Personalised Cooler Dialysate for Patients Receiving Maintenance Haemodialysis (MyTEMP): A Pragmatic, Cluster-randomised Trial

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NIH Pragmatic Trials Collaboratory Grand Rounds
04-21-2023

we have learned so much from the NIH collaboratory …

Réseau de recherche sur les données de santé du Canada

Health Data Research Network Canada

National Pragmatic Trials Training Program

funded by

CIHR IRSC
Canadian Institutes of Health Research
Instituts de recherche en santé du Canada

thank you to Dr. Kevin Weinfurt
for all the support & collaboration

newly created educational materials will be free
and hopefully of use to this community

institutional review board (IRB) = research ethics board (REB)

Common Rule TCPS

Federal (U.S.) Policy for the Protection of Human Subjects

Overview of the MyTEMP trial

- ethics
- statistics

Dr. Steph Dixon

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

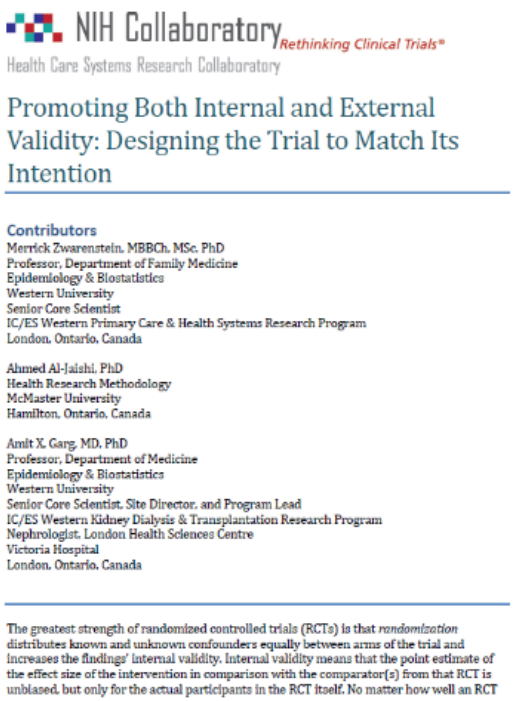
November 13, 2020: Pragmatic and Explanatory Attitudes to RCTs: Using the PRECIS-2 Tool to Describe the Design of the MyTEMP Trial (Ahmed Al-Jaishi, PhD; Amit Garg, MD, PhD, Merrick Zwarenstein, MBBCh, MSc, PhD)

Dr. Merrick Zwarenstein

August 30, 2021: New Living Textbook Materials on Designing a Trial to Match Its Intention

The Living Textbook has recently published materials that explore how randomized trials can be designed to promote both internal and external validity. The new contributions, from Drs. Merrick Zwarenstein, Ahmed Al-Jaishi, and Amit Garg, explain that consideration of the trial's intention, whether pragmatic or explanatory, is the key to designing a trial that successfully answers its primary research question. While there is a contrast between pragmatic and explanatory intentions, there is not a dichotomy. Instead, trials will vary across the spectrum of design decisions leaning toward choices that match the trial's purpose. The PRECIS-2 tool can help investigators design their trial to align with its intention. The authors illustrate these points in a new Living Textbook section, PRECIS-2 Case Study, which contrasts the design decisions made for two trials in a renal dialysis setting.

"The purpose should be decided before embarking on designing a trial, and each element of the trial design should be aligned to the chosen purpose."– Zwarenstein et al. 2021


NIH Collaboratory Rethinking Clinical Trials®
Health Care Systems Research Collaboratory

Promoting Both Internal and External Validity: Designing the Trial to Match Its Intention

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The greatest strength of randomized controlled trials (RCTs) is that *randomization* distributes known and unknown confounders equally between arms of the trial and increases the findings' internal validity. Internal validity means that the point estimate of the effect size of the intervention in comparison with the comparator(s) from that RCT is unbiased, but only for the actual participants in the RCT itself. No matter how well an RCT

Read more at:

- Promoting Both Internal and External Validity
- PRECIS-2 Case Study
- PCT Grand Rounds November 13, 2020

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Dr. Ahmed Al-Jaishi

EXPERIMENTAL DESIGNS AND RANDOMIZATION SCHEMES

SECTION 7

Covariate-Constrained Randomization

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SECTIONS

NIH 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
Journal canadien de la santé et de la maladie rénale

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

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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
Journal canadien de la santé et de la maladie rénale

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

DOI: 10.1177/20543581211041182
journals.sagepub.com/home/cjk
SAGE

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**

MyTEMP was possible because of the support of several agencies

CIHR IRSC
Canadian Institutes of Health Research
Instituts de recherche en santé du Canada

ONTARIO SPOR SUPPORT UNIT

Ontario Health
Ontario Renal Network

Heart&Stroke

Dialysis Clinic, Inc.
A Non-Profit Corporation

For more details, these presented results were published Nov 4, 2022 in

THE LANCET

I declare no conflicts of interest; declarations from other coauthors are in the publication

For each hemodialysis treatment we set the temperature of dialysate on the machine

photo by Anna Frodesiak/Wikimedia

typically done

standard temperature

36.5 ºC

or **37.0**

for all patients and all treatments in a centre

historical reason for this is unclear,
likely represents what was considered
the average body temperature of most patients

in a recent international survey of over 270 centres
nearly half now use

cooler temperature

dialysate in patient care

≤ 36.0 ºC

this change in practice is based on data which suggests

cooler (vs. standard) temperature dialysate is beneficial

↑ cardiac function
↑ peripheral vascular resistance

- SBP ↓ 20-30 mmHg in a HD session
- intradialytic hypotension is common

} physiologic benefits reported with ↓ in dialysate temperature as little as 0.3 ^{o}C

in small RCTs

- the drop in SBP was lessened by 10 mmHg
- ~ 70% ↓ in rate of intradialytic hypotension

2 cohort studies associated with
25% ↓ cardiovascular mortality

an RCT

↓ cardiac
↓ brain
injury seen on MRI

However, in **2 recent systematic reviews the overall quality of evidence for dialysate cooling was deemed to be low with a high risk of bias**

Ontario practice before MyTEMP

Standard temperature of dialysis fluids 36.5 ^{o} C

For the potential benefits, Directors of ≥ 8 centres, adopted a default centre-wide policy of **lower temperature dialysate**.

