduction in hypotensive events during hemodialysis. This is supported by a number of previous studies suggesting reduced dialysate temperatures reduces the severity of fatigue symptoms in hemodialysis patients and patients are more energetic after dialysis (17,18). Drowsiness has not been rigorously measured in the hemodialysis population with respect to dialysate temperature; however, there is the possible implication of reducing itchiness through reduced dialysate temperatures, which offsets the need for drowsiness inducing antihistamines and may directly promote sleep quality (19).

Nausea

The symptom of nausea in the hemodialysis populations can typically be associated with events of intradialytic hypotension, fluid overload, diet, and hemodialysis effects on the digestive system (20). Previous reports have shown that 18% of patients on maintenance hemodialysis experience nausea during their hemodialysis session (21). A cooler dialysate temperature increases peripheral vascular resistance, improves cardiac response, and alters the level of vasoactive peptides — all which may decrease the risk of intra-dialytic hypotension and thus, reduce the frequency of nausea (22,23). Other mechanisms that may be implicated with reduced dialysate temperature is through the promotion of more complete sessions and less frequent missed hemodialysis sessions to prevent fluid overload. Fluid overload, which may occur in patients not receiving complete sessions, can result in mucosal edema in the gastrointestinal system that may result in nausea (21).

Appetite

Loss of appetite is a symptom that occurs in 30 to 40% of patents on chronic hemodialysis (24). Previous research has linked the loss of appetite in hemodialysis patients to an increase in systemic inflammation, as measured through an increase in pro-inflammatory cytokines (25). Fluid overload has also been linked to a reduction in appetite, as mucosal edema can coincide with early satiety (21). In addition to a loss of appetite affecting a patient's quality of life, reduced appetite has also be linked to a substantial increase in mortality for patients on maintenance hemodialysis(25). Self-reported measures of appetite have revealed that a loss of appetite is worse on days when the patient is undergoing hemodialysis treatment, which may lead to the suggestion that approaches to alter hemodialysis sessions may lead to better appetite outcomes(26,27). Uremic toxins are believed to be implicated in the process of anorexia development in end-stage renal disease patients on hemodialysis (28).

Previous reports show a lower dialysate temperature results in higher urea removal, which may be implicated in reduced appetite in hemodialysis patients (29). However, there may be added benefits to the use of reduced dialysate temperatures and its implications on appetite. A reduction in gastrointestinal edema through the promotion of fluid removal, using reduced dialysate temperatures, could ultimately limit anorexia in hemodialysis patients.

Shortness of Breath

Many patients on hemodialysis experience fluid overload. Previous reports show 100% of chronic kidney disease patients experience at least mild chronic dyspnea; however, in most circumstances, this is treated adequately through dialysis. Shortness of breath typically occurs in patients with fluid overload due to a build-up of fluids in the lungs that limits oxygen exchange. Dialysis can address the issue of fluid overload; however, breathlessness is not always improved

in patients following treatment (30). Congestive heart failure, chronic lung disease, pulmonary hypertension, lung fibrosis, air micro-embolism, dialyzer bio-incompatibility, anemia, and sodium overload are other causes that can be linked to the etiology of breathlessness in dialysis patients (30).

A reduction in dialysate temperatures may provide additional benefits to lowering the incidence of dyspnea in hemodialysis patients. Due to hemodialysis sessions being complicated with intradialytic hypotension, lower dialysate temperatures will promote less missed sessions and less intradialytic complications to meet fluid removal goals. A reduction in pulmonary fluid may have the added benefit of limiting dyspnea both during dialysis and on days between hemodialysis treatments.

Depression

Depression has been reported to occur in 43% of patients on hemodialysis (as reported through Beck's Depression Inventory) and is associated with lower self-rated quality of life (31,32). It is important to understand the etiology and treatment options for patients with chronic kidney disease, as patients who show depressive symptoms have an increased risk of death and hospitalizations (33). Previous links have been found between depression and the following factors: dialysis shift, high levels of phosphorus, and lower levels of hemoglobin (31).

In the typical stroke population, depression is a symptom that occurs in approximately 33% of the survivors (34,35). New evidence has also provided support for the idea that hemodialysis can directly cause progressive white matter injury; the level of damage in the brain has been associated with dialysis-induced blood pressure instability (36). Should direct white matter injury be linked to the development of more frequent or severe depression, the use of personalized

dialysate temperatures may provide benefit to the prevention of white matter damage through an increase in hemodynamic tolerability (36).

