Educational Sessions

Dr. Amit Garg

Implementing without coordinators for pragmatic trials/My TEMP

Equity, Diversity and Inclusion - where do pragmatic trials fit in?

Dr. Laura Dember

Dr. Steph Dixon

Statistics design for MyTEMP

Gardener's Grove 2023

Large pragmatic randomized trials embedded into routine care that do not need research coordinators at hemodialysis centres

-- Dr. Amit Garg

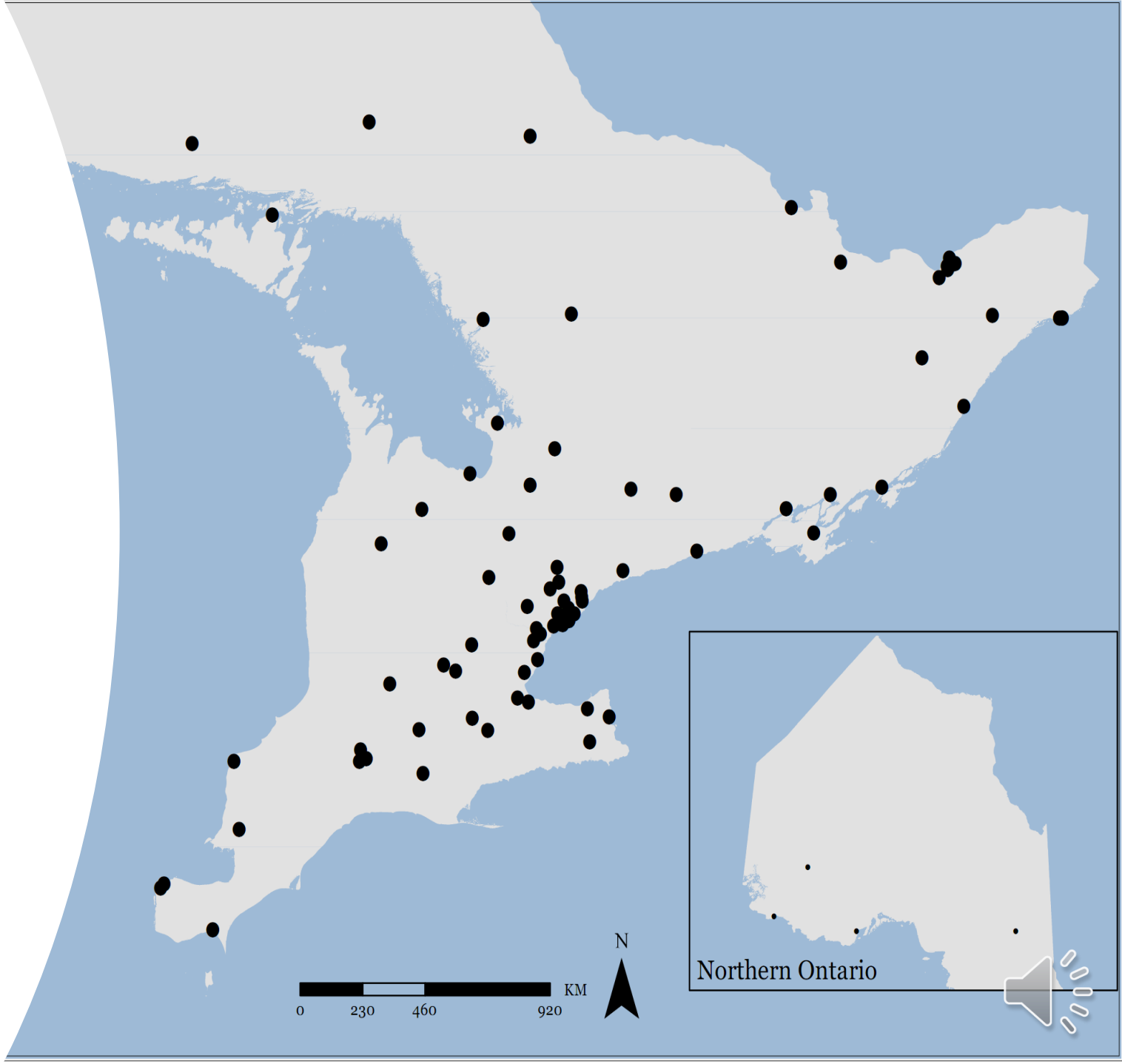
photo from www.princeedwardisland.ca

> 84 hemodialysis centres in **Ontario**

~ 8000 patients at any time

~ 90 pts per centre

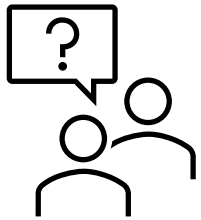
Most are community dialysis centres without research coordinators



Medical directors

set center-wide policies for components of the hemodialysis treatment
Individual nephrologists then may alter centre-wide policies for individual patient care

- **In routine care, nephrologists obtain consent from patients to receive hemodialysis**
- **They do <u>not</u> obtain consent for:**
  - 30+ different components of a hemodialysis treatment,
  - nor to existing or subsequent changes in center-wide policies, as this is not practical



- **Almost all <u>patients are unaware of most components of hemodialysis</u>**
- **Patients are also unaware how standards used in their centre differ from other centers**
- **Not sure of the right 'component' as most lack a reliable evidence base**
  - <u>not</u> in the best interest of patient care that over 90% of such decisions in current care lack a reliable evidence base
- **Lack of quality evidence has resulted in <u>practice variability</u>**

Why do we lack a reliable evidence base?

- **Large, multi-centre RCTs provide best estimates of treatment effects**
- **However, large RCTs done in traditional way inefficient/expensive, so rarely done**
  - We have an **unwieldy system** to generate high-quality trusted evidence