This was a fixed dialysate temp of 35.5^{o} C for all patients and all treatments.

As done in routine care, this change in default policy not discussed with patients (or approved by them)

- patients could discuss their dialysate temperature with their nephrologist, who could then make individualized changes.

We could have studied the association between lower temperature and outcome in a retrospective cohort study used deidentified data

- privacy compliant, requiring no research ethics board approval
- *concern*: 'residual confounding', unreliable estimates

photo aegismedicalcare.com

Medical directors establish centre-wide policies to deliver maintenance hemodialysis

Cooler dialysate can be **adopted** as

- a centre-wide policy *or*
- used in select patients such as those prone to intradialytic hypotension

Adopting cooler dialysate as a centre-wide policy (as done in some centres)

- allows for easier implementation
- has potential to benefit most patients, as intradialytic ↓ BP + CVD common
- is consistent with eligibility criteria of prior trials

Cooler dialysate can be **delivered** as

- a fixed temperature for a given hemodialysis treatment *or*
- as dynamically changing temperature through a treatment

but latter requires continuous blood temperature monitoring which is not available on many machines

A **drawback** of **cooler dialysate** fixed temperature for all patients (eg, 35·5°C)

shiver and feel uncomfortable cold

especially pre-dialysis body temperature is much higher than the set dialysate temperature

This seems to occur less often with a **personalised approach** to **cooling**,

dialysate temp for each treatment set **0.5 °C** below a patient's measured pre-dialysis body temperature (lowest setting 35.5 °C, highest 36.5 °C)

on this basis we did the

MyTEMP trial

to determine if

adopting a default centre-wide policy of

personalized cooler dialysate

superior

standard temperature dialysate 36.5 °C

↓ rate of CV related deaths or CV hospital admissions

↓ drop in SBP during hemodialysis

Is it well accepted by patients?

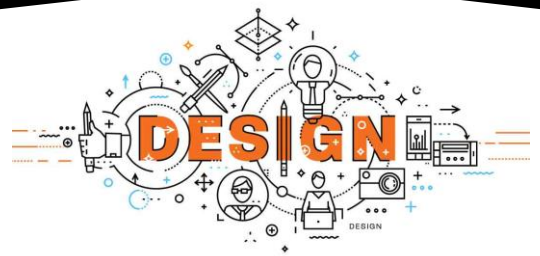
Intent: Influence the decision of what default centre-wide policy a dialysis director should use; where nephrologists / patients continue to have the option to individualize care

cluster RCT 84 HD centres in the province of Ontario, Canada

n=42

Personalized cooler dialysate

randomly allocated



n=42

Standard temperature dialysate

during 4 yr trial period there were

- ~8000 patients in dialysis treatments
- ~7400 patients in follow-up
- ~6% of patients received a kidney transplant, and
- ~8% transitioned to home dialysis

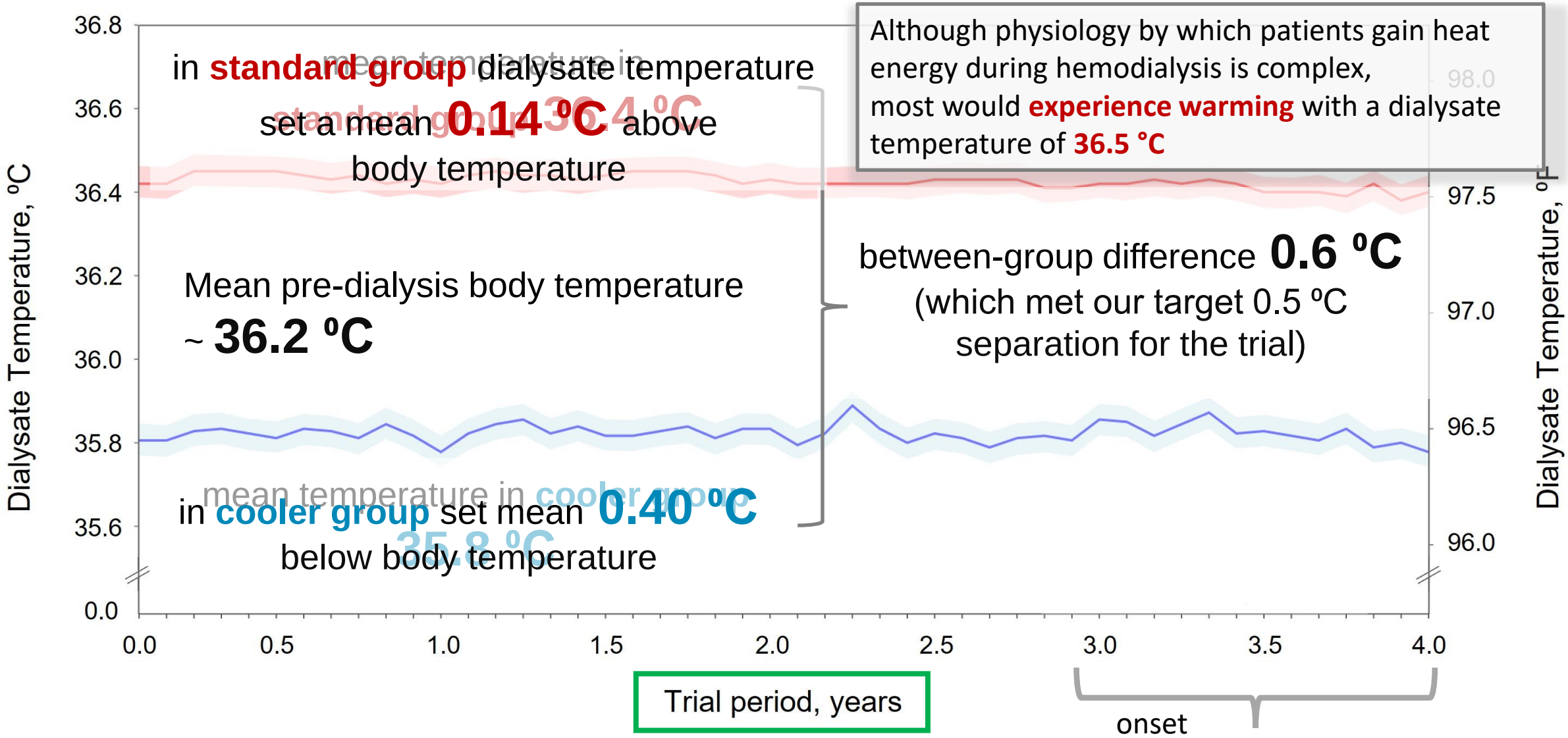
- ~implemented as part of learning healthcare system
- covariate constrained randomization
- registry-based (most baseline + outcome information came from existing databases)
- embedded in routine care
  - .. designed to have no research coordinators at the 84 centres
  - .. rather we trained over 2000 nurses to deliver personalized cooler dialysate
  - .. cluster design reduced risk of contamination bias
- approved to use opt-out consent (patients with ++ comorbidities were in trial)
- primary analysis used an intention to treat approach
- both the protocol and statistical analytic plan were published
- research was authored with patient partners
- generated high-quality information at fraction of cost of usual trial