Anxiety

The prevalence of anxiety in the hemodialysis population can vary dramatically across various studies; the reported incidence can range from 12% to 52%. A robust, and geographically relevant study to MyTEMP PRO, reported an anxiety disorder incidence of 45.7% in hemodialysis patients in Brooklyn, New York (37). Similar to depression, the etiology of anxiety in hemodialysis patients can be considered multifactorial. Anxiety, however, is a symptom that can be experienced alongside intradialytic hypotension. Reduced dialysate temperatures may be useful for the reduction in intradialytic hypotension, and therefore reduce the incidence and severity of anxiety behaviour and disorders. However, it is also important to consider the overlap of anxiety disorder causes in the hemodialysis population, as a life-threatening illness may invoke anxiety disorders from both a social and psychological perspective that is independent of the treatment itself.

Itchiness

Itchiness is one of the most concerning symptoms to both patients and physicians (5). Approximately 60-80% of dialysis patients experience itchiness that is related to hemodialysis (38). There is currently inadequate treatment for pruritus across the hemodialysis population, as traditional treatment options often fail in alleviating the symptoms.

Uremic toxins are believed to be the driving force for hemodialysis-induced Itchiness, which are largely derived from intestinal putrefaction and gastrointestinal dysbiosis. Through the mechanistic and physiological properties of dialysis, the hemodynamic stress placed on the gut

results in intestinal content translocation. The liver receives all products of intestinal absorption via the portal circulation and is the final barrier before the systemic circulation. Damage to the liver has been shown to lead to an impaired functional barrier, leading to a greater exposure to these substances systemically.

An unpublished study (19) has suggested a therapeutic benefit of reduced dialysate temperatures to limit the severity of uremic pruritus in the hemodialysis population. A robust controlled randomized clinical trial published results in 2017 provided further support to the idea that reduced dialysate temperatures improve itchiness outcomes in the hemodialysis population (39).

Wellbeing

Utilizing the Personal Wellbeing Index, previous research on wellbeing has shown that patients on hemodialysis show a mean score of 64.72, which is statistically different compared to the general population (mean score of 74.75) (40). Through the potential reductions in various symptoms previously mentioned, there is the possibility that well-being may be improved. Reducing complications, such as intradialytic hypotension, through the use of personalized dialysate may have a profound impact. A reduction in all symptoms previously discussed can be improved through reduction in both incidence and severity, and promoting the continuation of hemodialysis (fewer missed sessions and fewer sessions with early termination due to intra-dialytic complications). No studies have directly investigated this measure to date, thus descriptive results from this sub-study would help inform future studies.

Time to Recover Following Dialysis

Time to recover following dialysis is an important measure, as many patients are unable to return to their regular schedule immediately following the hemodialysis session. It is common for patients to tired or drowsy for hours after their hemodialysis session. The Dialysis Outcomes and Practice Patterns Study (2014) found that approximately 68% of patients take more than 2 hours to recover from their dialysis session, with approximately 27% of patients requiring more than 7 hours (6). Post-dialysis recovery time is likely multifactorial; however, previous research has suggested that reduced dialysate temperatures have the potential of drastically reducing recovery times in dialysis patients (41)

Self-Rated Temperature

Measuring how cold a patient feels on dialysis is integral to understanding the systemic effects of personalized dialysate temperature. There have been previous reports that have shown that 20% of patients report feeling cold, and another study has reported 2 out of 10 patients shivering on lower dialysate temperatures of 35.0°C (18,42). Gathering further information in this sub-study would provide further insight into the differentiation in temperature sensations between personalized dialysate temperatures and standard 36.5°C.

Muscle Cramps

In a prospective cohort study of 103 patients on hemodialysis the cumulative occurrence of muscle cramps over 14,000 hemodialysis treatments was reported to be 86%. Patients on hemodialysis commonly experience lower extremity muscle cramping as a result of the removal of fluids causing a drop in systolic blood pressure between 20-30 mm Hg. This leads to the discomfort of patients in addition to increasing risk factors influencing cardiovascular events, as well as ischemic injury to the heart and brain (1). There are currently not many treatments to

prevent muscle cramps. However, a personalized lower dialysate temperature has the potential to reduce the risk for intradialytic hypotension by up to 70% and improve cardiovascular outcomes (2). By reducing the frequency and intensity of intradialytic hypotension patients may experience less frequent muscle cramping (44, 45).

Headaches

A frequently encountered neurological symptom in hemodialysis is headaches experienced by 27% - 70% of all patients with chronic kidney disease. The pathophysiology of hemodialysis headaches is not fully understood however, triggering factors that contribute to the onset of hemodialysis headaches include changing levels in blood pressure, body weight, serum sodium and magnesium. (46). It has also been reported that duration of time between dialysis sessions increases the occurrence of headaches (46). Treatments to alleviate headache symptoms include maintenance of blood volume, electrolytes and blood pressure and avoidance of caffeine. In addition a personalized dialysate temperature has the potential to reduce intradialytic hypotension episodes ultimately decreasing headache like symptoms.