  - Major expense is **research coordinators at centers**, to obtain consent, deliver treatment, collect data
  - Patients who enroll in traditional RCTs differ from those in routine care (exclude most vulnerable)
  - Community hemodialysis centres often do not participate
  - Busy healthcare professionals focus their limited time in dialysis centres on pressing medical issues. For large #s of patients, they are unable / unwilling to obtain or record consent, even when streamlined methods of consent such as integrated consent are used.
    - Health professionals support need for research.
    - In a stressed healthcare system, they indicate they don't have time to undertake additional activities.

⇨ *a way forward*

- **if we can find a responsible way to conduct trials of some types of interventions without research coordinators at hemodialysis centres, we could ↓ trial costs by 75 to 90%**

a trial done without research coordinators at 84 centres, to obtain consent, deliver treatment, collect data

Personalized cooler dialysate for patients receiving maintenance hemodialysis

a pragmatic, cluster-randomized trial

AX Garg, AA Al-Jaishi, SN Dixon, JM Sontrop, SJ Anderson, A Bagga, DS Benjamin, WAD Berry, PG Blake, LC Chambers, PCK Chan, NF Delbrouck, PJ Devereaux, RJ Goluch, LH Gregor, JM Grimshaw, GJ Hanson, EA Iliescu, AK Jain, L Killin, CE Lok, B Luo, RA Mustafa, BC Nathoo, GE Nesrallah, MJ Oliver, S Pandeya, MS Parmar, DN Perkins, J Presseau, EZ Rabin, JT Sasal, TS Shulman, DM Smith, MM Sood, AW Steele, PYW Tam, DJ Tascona, DB Wadehra, R Wald, M Walsh, PA Watson, WP Wodchis, PG Zager, M Zwarenstein, and CW McIntyre **on behalf of the MyTEMP Investigators**

Budget ~ 2.5 million (vs. > 10 million)

THE LANCET

Lancet. 2022 Nov 12;400(10364):1693-1703

U.S. National Library of Medicine

ClinicalTrials.gov

NCT02628366

protocol

Canadian Society of Nephrology/ Société canadienne de néphrologie
CANADIAN JOURNAL OF KIDNEY HEALTH AND DISEASE