The 2 groups were well balanced on baseline characteristics

Some Baseline Characteristics

	Personalized Cooler Dialysate	Standard Temp Dialysate
Mean age, years	66	66
> 80 years	18%	20%
nursing home	5%	5%
Women	39%	40%
Coronary artery disease (+ angina)	53%	54%
Diabetes	59%	59%
Major Cancer	17%	16%
Depression	11%	11%

Dialysate temperatures used in the 2 groups

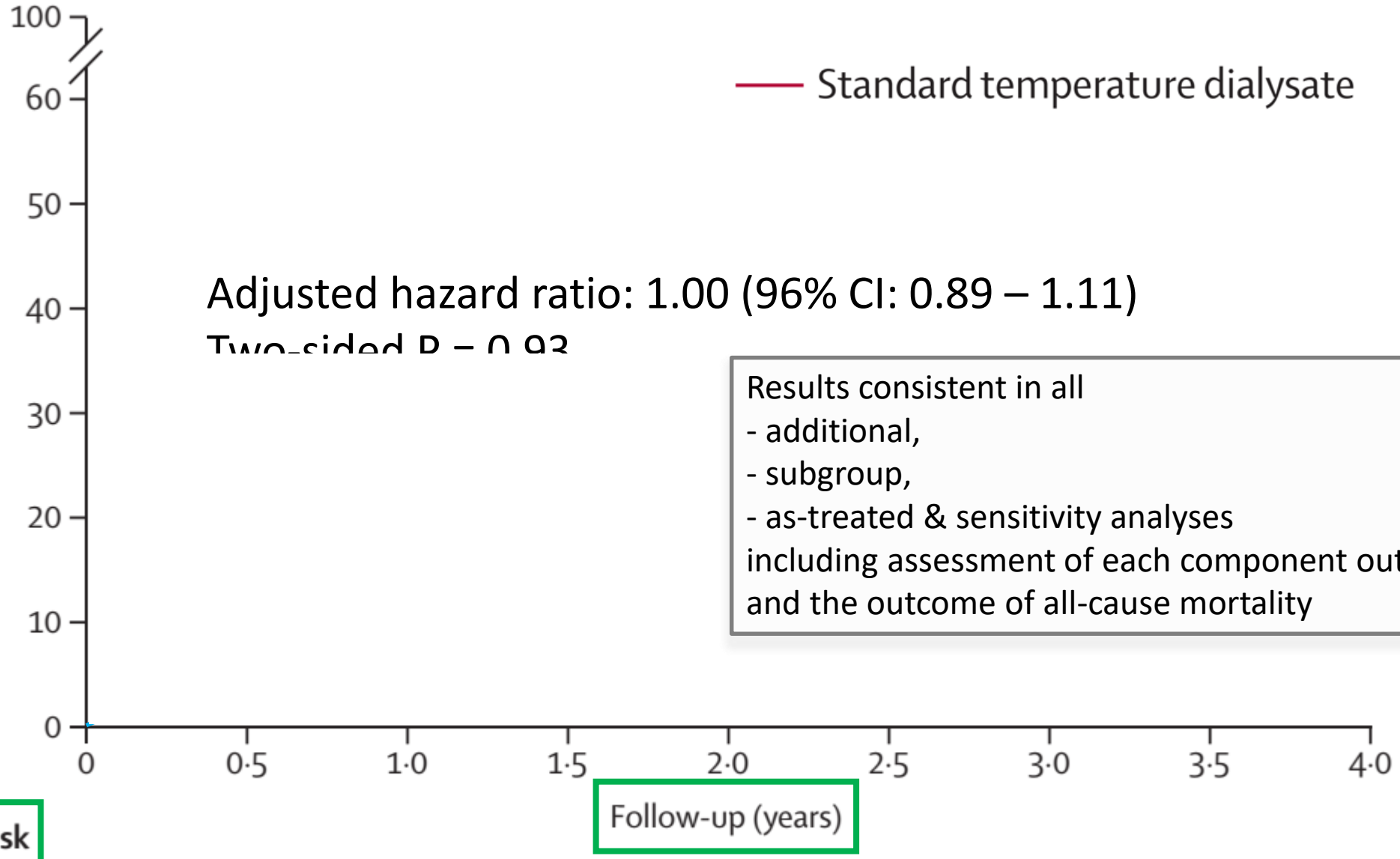


Main Results

Primary composite outcome

CV mortality or hospital admission with MI, stroke or heart failure

Cumulative Incidence Estimates of the Primary Outcome



Adjusted hazard ratio: 1.00 (96% CI: 0.89 – 1.11)

