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).\textsuperscript{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.\textsuperscript{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.\textsuperscript{6–8} Lowering the dialysate temperature stabilizes intradialytic blood pressure and decreases the risk of experiencing hypotensive events during hemodialysis treatments\textsuperscript{9} – experiencing frequent hypotensive events during hemodialysis is associated with a greater risk of all-cause mortality and cardiovascular events.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{22} This inability to mount a normal response has been partly attributed to impairment in myocardial contractile reserve due to cardiomyopathy.\textsuperscript{23,24} Beyond ultrafiltration, there are multiple patient and dialysis-associated factors that contribute to intra-dialytic hypotension including poor sympathetic responsiveness,\textsuperscript{25} poor cardiac function,\textsuperscript{26,27} older age (possibly related to increasing comorbid conditions),\textsuperscript{28} medication use (e.g. use of anti-hypertensive agents),\textsuperscript{29} body heating,\textsuperscript{30–32} release of vasodilator agents,\textsuperscript{33,34} and osmolar and electrolyte changes.\textsuperscript{35–38}

Large drops (greater than 20 mmHg) in blood pressure complicate up to 50\% of hemodialysis sessions.\textsuperscript{22} Intradialytic hypotension increases the risk of coronary hypoperfusion that can lead to myocardial stunning,\textsuperscript{39,40} which is associated with left ventricular dysfunction.\textsuperscript{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.\textsuperscript{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.\textsuperscript{30,32,45–50} \textsuperscript{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. 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. 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. 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 (25th, 75th percentile). We confirmed the delivered dialysate 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 °F). 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. 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. 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. 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.

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. 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** | 12         | Fixed temperature 35.5 °C; duration: one session                                        | Change in SBP: -6 ± 2 mmHg  |
| 2004          |            | Vs                                                                                    | Change in SBP: -0.8 ± 22.7 mmHg |
|               |            | Fixed temperature 36.0 °C; duration: one session                                        |                             |
| **Beerenhout** | 12         | BTM (mean dialysate temperature 35.2 °C); duration: one session                      | SBP pre-dialysis: 146 ± 5 mmHg |
| 2004          |            | Vs                                                                                    | SBP post-dialysis: 140 ± 6 mmHg |
|               |            | Fixed temperature 37.5 °C; duration: one session                                        |                             |
| **Chesterton** | 10         | Fixed temperature 35 °C; duration: one session                                         | Percent change in SBP: 2.71% above baseline ± 0.97% |
| 2009          |            | Vs                                                                                    | Percent change SBP: 7.54% below baseline ± 1.92% |
|               |            | Fixed temperature 37 °C; duration: one session                                         |                             |
| **Cruz**      | 19         | Fixed temperature 35.5 °C; duration: nine sessions                                     | SBP pre-dialysis: 132 ± 3.3 mmHg |
| 1999          |            | Nadir SBP: 103 ± 2.9 mmHg                                                             | SBP pre-dialysis: 132.7 ± 3.4 mmHg |
|               |            | Nadir SBP: 90.6 ± 2.5 mmHg                                                            |                             |
| Study          | Patient Count | Conditions                                                                 | SBP post-dialysis | Change in SBP between post- and pre-dialysis readings |
|---------------|---------------|------------------------------------------------------------------------------|-------------------|-------------------------------------------------------|
| Maggiore 2002 | 95            | BTM isothermic; duration: 12 sessions on average                             | SBP post-dialysis: 118 ± 3.5 mmHg | Change in SBP between post- and pre-dialysis readings: -14 ± 17 mmHg |
|               |               | BTM thermoneutral; duration: 12 sessions on average                         |                   | * Post-dialysis SBP was 14 mmHg below pre-dialysis SBP |
| Parker 2007   | 7             | Fixed temperature 35 °C; duration: one session                              | Intra-dialytic SBP: 137 ± 11.4 mmHg | Intra-dialytic SBP: 130.7 ± 11.4 mmHg                |
| Selby 2006    | 10            | Fixed temperature 35 °C; duration: one session                              | Intra-dialytic SBP: 159 ± 14 mmHg | Intra-dialytic SBP: 142 ± 17 mmHg                   |
| Study | N | Temperature | Duration | SBP Pre-dialysis | Max ↓ in SBP | SBP Post-dialysis | SBP Pre-dialysis | Max ↓ in SBP | SBP Post-dialysis |
|-------|---|-------------|----------|------------------|-------------|------------------|------------------|-------------|------------------|
| van der Sande 1999 | 9 | Fixed temperature 35.5 °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 |
| | | vs | Fixed temperature 37 °C; duration: one session | | | | | | |
| Kaufman 1998 | 17 | BTM isothermic; BTM cooling 0.5 °C below body temperature; 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 |
| | | vs | BTM thermoneutral; duration: 1.5 sessions on average | | | | | | |
| Zitt 2008 | 17 | Fixed temperature 35 °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 |
| | | vs | Fixed temperature 37 °C; duration: not clear | | | | | | |