Study Protocol-Clinical Research

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

Canadian Journal of Kidney Health and Disease
Volume 7: 1–18
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SAGE

patient partnership

Patient and caregiver involvement in a multicentre clustered hemodialysis trial

CMAJ 2018;190(Suppl 1):S32-S33. doi: 10.1503/cmaj.180403

intervention implementation

RESEARCH Open Access

CrossMark

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

statistical analytic plan

Canadian Society of Nephrology/ Société canadienne de néphrologie
CANADIAN JOURNAL OF KIDNEY HEALTH AND DISEASE

Clinical Research Protocol

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

Canadian Journal of Kidney Health and Disease
Volume 8: 1–11
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obtain consent

photo - https://www.fda.gov/

Dialysis director (healthcare provider) needed to provide consent for centre MyTEMP participation

Patients notified about MyTEMP through

- poster
- letter
- presentations to patient and family advisory councils

A patient or their nephrologist could decide to opt-out of the randomly allocated dialysate temperature

Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS 2 [2022])

Articles 3.1 to 3.5 Consent Process "**Choice**"

3.1 Voluntary (not disadvantaged if withdraw)

3.2 Informed

3.3 Ongoing Process

3.4 Notified of Incidental Findings

3.5 Consent proceeds Research Data Collection

streamlined manner

"responsible"
balancing
feasible - comprehensive

Articles 3.12 Consent Documented

Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS 2 [2022])

Article 3.7A The REB may approve research that involves an alteration to consent

REB approved our request for MyTEMP to use altered patient consent

(i) research is of **minimal risk** to patients

(ii) altered consent requirements **unlikely to adversely affect patient welfare**

(iii) otherwise **impossible or impractical to carry out research** and answer question

(iv) precise **nature** and extent of proposed **alteration is defined**

(v) **plan to debrief**, that may offer patients choice to refuse consent and/or withdraw data

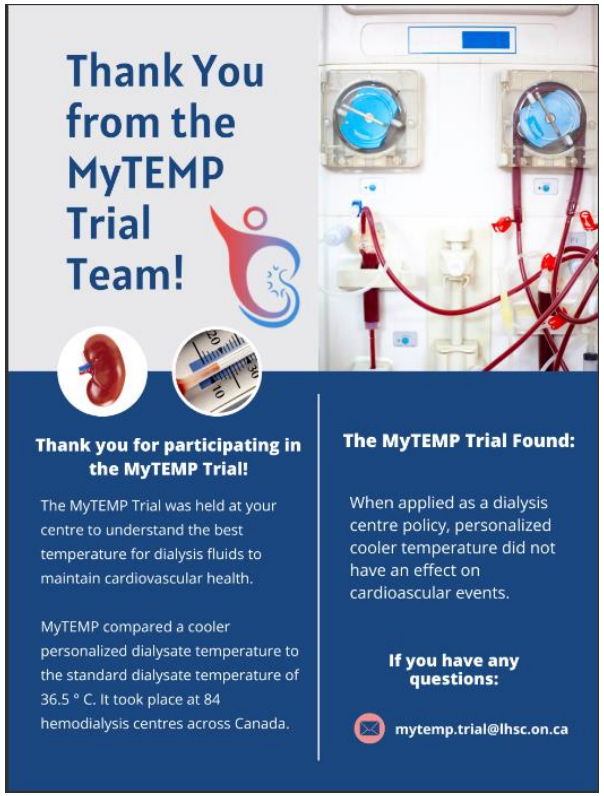
Judgement call

Patient and caregiver involvement in a multicentre clustered hemodialysis trial

CMAJ 2018;190(Suppl 1):S32-S33. doi: 10.1503/cmaj.180403

- Trial developed and authored with patient partners
- Trial presented to Kidney Patient and Family Advisory Councils
  - which resulted in addition of outcomes
  - made suggestions to the trial letter
- Answered a question that matters to patients and providers
- Indigenous consultation

After trial debrief



(v) **plan to debrief**, that may offer participants choice to refuse consent and/or withdraw data

- Inform (respect for persons), allow choice (opt out; respects autonomy)
- *Balance*: expend certain amount of research resources (that are not prohibitive), to provide a responsible level of notification (~ decide about what information), which results in reasonable level of patient understanding
- Have confidence this is occurring in all dialysis centres in the trial
  - Poster in each dialysis center
  - Trial letters handed out to all patients (+ substitute decision makers, + explained)
  - Nephrologists (and nurses) aware of the trial and allocation (open label)
- Patient and/or their nephrologist could change the dialysate temp if they wanted to do so (opt out)
- Patients could not opt out of de-identified healthcare admin data

This centre is participating in

DIALYSATE MAGNESIUM TRIAL

to find the amount of magnesium in dialysate that is the most beneficial for patient health.