Two-sided P = 0.93

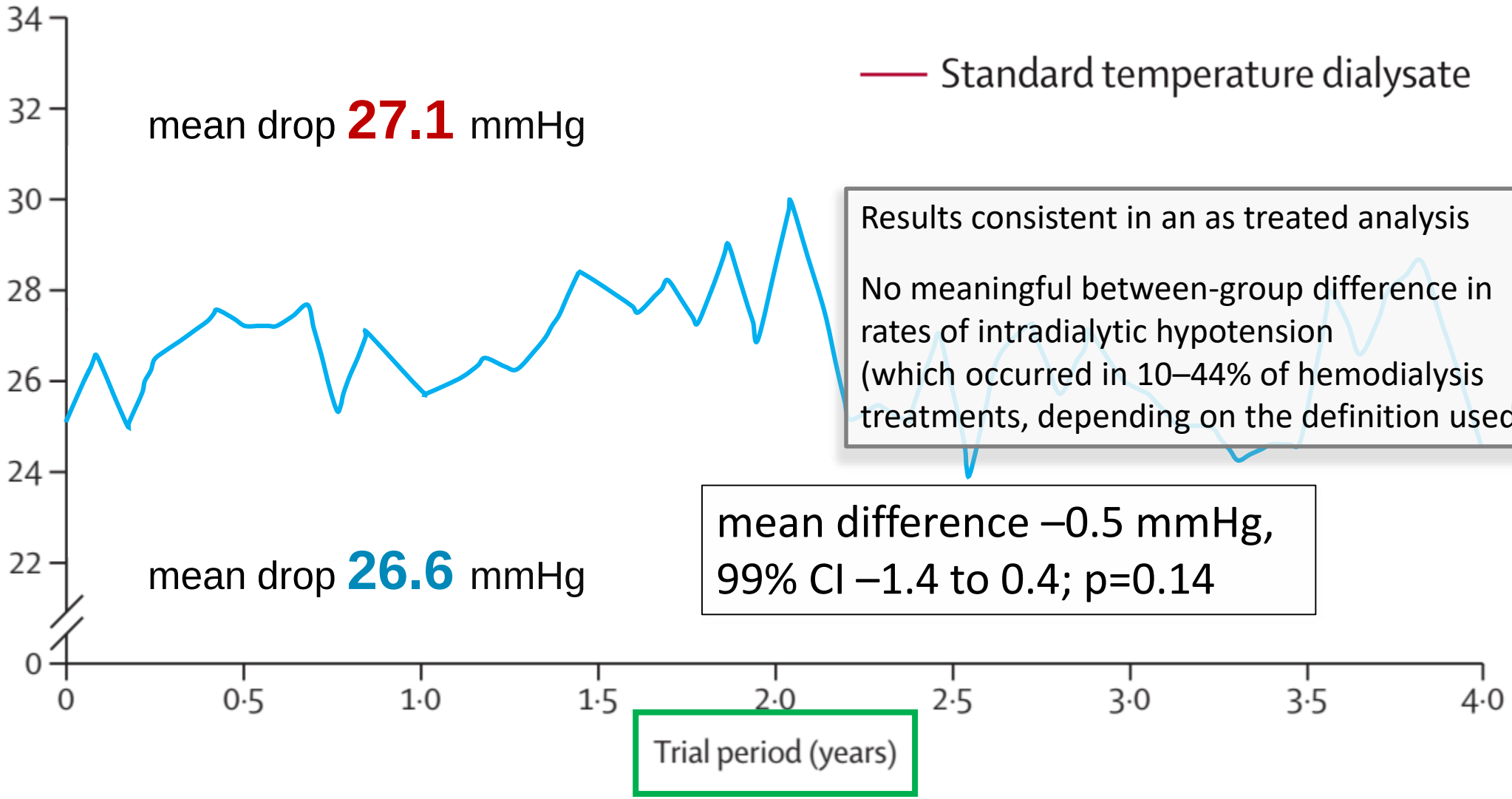
Results consistent in all
- additional,
- subgroup,
- as-treated & sensitivity analyses

including assessment of each component outcome, and the outcome of all-cause mortality

Number at risk
Personalised
Standard

Drop in intradialytic systolic blood pressure (SBP)

(predialysis SBP – nadir SBP during a hemodialysis treatment)



we examined self-reported symptoms in a cross-sectional survey in 10 centres

Patients were asked how much "a feeling of being cold on dialysis" bothered them in the <u>past week</u>

	Not at all	0	1 2	3 4	5 6	7 8	9 10	Worst possible feeling
standard temperature		21%	17%	15%	18%	23%	6%	
personalized cooling		13%	9%	10%	22%	21%	26%	

patients were **more likely** to report feeling **uncomfortably cold on dialysis**

Main Implications of MyTEMP

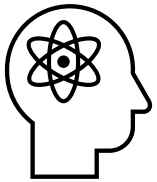
for **Medical directors**

- a lack of cardiovascular benefit
- compounded by the likelihood of patient discomfort

provides **no justification to adopt cooler dialysate** as a center-wide policy vs use of 36.5^{o}

for **Nephrologists** such as myself who currently use **cooler dialysate** in individualized patient care

- the MyTEMP results provide an opportunity to reflect on practice
- if I do prescribe cooler dialysate for certain patients such as those with refractory intra-dialytic hypotension, I plan to do so more carefully, and monitor how well it is tolerated
- I would be more confident about its use in such patients if future well-conducted multi-centre trials with restricted eligibility show the benefits outweigh the risks



for **Researchers**

- the experience we developed with innovative design elements in MyTEMP may help streamline future large trials testing interventions to improve kidney care