Objective

Report descriptive statistics for both intervention and control arms of MyTEMP on the symptoms of patients through the use of the Edmonton Symptom Assessment System (Revised): Renal. Descriptive statistics will also be reported for time to recover following dialysis, and self-rated health.

Methods

Study Design

MyTEMP PRO is a nested patient-level cross-sectional qualitative and registry-based study that will gather patient reported outcome (PRO) data from the 10 centres participating in the MyTEMP trial (~600 patients).

Study Setting

MyTEMP PRO will involve 10 centres participating in MyTEMP and part of the London Health Sciences Centre Renal Program that care for approximately 600 patients. These sites include:

Parent MyTEMP Intervention arm:

- Adam Linton Dialysis Unit (London, Ontario)
- Bluewater Health (Sarnia, Ontario)
- Chatham-Kent Health Alliance (Chatham, Ontario)
- Huron Perth Hopps Partnership (Stratford, Ontario)
- London Health Sciences Centre (London, Ontario)

Parent MyTEMP Control arm:

- Grey-Bruce Health Services (Owen Sound, Ontario)
- Hanover and District Hospital (Hanover, Ontario)
- Tillsonburg District Memorial Hospital (Tillsonburg, Ontario)
- Woodstock General Hospital (Woodstock, Ontario)
- Westmount Kidney Care Centre (London, Ontario)

Eligibility Criteria

All patients at each of the centres may participate in this study if they meet the following requirements:

- Able to provide consent
- 18 years of age or older
- No communication impairment at baseline (blind/deaf)
- Reasonable use of English language

Other Trials

This is a one-time cross-sectional study, thus there will be no issue for patients to participate in other trials.

Intervention

There is no active intervention for the current study (MyTEMP PRO); the study is utilizing assignments in the parent MyTEMP trial.

Monitoring:

This is a one-time cross-sectional survey with no follow-up and thus will not require monitoring.

Safety Oversight:

An independent Data and Safety Monitoring Board (DSMB) has been established for the parent MyTEMP clinical trial. If the MyTEMP trial is stopped for any reason, the research ethics board for MyTEMP PRO will be notified and the study will be ceased. All centres will be

notified of any concerns. No known direct risks are associated with items found in the MyTEMP PRO assessment.

Outcome:

The outcome measure will involve the scores on each of the ESASr: Renal item scores, self-rated temperature, self-rated cramp severity, self-rated health, missed sessions, and time to recover following dialysis. Descriptive statistics will be reported for both personalized dialysate temperature (MyTEMP intervention) and standard 36.5°C dialysate temperature (MyTEMP control).

Study Methods

MyTEMP PRO will utilize ESASr: Renal to gather PRO data on dialysis-related symptomology and will also collect additional data on self-rated temperature, self-rated cramp severity, self-rated health, missed sessions and time to recover following dialysis. Patients will be approached by a nurse within their circle of care during their hemodialysis session. Patients will be provided with a tablet to view a short three-minute video introducing the MyTEMP PRO questionnaire. Patients will also have access to a full letter of information via the tablet, or a nurse will provide a printed copy if desire. The video and letter of information will provide patients with an overview of the study procedures, voluntary participation, confidentiality and what to do should they choose not to participate.

The idea of an introductory video was presented by patient partners as an additional aid to allow patients with physical limitations such as double vision to participate in the trial. The script within the study introductory video will be presented by patient partners, in an attempt to deliver information at a peer to peer level.

A nurse (part of the circle of care) will ask the patient to complete the assessment on a provided tablet should they choose to participate. If the patient is physically unable to complete the questionnaire, and a caregiver is not present, the nurse will read aloud each item and record the patient's response. No further contact will be made with the patients following the completion of the online symptom assessment.

Participant Timeline

Data collection is a one-time event that will take approximately 2-5 minutes to complete. There will be no additional follow-up with patients. Only interaction will be during the consent process and data collection.

Sample Size

All patients at each of the centres will have the opportunity to enroll into the trial, if they meet the inclusion criteria. We aim to recruit as many patients as possible that are receiving hemodialysis across the LHSC renal program.

Recruitment

A nurse (within the circle of care) will introduce the study to the patient verbally. Immediately following the nurse's description of the study, we will ask if we have verbal consent to continue. The patient will also be given the option to think about participating in this study and if they choose, they may complete the questionnaire while at their next dialysis treatment. If the patient is interested in participating, they will be provided a video outlining the study procedures, consent process, and who has access to the study data.