100+ participating centres across several provinces in Canada

The trial is expected to run for several years

All patients in this centre will be a part of the Dialysate Magnesium Trial

If you have any questions, please contact <name of local PI will be inserted here, along with their contact information>

The fluid used in dialysis, the dialysate, contains magnesium.

Magnesium helps with important body processes, including those that keep your bones strong, heart healthy, and muscles functioning well.

To find out the optimal amount of magnesium in the dialysate, this trial will compare different concentrations of dialysate magnesium currently used in Canada as a standard of care.

To learn more about the trial, please ask your healthcare team for a patient information handout.

Improvements to Dial Mag Canada to better inform patients of the trial [manageable, higher cost than MyTEMP]

- ~ 25,000 patients in the trial
- Letters of information q 6 months
  - with monitoring with dialysis centers (desk clerk) to confirm handed out
- Letters in 19 languages (including Oji Cree)
- Trust dialysis centers to communicate information to patients (or substitute decision-maker; verbal explanations if cannot read letters)
- *Balancing*:
  - What information (what should patients know)?
  - logistics / cost + certainty info seen + understood

Oji Cree

Dial-Mag CANADA

Dialysate Magnesium Trial

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2 MILLION people worldwide

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(i) research is of **minimal risk** to patients

- the trial introduced no more than minimal risk beyond usual care
  (the same as switching to an alternate dialysis center;
  similar to a quality control measure implemented by hemodialysis director)
- does not mean the intervention is minimal risk
  - *all* interventions have some risk
  - some risks *unknown* until trial is completed

- **What if** in MyTEMP, personalized cooler dialysate reduced risk of CV events vs. standard temperature dialysate?

- Historically most centers used standard temperature dialysate
  - Patients in the trial in intervention group realized a reduced risk of CV events
  - Consider if my father received dialysis in centre will cooler temp policy, randomly allocated to standard temp during the trial, suffered a heart attack during trial period. Acknowledging causes of heart attacks are complex, would I feel trial team acted ethically and responsibly, or would I be concerned?

(iii) otherwise **impossible** or **impractical** to carry out research and answer question

- *judgement*: some research is possible with +++ more resources
  if each trial requires > $10 million, not possible to generate evidence
  for most interventions in care (accept we can't practice evidence-based medicine)
- when set center-wide policy, it affects current as well as future patients
  - in open-label cluster RCT, if obtain consent after random allocation,
    may have differential participation in arms, which introduces bias

Originally executed as a cluster RCT

Centre randomly allocated to low serum phosphate (usual care)

- Do you consent to receive what we always have done?
- Yes!

Centre randomly allocated to high serum phosphate

- Do you consent to a more liberal diet, which is something we have not usually done but may be beneficial?

(this "sounds" experimental; I already have enough to deal with, don't want to rock the boat) – No!

vulnerable patients in the trial

- e.g., lack decision-making capacity, language, sensory issues
- currently receive centre-wide policies in routine dialysis care
- wish to generate treatment estimates that also apply to vulnerable patients
- do so responsibly
  - **inform** patients about the trial: test and improve materials and processes
  - **consent** (opt-out): information for substitute decision makers, health professionals

Ethical considerations not black or white

- Nicholls *et al.* Can J Kidney Health Dis. 2021
- Nicholls *et al.* Can J Kidney Health Dis. 2020
- Al-Jaishi AA *et al.* Trials. 2020
- Goldstein C *et al.* Am J Kidney Dis 2019

Ethical pitfalls

1. Justifying cluster design
2. Vulnerable research participants
3. Health providers as participants
4. Usual care ≠ minimal risk
5. Local policy ≠ cluster-level intervention
6. False dichotomy with consent

Dr. Charles Weijer

https://www.youtube.com/watch?v=HlK3iL82gvE

Photo from www.blueridgejournal.com/

collect data

99% of data coming from large administrative healthcare databases

Institute for Clinical Evaluative Sciences

http://www.ices.on.ca/

Coders unaware of the trial (open label trial)

deliver treatment

Research coordinator

vs.