Practice in Ontario <u>after</u> MyTEMP

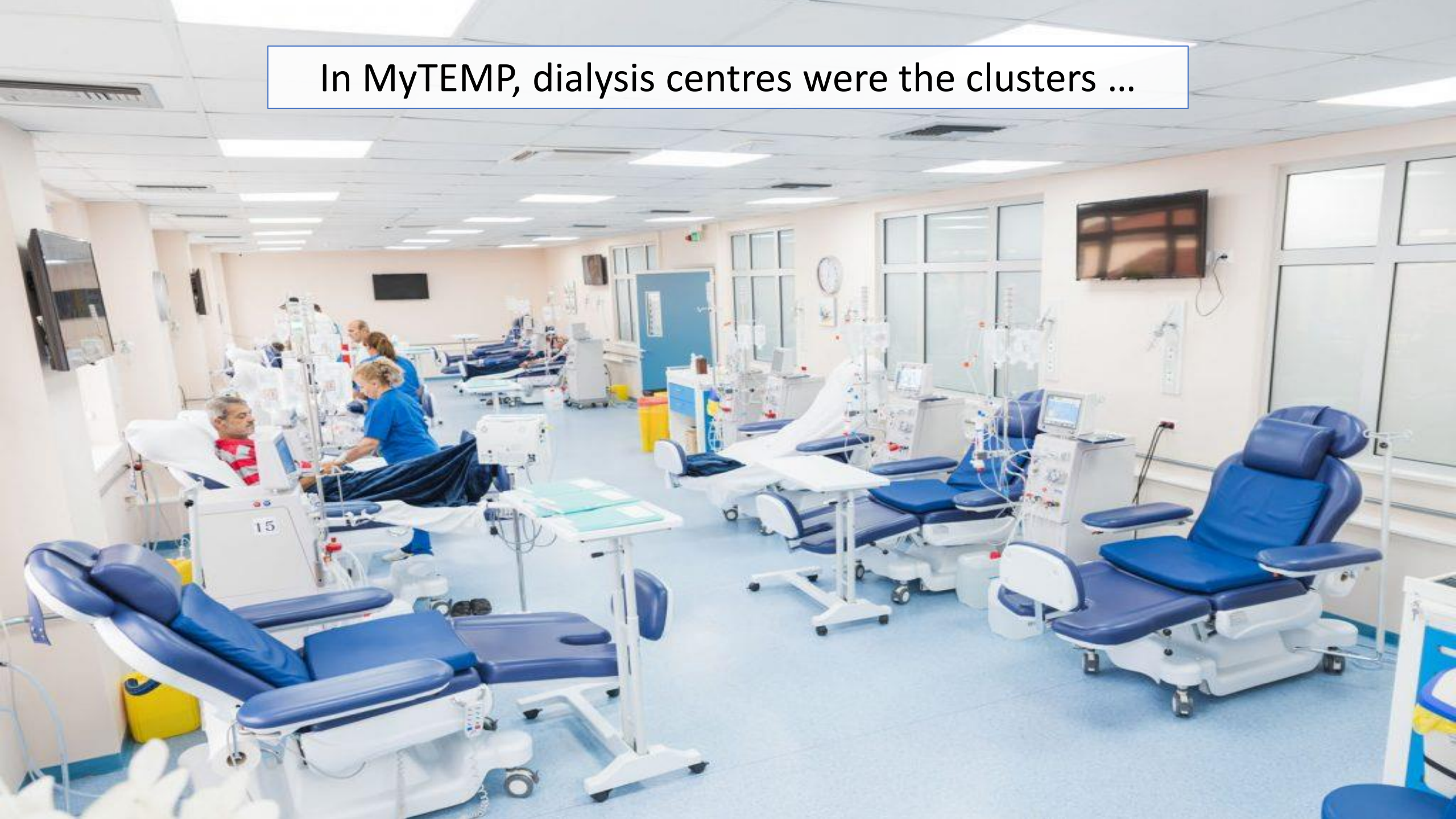
No more centres adopted colder temperature dialysate as a centre-wide policy.

Centres returned to using a standard dialysate temperature of 36.5 ^{o} C as their centre-wide policy.

Resulted in patients having less discomfort from hemodialysis.

- ethics
- statistics

In MyTEMP, dialysis centres were the clusters …



Motivations of a clinician researcher

(hemodialysis director, in practice for 20 years)

Cluster RCTs of hemodialysis centre-wide policies raise complex ethical issues

Recognize many patients who receive hemodialysis are vulnerable
… privilege and responsibility to provide care
… desire to be transparent, accountable, and maintain trust in my research activities

Committed to making dialysis better:
… where I know best components of dialysis for best patient outcomes,
… for all patients who receive dialysis (not just a subset who are healthier),
… it is not in the best interest of patient care that over
90% of our decisions in hemodialysis care lack a reliable evidence base,
in large part because of large cost and difficulties conducting trials in the traditional way.
… do patients expect/demand the health care system is iterating to improve (learning system)?

No commercial interest

COI: want to recognized for contributions (fame; more research funding)

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

Dialysis director (healthcare provider) needed to provide consent for MyTEMP participation (84 centres)

Patients notified about MyTEMP through

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

A patient or their nephrologist could decide to <u>opt-out</u> of the randomly allocated centre-wide default policy

(+ opt out of symptom data
but not de-identified health records)

No documentation of consent to trial participation

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 Proceeds Collection of Research Data

"Responsible"
balancing what is
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 process

REB approved our request for MyTEMP to use an altered patient consent process

(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 participants choice to refuse consent and/or withdraw data

Judgement call

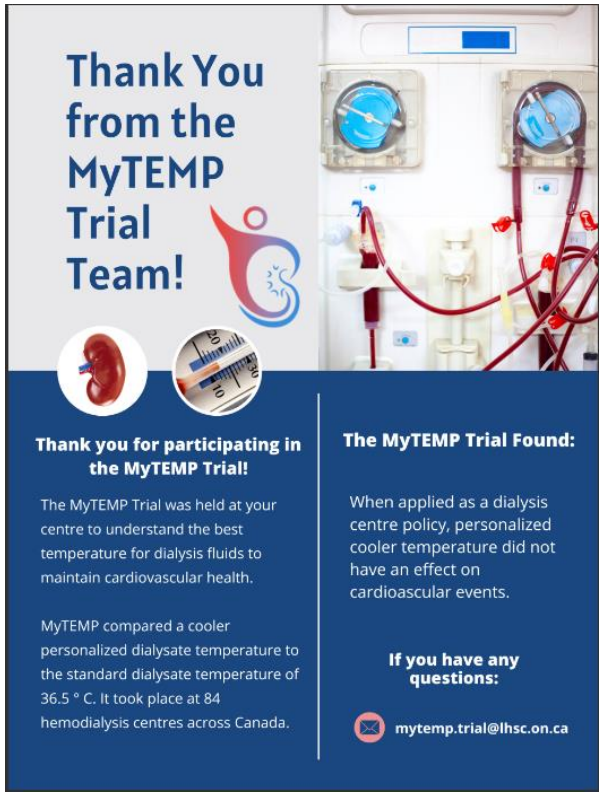
Patient and caregiver involvement in a multicentre clustered hemodialysis trial

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 guided choice of additional of outcomes
  - resulted in updates to the trial information letter
- Symptom substudy developed with patient partners
  - A patient partner featured in the introductory video explaining study
- Indigenous consultation

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

After trial debrief



- Inform (respect for persons), allow choice (opt out; respects autonomy)
- *Balance*: expend certain amount of research resources, to provide a responsible level of notification, which results in reasonable level of patient awareness and 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 (relied on local staff to engage ± substitute decision makers, ± verbally explain)
- Patient and/or their nephrologist aware of allocation, could talk to patients and change it if they wanted to do so (opt out)
- Patients could opt out of symptom data collection, but not de-identified provincial administrative 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.