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

¥ Information presented is Mean ± SD
**Table 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.
**Table 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 (25th, 75th percentile).

To convert °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. 

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### 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 1\(^{st}\), 1990. | 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/CIIH-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*                      | CIH/ODB/OHIP    |
| Diabetes mellitus                | ORRS/CIHI-DAD/OHIP |
| Fracture                         | CIHI-DAD        |
| 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 |
| Condition                                           | Data Sources          |
|----------------------------------------------------|-----------------------|
| Lung disease (COPD)                                | ORRS/ CIHI-DAD/OHIP   |
| Malignancy                                         | ORRS /CIHI-DAD/OHIP   |
| Myocardial infarction ++                           | ORRS/ CIHI-DAD        |
| Other serious illness that would shorten life      | ORRS                  |
| expectancy less than 5 years                      |                       |
| 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| NACRS                 |
| months                                             |                       |
| 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                                      | Case Report Forms** |
|-----------------------------------------------------|---------------------|
| Dialysate Temperature (baseline)                    |                     |
| Pre-dialysis systolic blood Pressure (baseline)      |                     |
| Pre-dialysis diastolic blood pressure (baseline)     |                     |
| Mean intra-dialytic nadir systolic blood pressure (baseline) |                     |
| Diastolic blood pressure accompanying the intra-dialytic nadir systolic blood pressure (baseline) |                     |
| 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 A, ¥           | ORGD: Leading Cause of Death                                               | N/A              | Not available        |
|                                             | 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                                  |                  |                      |
| Cardiovascular-related death                | ICD-10:                                                                 |                  |                      |
|                                             | I00 - 178 AND Dischdisp="07" or death in Registered Persons Database     |                  |                      |
|                                             | during the hospital stay                                                 |                  |                      |
| Hospital admission with ischemic stroke     | ICD-10:                                                                 |                  |                      |
|                                             | I63 (excl. I63.6), I64, H341                                             |                  |                      |
| Hospital admission with myocardial infarction| ICD-10:                                                                 |                  |                      |
|                                             | I21, I22                                                                 |                  |                      |
| Hospital admission with heart failure       | ICD-10:                                                                 |                  |                      |
|                                             | I50                                                                       |                  |                      |

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

* 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, 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. The cumulative contribution of hypotensive events to cardiovascular events have been significant. 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.
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. 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). 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. Major fractures (hip, forearm, pelvis, or proximal humerus) are also common occurring in nearly 6% of patients each year. 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. Intradialytic 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. 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:

1. 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.\textsuperscript{53,94,97}

c) At least a 25% relative reduction in nadir systolic blood pressure from pre-dialysis systolic blood pressure.\textsuperscript{53,94,97}

d) A drop in nadir systolic blood pressure by ≥ 35 mmHg from pre-dialysis systolic blood pressure.\textsuperscript{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) |
|-----------------------------------------------|---------------------------------------------------------------|
| 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 = 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.

| CV  | 90% | 92% | 93% | 94% |
|-----|-----|-----|-----|-----|
| 0.75| 90% | 92% | 93% | 94% |
| 0.8 | 71% | 74% | 76% | 79% |
| 0.85| 45% | 47% | 50% | 52% |
| 0.9 | 21% | 23% | 24% | 25% |
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).

| 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,\textsuperscript{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.\textsuperscript{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
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. Veljančič 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, 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. Isothermal 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/gfi126
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.