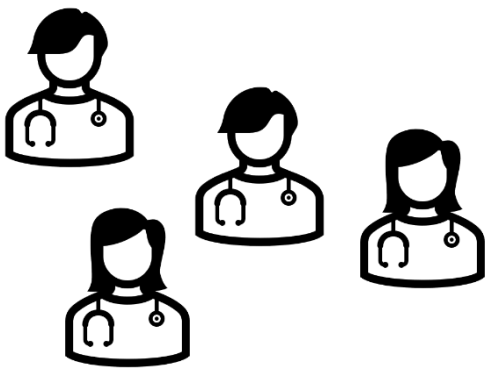
Routine healthcare worker

train **2000+** busy dialysis nurses across 42 centres to deliver personalized temperature

How you get health professionals to implement a protocol for care?

- Barriers to clinical behavior change may be complex and involve multiple factors at multiple levels

- Prior to trial launch. Presseau J. *et al.* Trials 2017



- 9 dialysis nurses & 9 dialysis physicians interviewed

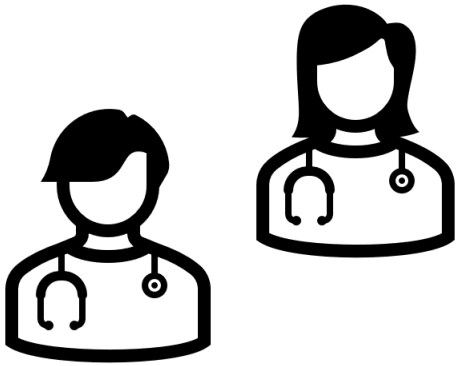
- They shared what they perceived were the barriers and facilitators to adopting the intervention

Health Psychologist

Belief about consequences

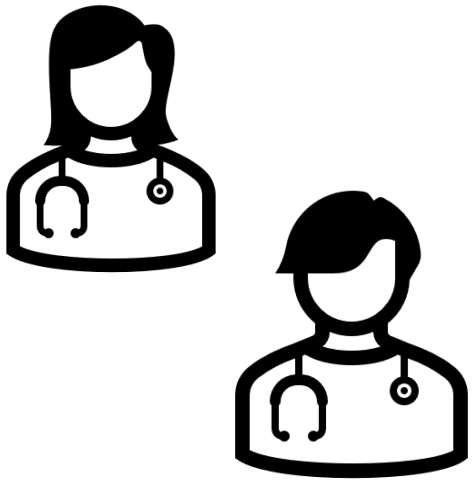
Barrier: (Nurse) my workload will increase

"Evidence suggests less intra-dialytic hypotension; this could ↓ workload and stress"



Environmental Context & Resources

- Some dialysis machines only change in 0.5 ^{o} increments
- Not enough thermometers
- Type of thermometer available
- Patient drinking liquids, or climate outside, affecting temp readings



Social / Professional Role

- We need a global order/ policy change/ medical directive so nurses can set personalized dialysate temperature

Knowledge

- Lowering the dialysate temperature only useful in patients experiencing intra-dialytic hypotension