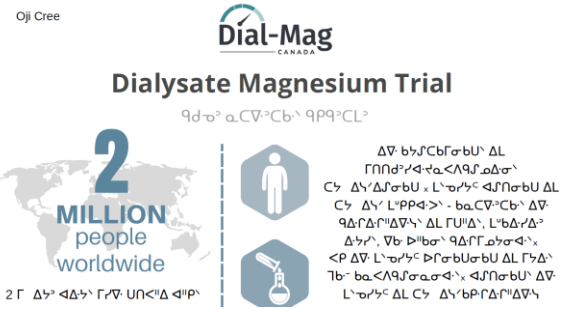
To learn more about the trial, please ask your healthcare team for a patient information handout.

We learned and improved patient notifications in Dial Mag Canada

- ~ 25,000 patients in the trial, 137 clusters in 4 provinces (approved by all centre dialysis directors and nephrologists)
- Letters of information q 6 months
  - + monitor dialysis centers (desk clerk) to confirm handed out
  - q 6 month reminder about trial with muscle cramp collection
- Letters in 19 languages (including Oji Cree)
- Still trusting dialysis centers to communicate info to patients

  ± substitute decision-maker;

  ± verbal explanations if cannot read letters
- *Balance*:
  - Amount of effort to make patients aware of trial
  - What information would patients want to know
  - logistics / cost + certainty info seen + understood



(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)
- it does not mean the intervention is minimal risk
  - *all* interventions have some risk
  - some risks *unknown* until trial is completed

(Scenario) **What if**?

- lower vs. usual dialysate temperature reduced risk of CV events
- before MyTEMP: my father was receiving dialysis in a lower temperature centre
- during MyTEMP: his centre was allocated to receive usual temperature dialysis,
  his care was switched,
  he suffered a heart attack during the trial period

Knowing causes of heart attacks are complex,
would I feel trial team acted 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!

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

Photo from www.blueridgejournal.com/

In Ontario setting, trial would not have been done without REB approval for consent process used

In terms of societal benefit
- trial resulted in trusted evidence that influenced practice

REB approval of altered consent process made MyTEMP feasible

- embedded into routine care
- *designed*: no research coordinators at dialysis centers

  to obtain consent, deliver treatment, or collect data
- routine dialysis nursing staff delivered intervention

  .. trained to deliver intervention; center standard operating procedure

  .. became routine practice, was part of orientation
- ~ 99% of info came from de-identified databases
- data safety and monitoring board met 5 times
- **cost $ 2 – 2.5 million**

  … vs. traditional trial ~ $ 10 - $15 million
- design aligned with intent to answer question

  "what is the best default centre-wide policy to use"
- included all patients who received dialysis in routine care

  … to generate results meaningful for all
- full participation of community sites (who have no coordinators)
- trial was completed as planned ('more predictable')

- ethics
- statistics

Dr. Steph Dixon

On behalf of the investigators

MyTEMP

Thank you for listening

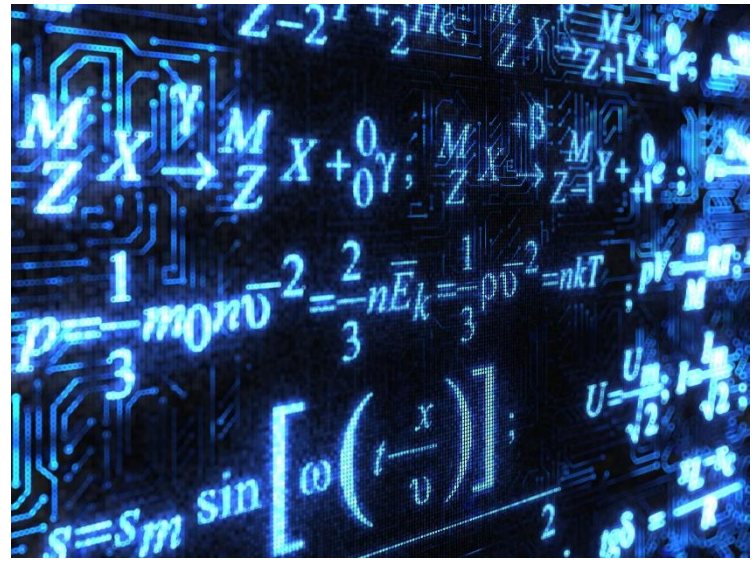
Methods

› Can J Kidney Health Dis. 2021 Aug 27;8:20543581211041182. doi: 10.1177/20543581211041182. eCollection 2021.

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

Stephanie N Dixon [1 2 3], Jessica M Sontrop [1 3], Ahmed Al-Jaishi [1 2 4], Lauren Killin [1 2], Christopher W McIntyre [1 3 5], Sierra Anderson [1], Amit Bagga [6], Derek Benjamin [7], Peter Blake [1 3 5], P J Devereaux [4], Eduard Iliescu [8], Arsh Jain [2 3 5], Charmaine E Lok [9], Gihad Nesrallah [10 11], Matthew J Oliver [10 12], Sanjay Pandeya [13], Manish M Sood [2 14 15], Paul Tam [16], Ron Wald [2 10 17], Michael Walsh [4 18], Merrick Zwarenstein [2 3], Amit X Garg [2 3 4 5]
On behalf of the MyTEMP investigators