Due to the extensive amount of symptoms often experienced during hemodialysis (ex. double vision, nausea) our patient partners have expressed that providing a video for patients outlining the trial details would be beneficial. The extensive amounts of written material provided during the consent process may become overwhelming for patients during their hemodialysis session; therefore we believe the study's introduction video will provide a clear and efficient presentation to recruit a wider range of participants. In addition, an electronic copy of a full letter of information will be available for patients via the tablet, as well as paper copies if required.

Both the video and the letter of information will include sections such as risk, benefits, study procedures, an outline of voluntary participation, and confidentiality. Upon receiving the information from the video and letter of information, patients will be prompted to agree to participate in the study by clicking on the "I agree to the terms and conditions of patient reported outcomes while on hemodialysis and consent that my participation in this study is voluntary" button. Patients will also have the option to decline participation and hand the tablet back to the nurse.

Blinding:

Patients participating in MyTEMP PRO are not blinded to their allocation in the parent MyTEMP trial.

Data Collection:

The Edmonton Symptom Assessment System revised: Renal (ESASr: Renal) questionnaire has been converted into a web-based electronic questionnaire. We are utilizing all items found on the ESASr: Renal to assess symptoms. The same scale as the ESASr: Renal will be used; where patients will place their finger on the numbered scale that corresponds to their symptom severity (**Appendix 1**).

Electronic PRO Measurement Validation

With the use of the electronic system, there is no concern of duplicate entries by patients. A pilot study in home dialysis clinics concluded that patients were satisfied with instrument completion over a tablet (43). The Ontario Renal Network is also currently utilizing the Interactive Symptom Assessment Collection (ISAAC) tool to assess patient symptomology through touch screen kiosks or over the internet on a specifically designed website (https://isaac.cancercare.on.ca/). The ISAAC tool contains ESAS to assess general symptoms using the same 0 to 10 scale for each ESAS instrument item.

Sensation responses to the dialysate temperature will be measured utilizing a 0 to 10 scale, similar to the ESAS instrument. The lower end (0) will be labelled as "No Feeling of Being Cold on Dialysis" and the higher end (10) will be labelled as "Worst Possible Feeling of Being Cold on Dialysis".

We will also be utilizing a measurement of dialysis recovery time that has been validated in a large-scale dialysis study (6). The question is as follows: How long does it take you to recover from a dialysis session and resume your normal, usual activities? Patients will record the total number of minutes it typically takes to recover from their hemodialysis session.

A health thermometer will also be used to assess the patient's self-rated health on a scale of 0 – worst possible health to 100 – best possible health.

Harms and Benefits:

There are no expected harms in the completion of the MyTEMP PRO questionnaire; however, as with any questionnaire study, there is a minimal risk of privacy breach and some participants may feel uncomfortable completing questions related to their symptomology. Should patients feel uncomfortable, the participant will not be required to answer the question. The patients will be made aware that their survey responses are being used to assess the impact of dialysis temperature, not to be used to influence their clinical care. Patients will be asked to communicate symptom concerns to their healthcare team.

The results of MyTEMP PRO will provide further information on potential benefits of personalized dialysate. Because no statistical comparisons are being made in this study, MyTEMP PRO will set a foundation for future patient-reported outcome studies investigating personalized dialysate temperatures.

Data linkage

We are not collecting any participant identifiers and as such, collected data will not be linked to any additional database.

Data Privacy and Security:

We will not be recording personal identifiers. All questionnaire responses will be recorded and stored on the tablet. All data will be encrypted.

Data Destruction:

Any data generated by this study will be destroyed within 8 years of study completion (expected date of study completion is March 31st, 2021, expected date of destruction is March 31st, 2029). Study data specified for destruction will be destroyed according to Western University and Lawson Health Research Institute's standard operating procedures, which include document shredding, electronic erasure, and physical destruction of electronic media.

Statistical Analysis:

We will report descriptive statistics for MyTEMP PRO outcomes for each arm of MyTEMP. This will include the mean, standard deviation, median, and interquartile ranges for each individual ESASr: Renal item, feeling of coldness, cramp severity, missed sessions, self-rated health and time to recover following dialysis.

Missing Data:

In cases where a patient does not record their response for an item, it will be disregarded and not included in the analysis. The final report will include the number of missing data elements for each questionnaire item.

Ethics and Dissemination

Research Ethics Approval:

MyTEMP PRO will be submitted to the local research ethics board (REB) for review and approval.

Protocol Amendments:

Should any changes be made to the MyTEMP PRO protocol, the local REB will be notified of the respective changes. This will be done through online submissions.