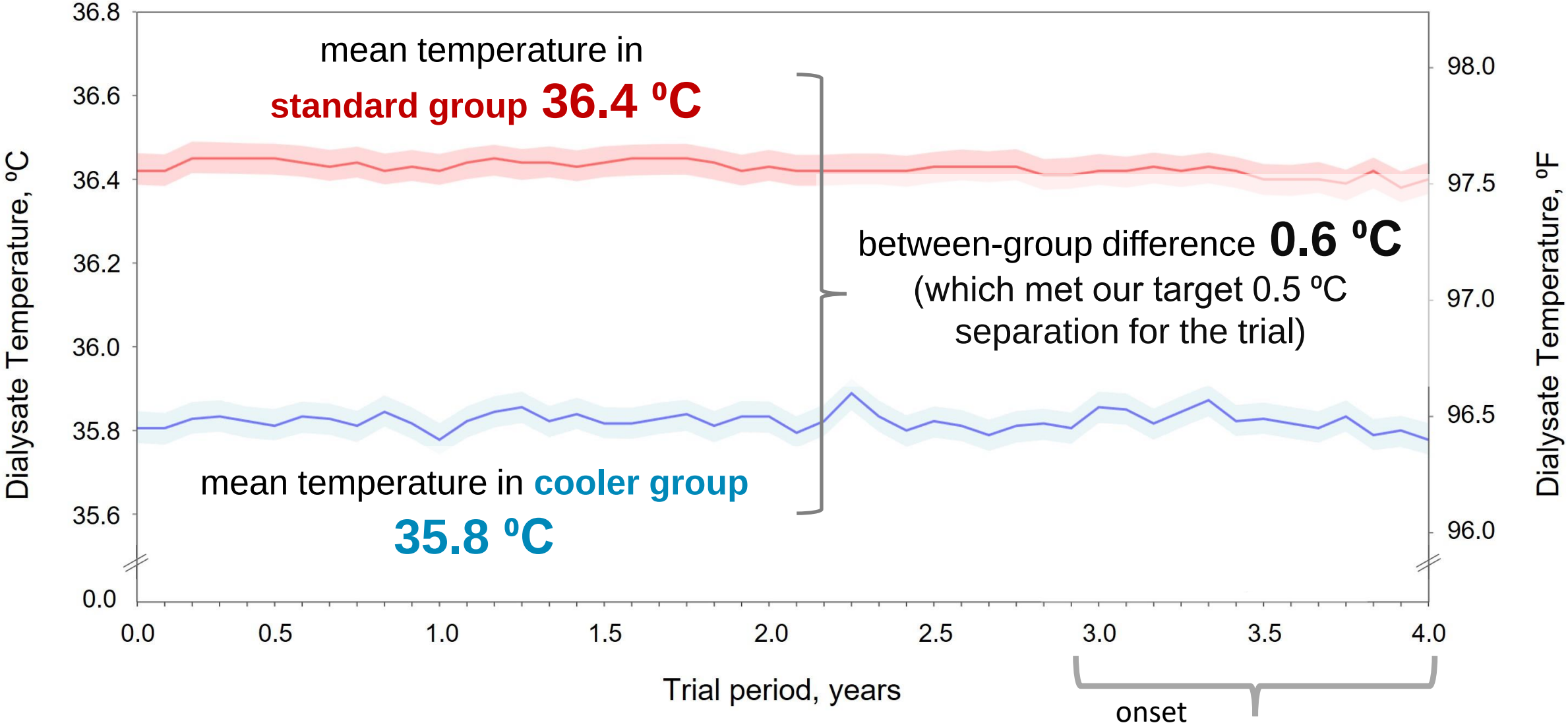
Optimize Intervention & Delivery Before Trial

Photo https://wpengine.com/

- Orientation, in-services, communications
- Print materials, FAQ
- Monitoring and feedback

useful for post-trial implementation

Dialysate temperatures used in the 2 groups

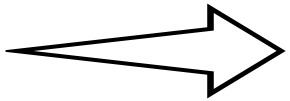


onset

Covid Pandemic

in last year did not appreciably affect the trial

In conclusion



a way forward

if we can find a responsible way to conduct trials of some types of interventions without research coordinators at hemodialysis centres, we could ↓ trial costs by 75 to 90%

in best interest of patient care, as over 90% of components currently used in hemodialysis care lack a reliable evidence base

On behalf of the investigators

MyTEMP

Thank you for listening