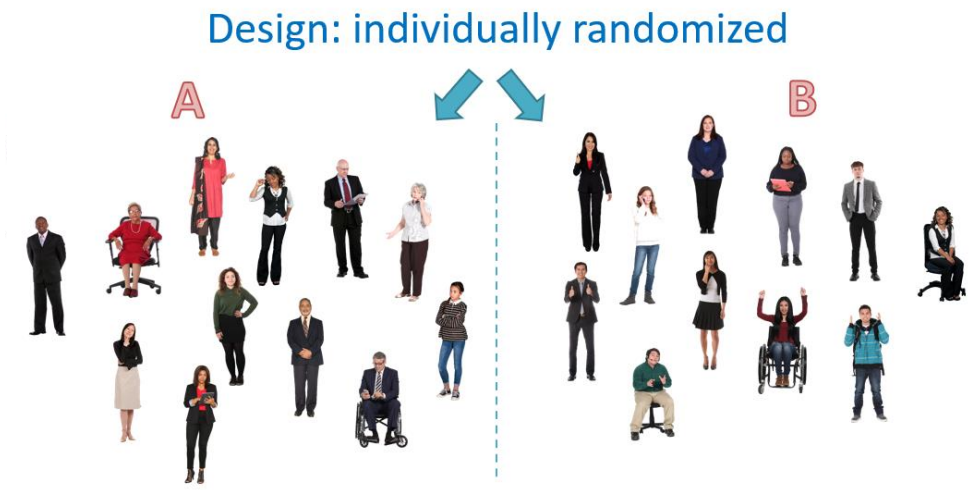
Considerations

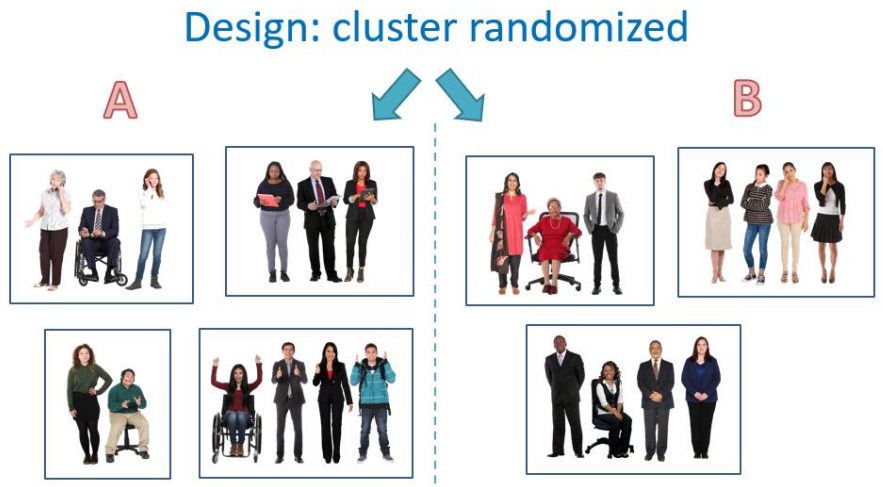


- Design:
  - Cluster-Randomized Trial
  - Covariate-constraint randomization
- Objective: to examine the effect of the intervention on
  1. a composite outcome of cardiovascular-related death or major cardiovascular-related hospitalization
  2. the mean drop in intradialytic systolic blood pressure
- Type of outcome & data collection
- Interpretation

Design considerations

- Cluster randomized trials:





  - Correlation of outcomes within clusters
  - Varying cluster sizes
  - Effective sample size
  - Statistical efficient designs (i.e., matching, stratification, constraining)

Design considerations

- Covariate constrained randomization:
  - Select important prognostic characteristics
  - Increase chance of balancing on cluster- and individual-level characteristics
  - Can offer gain in power

› Trials. 2021 Sep 15;22(1):626. doi: 10.1186/s13063-021-05590-1.

Simple compared to covariate-constrained randomization methods in balancing baseline characteristics: a case study of randomly allocating 72 hemodialysis centers in a cluster trial

Ahmed A Al-Jaishi [1 2 3], Stephanie N Dixon [4 5 6 7], Eric McArthur [5], P J Devereaux [8], Lehana Thabane [8], Amit X Garg [4 8 5 6]

› BMC Med Res Methodol. 2022 Apr 13;22(1):111. doi: 10.1186/s12874-022-01588-8.

Mind the gap: covariate constrained randomisation can protect against substantial power loss in parallel cluster randomised trials

Caroline Kristunas [1 2], Michael Grayling [3], Laura J Gray [4], Karla Hemming [5]

Design considerations

- Understanding clusters
  - Impact of variable cluster sizes at design and analysis

> Int J Epidemiol. 2006 Oct;35(5):1292-300. doi: 10.1093/ije/dyl129. Epub 2006 Aug 30.

Sample size for cluster randomized trials: effect of coefficient of variation of cluster size and analysis method

Sandra M Eldridge [1], Deborah Ashby, Sally Kerry

  - Small number of clusters
    - Adjustments depending on the model when < 40 clusters in trial

> Int J Epidemiol. 2018 Jun 1;47(3):1012. doi: 10.1093/ije/dyy057.

Cluster randomized trials with a small number of clusters: which analyses should be used?

Clémence Leyrat, Katy E Morgan, Baptiste Leurent, Brennan C Kahan

Design considerations

- Interpretation
  - Target treatment effects
    - Participant-average
    - Cluster-average
  - Informative cluster sizes
    - Outcomes differ
    - Treatment effect differs

Int J Epidemiol. 2023 Feb 8;52(1):107-118. doi: 10.1093/ije/dyac131.

Estimands in cluster-randomized trials: choosing analyses that answer the right question

Brennan C Kahan [1], Fan Li [2 3], Andrew J Copas [1], Michael O Harhay [4 5]

Comment Int J Epidemiol. 2023 Feb 8;52(1):116-118. doi: 10.1093/ije/dyac174.

Commentary: Estimands in cluster trials: thinking carefully about the target of inferenceand the consequences for analysis choice

Karla Hemming [1], Monica Taljaard [2 3]

https://rethinkingclinicaltrials.org/news/grand-rounds-march-10-2023-estimands-in-cluster-randomized-trials-choosing-analyses-that-answer-the-right-question-brennan-kahan-phd/

Primary Analysis

- By Design, we need to account for:
  - Correlation of outcomes in dialysis centres (the “clusters”)
  - Variables used in the constrained randomization
- Intention-to-treat approach: analyzed according to index center’s intervention allocation
- Cohort, characteristics, outcomes and censoring events through ICES
  - Outcome: is a composite of cardiovascular-related death or hospital admission with myocardial infarction, congestive heart failure, or ischemic stroke
  - What about non-cardiovascular death?
- Follow up until outcome, emigration, non-cardiovascular death, maximum follow-up date

Primary Analysis

- High rate of non-cardiovascular death
  - Individual-level multivariable GEE extension for the Fine and Grey's sub-distribution proportional hazards
  - supplement with the cause-specific hazard model

› Stat Med. 2017 Nov 30;36(27):4391-4400. doi: 10.1002/sim.7501. Epub 2017 Sep 15.