Declaration of Interests:

There are no financial or competing interests for the principal investigator or for any site.

Ancillary and Post-Trial Care

No changes in a patient's care will be made following their participation in the trial. There are no expected harms from their participation in regard to the completion of the online questionnaire.

Dissemination Policy:

Results of this study will be published in a well-respected journal.

References

1. Foley RN, Collins AJ. End-Stage Renal Disease in the United States: An Update from the United States Renal Data System. J Am Soc Nephrol [Internet]. 2007;18(10):2644–8. Available from: http://www.jasn.org/cgi/doi/10.1681/ASN.2007020220

2. Foote C, Ninomiya T, Gallagher M, Perkovic V, Cass A, McDonald SP, et al. Survival of elderly dialysis patients is predicted by both patient and practice characteristics. Nephrol Dial Transplant. 2012;27(9):3581–7.

3. Jassal SVS, Trpeski L, Zhu N, S F, Hemmelgarn B, Fenton S, et al. Changes in survival among elderly patients initiating dialysis from 1990 to 1999. Can Med …. 2007 Oct;177(9):1033–8.

4. Jun M, Manns B, Laupacis A, Manns L, Rehal B, Crowe S, et al. Assessing the extent to which current clinical research is consistent with patient priorities: A scoping review using a case study in patients on or nearing dialysis. Can J Kidney Heal Dis [Internet]. 2015;2(1):1–10. Available from: http://dx.doi.org/10.1186/s40697-015-0070-9

5. Manns B, Hemmelgarn B, Lillie E, Dip SCPG, Cyr A, Gladish M, et al. Setting research priorities for patients on or nearing dialysis. Clin J Am Soc Nephrol. 2014;9(10):1813–21.

6. Rayner HC, Zepel L, Fuller DS, Morgenstern H, Karaboyas A, Culleton BF, et al. Recovery time, quality of life, and mortality in hemodialysis patients: The Dialysis Outcomes and Practice Patterns Study (DOPPS). Am J Kidney Dis [Internet]. 2014;64(1):86–94. Available from: http://dx.doi.org/10.1053/j.ajkd.2014.01.014

7. Flythe J, Powell J, Poulton C, Westreich K, Handler L, Reeve B, et al. Patient-reported outcome instruments for physical symptoms among patients receiving maintenance

dialysis: a systematic review. Am J kidney Dis. 2015;66(6):1033–46.

8. Davison SN, Jhangri GS, Johnson JA. Cross-sectional validity of a modified Edmonton symptom assessment system in dialysis patients: A simple assessment of symptom burden. Kidney Int [Internet]. 2006;69(9):1621–5. Available from: http://dx.doi.org/10.1038/sj.ki.5000184

9. Davison SN. Pain in Hemodialysis Patients: Prevalence, Cause, Severity, and Management. Am J Kidney Dis [Internet]. 2003;42(6):1239–47. Available from: http://dx.doi.org/10.1053/j.ajkd.2003.08.025

10. Von Korff M, Dworkin SF, Le Resche L, Kruger A. An epidemiologic comparison of pain complaints. Pain [Internet]. 1988 Feb [cited 2018 Aug 23];32(2):173–83. Available from: http://www.ncbi.nlm.nih.gov/pubmed/3362555

11. Smith BH, Elliott AM, Chambers WA, Smith WC, Hannaford PC, Penny K. The impact of chronic pain in the community. Fam Pract [Internet]. 2001 Jun [cited 2018 Aug 23];18(3):292–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/11356737

12. Davison SN, Jhangri GS. The impact of chronic pain on depression, sleep, and the desire to withdraw from dialysis in hemodialysis patients. J Pain Symptom Manage. 2005;30(5):465–73.

13. Davison SN, Jhangri GS. Impact of Pain and Symptom Burden on the Health-Related Quality of Life of Hemodialysis Patients. J Pain Symptom Manage [Internet]. 2010;39(3):477–85. Available from: http://dx.doi.org/10.1016/j.jpainsymman.2009.08.008

14. Brown SA, Tyrer FC, Clarke AL, Lloyd-Davies LH, Stein AG, Tarrant C, et al. Symptom

burden in patients with chronic kidney disease not requiring renal replacement therapy. Clin Kidney J [Internet]. 2017;10(6):788–96. Available from: https://academic.oup.com/ckj/article-lookup/doi/10.1093/ckj/sfx057

15. Jhamb M, Weisbord SD, Steel JL, Unruh M. Fatigue in patients receiving maintenance dialysis: a review of definitions, measures, and contributing factors. Am J Kidney Dis [Internet]. 2008 Aug [cited 2018 Oct 11];52(2):353–65. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18572290

16. Sajadi M, Gholami Z, Hekmatpour D, Soltani P, Haghverdi F. Cold dialysis solution for hemodialysis patients with fatigue a cross-over study. Iran J Kidney Dis. 2016;10(5):319–24.

