Pragmatic Trials

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Commercial interests: None

Conflicts of interest: None

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IC/ES Western

Learning Objectives

- **Recognize** two intentions for RCT
  - Pragmatic: provide evidence for decision-makers to choose between interventions
  - Explanatory: test a hypothesis about mechanism
- **Design** the characteristics of their trial to match their intention, using PRECIS-2 tool
- **Apply** these insights to the opportunities and constraints that a renal dialysis setting offers, and design a pragmatic cluster RCT

Strength of RCT design:

Internal validity

Bothwell LE, Greene JA, Podolsky SH, Jones DS. Assessing the Gold Standard--Lessons from the History of RCTs. N Engl J Med. 2016 Jun 2;374(22):2175-81. doi: 10.1056/NEJMms1604593. PMID: 27248626.

Internal validity:
Valid measurement of effect size among trial participants, in trial setting only

Randomization: tends to equalize distribution between trial arms

- **confounders** (known and unknown)
- of **non-specific causes** (e.g. regression to mean)
- leaving only the **treatment effect or chance**

Face validity
Simple analysis, intuitive understanding

Traditional RCT design choices undermine external validity

1. **Particular patients, providers, sites**
2. **Changed care delivery**
3. **Irrelevant outcomes**
4. **Confusing comparators**

Traditional RCT design choices undermine external validity

1. Particular patients, providers, site

- Patients more severe, no comorbidity narrow age range, good adherers
- Trial sites or clinicians with more experience, better outcomes

2. Distorted care

3. Irrelevant outcomes

4. Confusing comparators

Traditional RCT design choices undermine external validity

Kennedy-Martin *et al. Trials* (2015) 16:495
DOI 10.1186/s13063-015-1023-4

TRIALS

REVIEW Open Access

CrossMark

A literature review on the representativeness of randomized controlled trial samples and implications for the external validity of trial results

Tessa Kennedy-Martin[1*], Sarah Curtis[2], Douglas Faries[2], Susan Robinson[1] and Joseph Johnston[2]

The participants in 71% of RCTs are different in important ways from the patients in the setting in which that treatment would be used once approved.

Traditional RCT design choices undermine external validity

1. Selected patients, clinicians, sites

2. Distortion of care

- Extra intervention, investigation
- Protocols for treatment
- Monitor, remind, enforce adherence
- Intensive, intrusive data collection

3. Distracting outcomes

4. Confusing comparators

Traditional RCT design choices undermine external validity

1. **Selected patients, clinicians, sites**
2. **Distorted care processes**
3. **Irrelevant outcomes**
   - Outcomes short term
   - Not patient-centred
4. **Confusing comparators**

Traditional RCT design choices undermine external validity

1. **Selected patients, clinicians, sites**
2. **Distorted care processes**
3. **Distracting outcomes**

4. **Confusing comparators**

- Compare to low dose, old drug
- Compare to placebo

What is the relationship between Internal and External Validity?

Is it a zero-sum game?

Increase in external validity reduces internal validity

OR

Are they independent?

Increase in external validity has no impact on internal validity

Originally published in English as :

Pragmatic and Explanatory attitudes in Therapeutical Trials .
Schwartz D, Lellouch
Journal of Chronic Diseases, 1967.

Reprinted in facsimile form :

Explanatory and pragmatic attitudes in therapeutical trials
Schwartz D, Lellouch J. J Clin Epi. 2009;62(5):499-505

(successor journal to Journal of Chronic Disease,

EXPLANATORY AND PRAGMATIC ATTITUDES IN THERAPEUTICAL TRIALS

DANIEL SCHWARTZ and JOSEPH LELLOUCH

Unité de Recherches Statistiques, Institut National de la Santé et de la Recherche Medicale, 94 Villejuif, France

(*Received* 6 *January* 1967; *in revised form* 24 *March* 1967)

"It is the thesis of this paper that most trials are inadequately formulated. Their inadequacy is basic, in that trials may be aimed at the solution of one or other of two radically different kinds of problem."