Practical recommendations for reporting Fine–Gray model analyses for competing risk data

Peter C Austin [1 2 3], Jason P Fine [4 5]

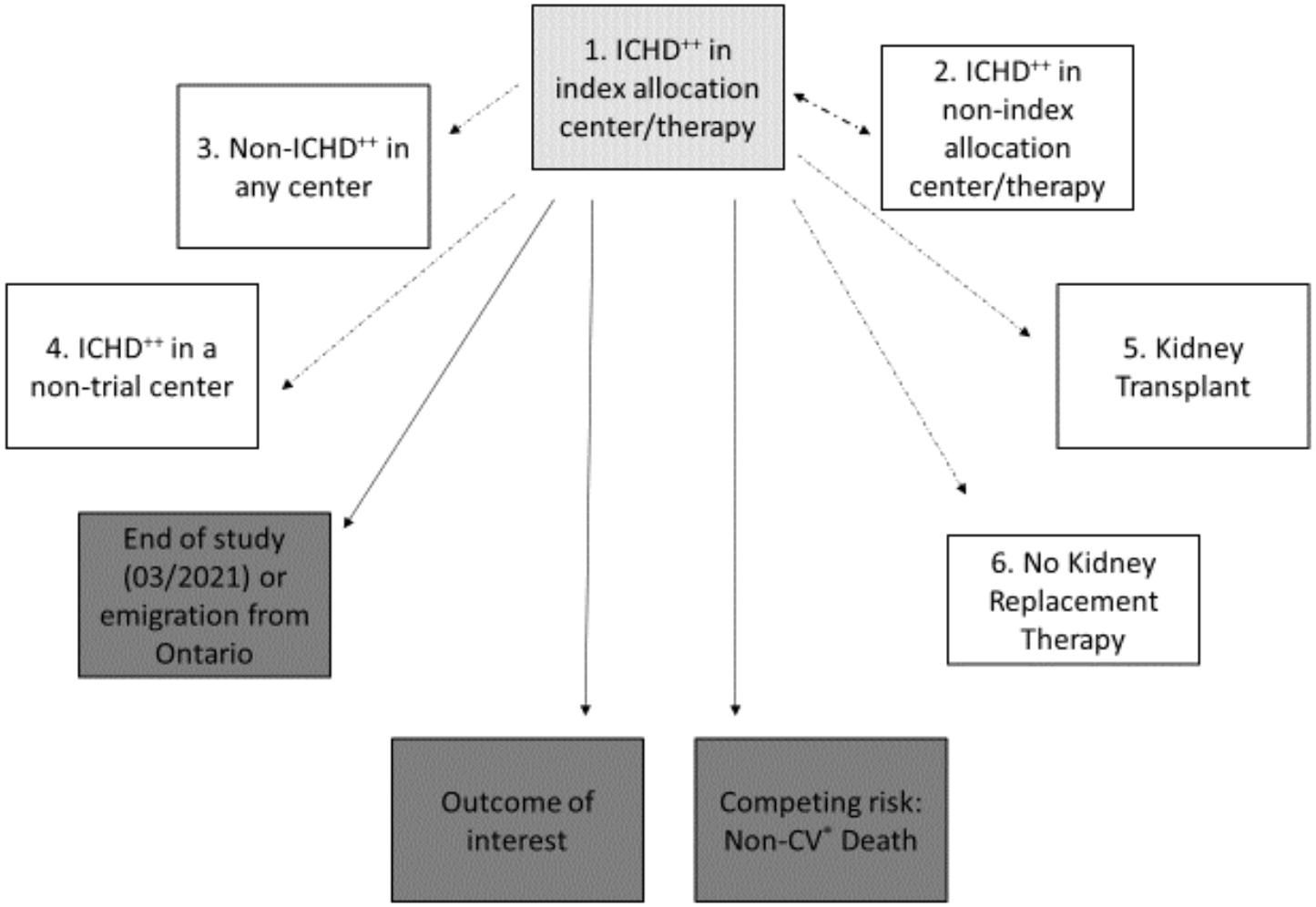
Review › Stat Med. 2017 Apr 15;36(8):1203-1209. doi: 10.1002/sim.7215. Epub 2017 Jan 19.

Accounting for competing risks in randomized controlled trials: a review and recommendations for improvement

Peter C Austin [1 2 3], Jason P Fine [4 5]

Robust findings

- Descriptively & visually
- Components of the composite
- Additional outcomes
- Additional analyses
  - As-treated
  - Unadjusted
  - Additional competing risk and censoring events
  - Recurrent event
  - Subgroups



Reporting

CONSORT TRANSPARENT REPORTING of TRIALS

http://www.consort-statement.org/extensions

Guideline > PLoS Med. 2012;9(11):e1001346. doi: 10.1371/journal.pmed.1001346. Epub 2012 Nov 20.

The Ottawa Statement on the Ethical Design and Conduct of Cluster Randomized Trials

Charles Weijer [1], Jeremy M Grimshaw, Martin P Eccles, Andrew D McRae, Angela White, Jamie C Brehaut, Monica Taljaard, Ottawa Ethics of Cluster Randomized Trials Consensus Group

Cochrane Methods Bias

Trusted evidence.
Informed decisions.
Better health.

https://methods.cochrane.org/bias/resources/rob-2-revised-cochrane-risk-bias-tool-randomized-trials

Guideline > BMJ. 2012 Sep 4;345:e5661. doi: 10.1136/bmj.e5661.

Consort 2010 statement: extension to cluster randomised trials

> Res Integr Peer Rev. 2018 Oct 29;3:9. doi: 10.1186/s41073-018-0053-3. eCollection 2018.

Protocol for the development of a CONSORT extension for RCTs using cohorts and routinely collected health data

> BMJ. 2008 Nov 11;337:a2390. doi: 10.1136/bmj.a2390.

Improving the reporting of pragmatic trials: an extension of the CONSORT statement

On behalf of the investigators

MyTEMP

Thank you for listening