17. Azar AT. Effect of dialysate temperature on hemodynamic stability among hemodialysis patients. Saudi J Kidney Dis Transplant [Internet]. 2009;20(4):596–603. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19587499

18. Ayoub A, Finlayson M. Effect of cool temperature dialysate on the quality and patients ' perception of haemodialysis. 2004;19(1):190–4.

19. Tamadon M. Effect of hemodialysis fluid cooling uremic pruritus in hemodialysis patients. 2012;1(2):27–8.

20. Daugirdas JT. Measuring Intradialytic Hypotension to Improve Quality of Care. J Am Soc Nephrol [Internet]. 2015;26(3):512–4. Available from: http://www.jasn.org/cgi/doi/10.1681/ASN.2014090860

21. Chong VH, Tan J. Prevalence of gastrointestinal and psychosomatic symptoms among

Asian patients undergoing regular hemodialysis. Nephrology [Internet]. 2013 Feb [cited 2018 Aug 23];18(2):97–103. Available from: http://doi.wiley.com/10.1111/nep.12000

22. 1982 - Maggiore et al. - Blood temperature and vascular stability during demodialysis and hemofiltration.pdf.

23. Parker LA, Limebeer CL, Rock EM, Sticht MA, Ward J, Turvey G, et al. A comparison of novel, selective fatty acid amide hydrolase (FAAH), monoacyglycerol lipase (MAGL) or dual FAAH/MAGL inhibitors to suppress acute and anticipatory nausea in rat models. Psychopharmacology (Berl). 2016;233(12).

24. Lopes AA, Elder SJ, Ginsberg N, Andreucci VE, Cruz JM, Fukuhara S, et al. Lack of appetite in haemodialysis patients - Associations with patient characteristics, indicators of nutritional status and outcomes in the international DOPPS. Nephrol Dial Transplant. 2007;22(12):3538–46.

25. Kalantar-Zadeh K, Block G, McAllister CJ, Humphreys MH, Kopple JD. Appetite and inflammation, nutrition, anemia, and clinical outcome in hemodialysis patients. Am J Clin Nutr. 2004;80(2):299–307.

26. Burrowes JD, Larive B, Cockram DB, Dwyer J, Kusek JW, McLeroy S, et al. Effects of dietary intake, appetite, and eating habits on dialysis and non-dialysis treatment days in hemodialysis patients: Cross-sectional results from the HEMO study. J Ren Nutr. 2003;13(3):191–8.

27. Burrowes JD, Larive B, Chertow GM, Cockram DB, Dwyer JT, Greene T, et al. Self-reported appetite, hospitalization and death in haemodialysis patients: Findings from the Hemodialysis (HEMO) Study. Nephrol Dial Transplant. 2005;20(12):2765–74.

28. Carrero JJ, Aguilera A, Stenvinkel P, Gil F, Selgas R, Lindholm B. Appetite Disorders in Uremia. J Ren Nutr [Internet]. 2008 Jan [cited 2018 Aug 23];18(1):107–13. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18089455

29. Muhd Ariffin NF, Naing L, Pisharam J, Maboud Khalil MA, Tamin N, Chong VH, et al. Appetite and Gastrointestinal Symptoms in End Stage Renal Disease Patients. J Clin Exp Nephrol [Internet]. 2016 [cited 2018 Sep 6];1(2). Available from: http://clinical-experimental-nephrology.imedpub.com/appetite-and-gastrointestinal-symptoms-in-end-stage-renal-disease-patients.php?aid=9441

30. Salerno FR, Parraga G, McIntyre CW. Why Is Your Patient Still Short of Breath? Understanding the Complex Pathophysiology of Dyspnea in Chronic Kidney Disease. Semin Dial [Internet]. 2017 Jan [cited 2018 Aug 23];30(1):50–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27680887

31. Teles F, de Azevedo V, Miranda C, Miranda M, Teixeira M, Elias R. Depression in hemodialysis patients: the role of dialysis shift. Clinics [Internet]. 2014 Mar 1 [cited 2018 Aug 23];69(3):198–202. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24626947

32. Watnick S, Kirwin P, Mahnensmith R, Concato J. The prevalence and treatment of depression among patients starting dialysis. Am J Kidney Dis [Internet]. 2003 Jan [cited 2018 Aug 23];41(1):105–10. Available from: http://www.ncbi.nlm.nih.gov/pubmed/12500227

33. Hedayati SS, Grambow SC, Szczech LA, Stechuchak KM, Allen AS, Bosworth HB. Physician-Diagnosed Depression as a Correlate of Hospitalizations in Patients Receiving Long-Term Hemodialysis. Am J Kidney Dis [Internet]. 2005 Oct [cited 2018 Aug

23];46(4):642–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16183419

34. Espárrago Llorca G, Castilla-Guerra L, Fernández Moreno MC, Ruiz Doblado S, Jiménez Hernández MD. Depresión post ictus: una actualización. Neurología [Internet]. 2015 Jan [cited 2018 Aug 23];30(1):23–31. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22901370

35. Whyte EM, Mulsant BH. Post stroke depression: epidemiology, pathophysiology, and biological treatment. Biol Psychiatry [Internet]. 2002 Aug 1 [cited 2018 Aug 23];52(3):253–64. Available from: http://www.ncbi.nlm.nih.gov/pubmed/12182931

36. Eldehni MT, Odudu A, McIntyre CW. Randomized Clinical Trial of Dialysate Cooling and Effects on Brain White Matter. J Am Soc Nephrol [Internet]. 2015;26(4):957–65. Available from: http://www.jasn.org/cgi/doi/10.1681/ASN.2013101086

37. Cohen SD, Cukor D, Kimmel PL. Anxiety in Patients Treated with Hemodialysis. Clin J Am Soc Nephrol [Internet]. 2016 Dec 7 [cited 2018 Aug 23];11(12):2250–5. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27660303

38. Keithi-Reddy SR, Patel TV, Armstrong AW, Singh AK. Uremic pruritus. Kidney Int [Internet]. 2007 Aug [cited 2018 Aug 23];72(3):373–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17429345

39. Rad M, Jaghouri E, Sharifipour F, Rakhshani MH. The Effects of Cool Dialysate on Pruritus Status During Hemodialysis of Patients With Chronic Renal Failure: A Controlled Randomized Clinical Trial. Iran Red Crescent Med J [Internet]. 2016 Jun 8 [cited 2018 Sep 6];19(1). Available from: http://ircmj.neoscriber.org/en/articles/16828.html

40. Bennett PN, Weinberg MK, Bridgman T, Cummins RA. The happiness and subjective well-being of people on haemodialysis. J Ren Care [Internet]. 2015 Sep [cited 2018 Aug 23];41(3):156–61. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25819036

41. Azar AT. Effect of dialysate temperature on hemodynamic stability among hemodialysis patients. Saudi J Kidney Dis Transpl [Internet]. 2009 Jul [cited 2018 Aug 23];20(4):596–603. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19587499

42. Toth-Manikowski SM, Sozio SM. Cooling dialysate during in-center hemodialysis: Beneficial and deleterious effects. World J Nephrol [Internet]. 2016 Mar 6 [cited 2018 Sep 7];5(2):166–71. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26981441

43. Schick-Makaroff K, Molzahn A. Strategies to use tablet computers for collection of electronic patient-reported outcomes. Health Qual Life Outcomes [Internet]. 2015 Jan 22 [cited 2018 Oct 11];13(1):2. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25608560

44. Benna, P., Lacquaniti, F., Triolo, G et al. ital. J Neuro Sci (1981) 2: 53 https://doi-org.proxy1.lib.uwo.ca/10.1007/BF02351687

45. Ward, Jordan M., et al "Patient and caregiver involvement in a multicentre clustered hemodialysis trial." *CMAJ: Canadian Medical Association Journal, 7, Nov, 2018, p. S32+*. Available from: https://www-ncbi-nlm-nih-gov.proxy1.lib.uwo.ca/pmc/articles/PMC6472463/ Accessed 29 May 2019

46. Melo, Eduardo S., Aguair, Filipe C., Rocha-Filho, Sampaio R et al “Dialysis Headdache: a Narrative Review.” *The Journal of Head and Face Pain. January 2017 P.161-164.*

Appendix 1

Consent

INSERT PATIENT VIDEO

Click HERE to access the full letter of information

Study Title: MyTEMP sub-study investigating Patient Reported Outcomes (MyTEMP PRO) while on hemodialysis.

Name of Principal Investigator: Dr. Amit Garg

Email: amit.garg@lhsc.on.ca

Phone: (519) 685-8500 extension 77867

Consent to Participate in Research

- I understand that I am being asked to complete a 2-5 minute survey of symptoms while I am on and shortly after my dialysis treatment.
- I have read, or have had it read to me, each page of this Participant Informed Consent Form.
- All of my questions regarding the sub-study and consent form have been answered to my satisfaction.
- I understand that upon consenting to the sub-study, my questionnaire cannot be retracted from the sub-study
- I voluntarily agree to participate in this sub-study.

☐ **I agree to the terms and conditions of "MyTEMP sub-study investigating Patient Reported Outcomes (MyTEMP PRO) while on hemodialysis" and consent that my participation in this study is voluntary**

Renal (ESAS-r: Renal) *Please circle the number that best describes, on average how this symptom has bothered you this past week.*		
No Pain	**0 1 2 3 4 5 6 7 8 9 10**	**Worst Possible Pain**

Renal (ESAS-r: Renal) *Please circle the number that best describes, on average how this symptom has bothered you this past week.*		
No Tiredness ***(Tiredness = lack of energy)***	**0 1 2 3 4 5 6 7 8 9 10**	**Worst Possible Tiredness**

Renal (ESAS-r: Renal) *Please circle the number that best describes, on average how this symptom has bothered you this past week.*		
No Drowsiness ***(Drowsiness = feeling sleepy)***	**0 1 2 3 4 5 6 7 8 9 10**	**Worst Possible Drowsiness**

Renal (ESAS-r: Renal) *Please circle the number that best describes, on average how this symptom has bothered you this past week.*		
No Nausea	**0 1 2 3 4 5 6 7 8 9 10**	**Worst Possible Nausea**

Renal (ESAS-r: Renal) *Please circle the number that best describes, on average how this symptom has bothered you this past week.*		
No Lack of Appetite	**0 1 2 3 4 5 6 7 8 9 10**	**Worst Possible Lack of Appetite**

Renal (ESAS-r: Renal) *Please circle the number that best describes, on average how this symptom has bothered you this past week.*		
No Shortness of Breath	**0 1 2 3 4 5 6 7 8 9 10**	**Worst Possible Shortness of Breath**

Renal (ESAS-r: Renal) *Please circle the number that best describes, on average how this symptom has bothered you this past week.*		
No Depression ***(Depression = feeling sad)***	**0 1 2 3 4 5 6 7 8 9 10**	**Worst Possible Depression**

Renal (ESAS-r: Renal) *Please circle the number that best describes, on average how this symptom has bothered you this past week.*		
No Anxiety ***(Anxiety = feeling nervous)***	**0 1 2 3 4 5 6 7 8 9 10**	**Worst Possible Anxiety**

Renal (ESAS-r: Renal) *Please circle the number that best describes, on average how this symptom has bothered you this past week.*		
Best Wellbeing ***(Wellbeing = how you feel overall)***	**0 1 2 3 4 5 6 7 8 9 10**	**Worst Possible Wellbeing**

Renal (ESAS-r: Renal) *Please circle the number that best describes, on average how this symptom has bothered you this past week.*		
No Itching	**0 1 2 3 4 5 6 7 8 9 10**	**Worst Possible Itching**

Renal (ESAS-r: Renal) *Please circle the number that best describes, on average how this symptom has bothered you this past week.*		
No Problem Sleeping	**0 1 2 3 4 5 6 7 8 9 10**	**Worst Possible Problem Sleeping**

Renal (ESAS-r: Renal) *Please circle the number that best describes, on average how this symptom has bothered you this past week.*		
No Restless Legs ***(Restless legs = moving legs due to discomfort)***	**0 1 2 3 4 5 6 7 8 9 10**	**Worst Possible Restless Legs**

Please circle the number that best describes, on average how this symptom has bothered you this past week.		
No Feeling of Being Cold on Dialysis	**0 1 2 3 4 5 6 7 8 9 10**	**Worst Possible Feeling of Being Cold on Dialysis**

Please circle the number that best describes, on average how this symptom has bothered you this past week.		
No Muscle Cramps **No Muscle Cramps** (A sudden painful muscle contraction—anywhere in the body — during dialysis or after dialysis — including at night)	**0 1 2 3 4 5 6 7 8 9 10**	**Worst Possible Muscle Cramps**

Please circle the number that best describes, on average how this symptom has bothered you this past week.		
No Headache on Dialysis	**0 1 2 3 4 5 6 7 8 9 10**	**Worst Possible Headache on Dialysis**

How *good* or *bad* is your health state TODAY?

0 . . . . . 10. . . . . 20 . . . . . 30 . . . . . 40 . . . . . 50 . . . . . 60 . . . . . 70 . . . . . 80 . . . . . 90 100

Worst Possible Health Best Possible Health

In the past *week* have you missed at least *one* dialysis session (where the session was NOT rescheduled)?

☐ Yes ☐ No

In the past *week* on average, how long did it take you to recover from a dialysis session and resume your normal, usual activities?

Minutes (There are 60 minutes in an hour)