Explanatory vs Pragmatic Approach

Different purpose requires different design choices

Pragmatic attitude

Intention: To help decision makers choose between interventions

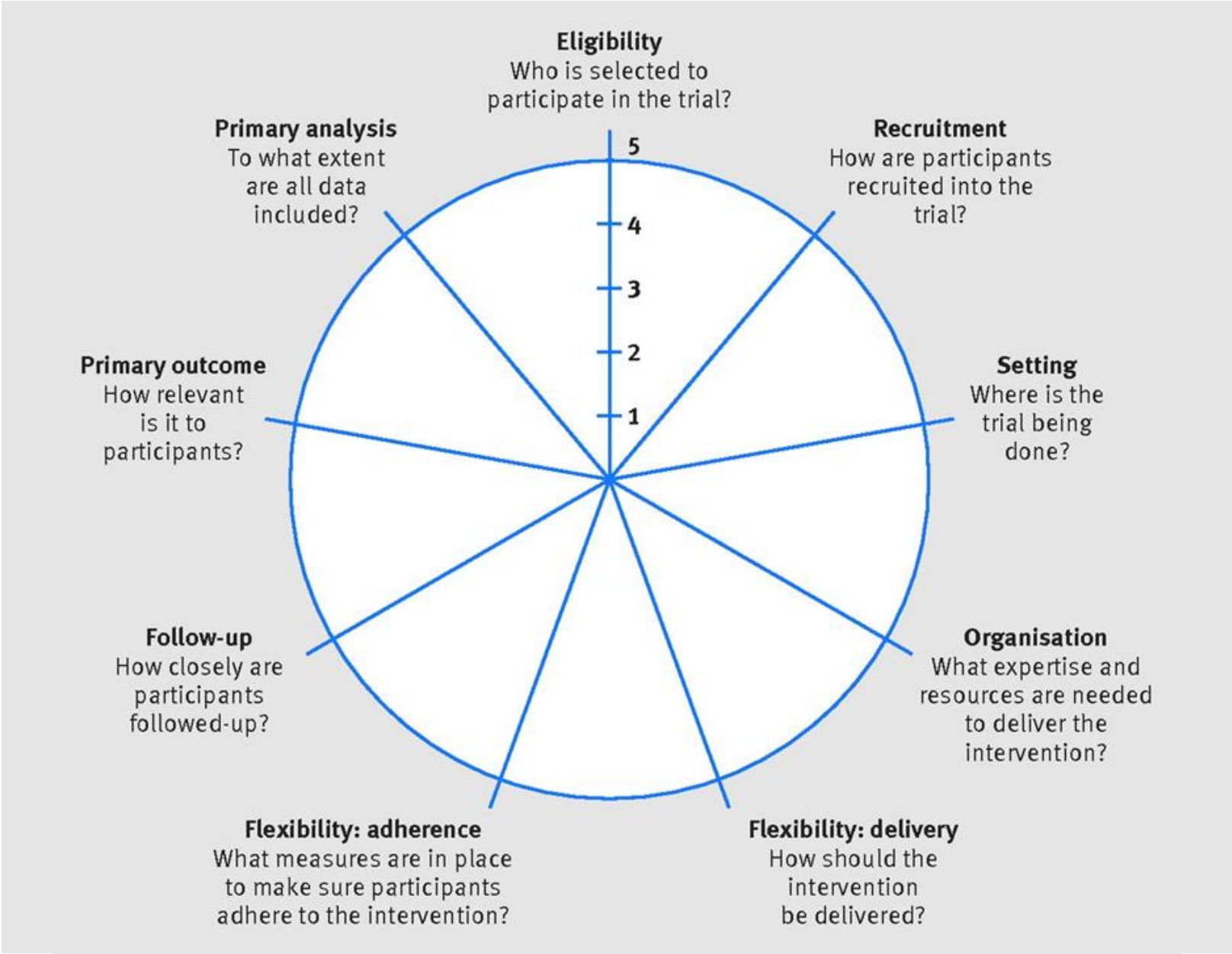
Explanatory attitude

Intention: To test a hypothesis that a specific causal mechanism is activated by a treatment

PRECIS-2 tool

1. Define intention
2. Align design to intention
3. Plot on wheel
4. Reiterate

Loudon K. Treweek S, Sullivan P, Donnan P, Thorpe KE, Zwarenstein M. The PRECIS-2 tool: Designing trials that are fit for purpose. BMJ 2015;350:h214
Download PRECIS-2 toolkit for designing or assessing pRCT
PRECIS-2 Website: www.PRECIS-2.org



PRECIS-2

1. Eligibility

Eligibility: To what extent are the participants in the trial like those who would receive this intervention if it was part of usual care?

Score 1 for a very explanatory approach with lots of exclusions (e.g., non-compliers, non-responders, at low risk for primary outcome, children, elderly, or defines patients using diagnostic tests not used in usual care.)

Score 5 for very pragmatic criteria essentially identical to those in usual care;

PRECIS-2

2. Recruitment

Recruitment: How much extra effort is made to recruit participants over and above what would be used in the usual care setting to engage with patients?

PRECIS-2

3. Setting
4. Organization

Setting: How different are the settings of the trial from the anticipated usual care setting?

Organization: How different are the resources, provider expertise and the organization of care delivery in the trial and those available in the anticipated usual care situation? Are extra resources added?

PRECIS-2

5.Delivery
6.Adherence
7.Data collection

Flexibility (delivery): How different is trial flexibility of delivery from flexibility anticipated in future usual care?

Flexibility (adherence): How different is trial flexibility in monitoring or encouraging adherence from the flexibility anticipated in usual care?

Follow-up: How intrusive is measurement and follow-up of participants in trial vs anticipated follow-up in usual care?

PRECIS-2

8. Primary Outcome
9. Primary Analysis

Primary outcome: To what extent is the trial's primary outcome directly relevant to participants?

Primary analysis: To what extent are all data included in the analysis of the primary outcome?

PRECIS-2

Possible new domain for Comparator

Possible other changes

Pragmatic :

Novel intervention vs No Treatment

Proven intervention vs Usual care

Proven interventions to each-other

Explanatory :

Placebo with blinding

Standard of care comparator

Protocolized care

Current usage of “Pragmatic”

Researchers:
-use “pragmatic” rhetorically
-substantively more inclusive of patients
-longstanding trend towards ITT

Funders: NIH, PCORI
-Administrative, EMR data
-Characterized, protocolized comparator
-Active comparator for CER
-Patient engagement in design

Summary

Choose an intention explicitly

Match design to intention
-Which intervention do we prefer?
-Does this mechanism exist?

Pragmatic and Explanatory trials are not a dichotomy

No tradeoff between internal validity and external validity

Pragmatic characteristics make trial easier for patients, clinicians, researchers and users of the findings

Example of Explanatory vs Pragmatic Trial

Two RCTs of Temperature in Dialysis

-Individual RCT

-MyTEMP Study

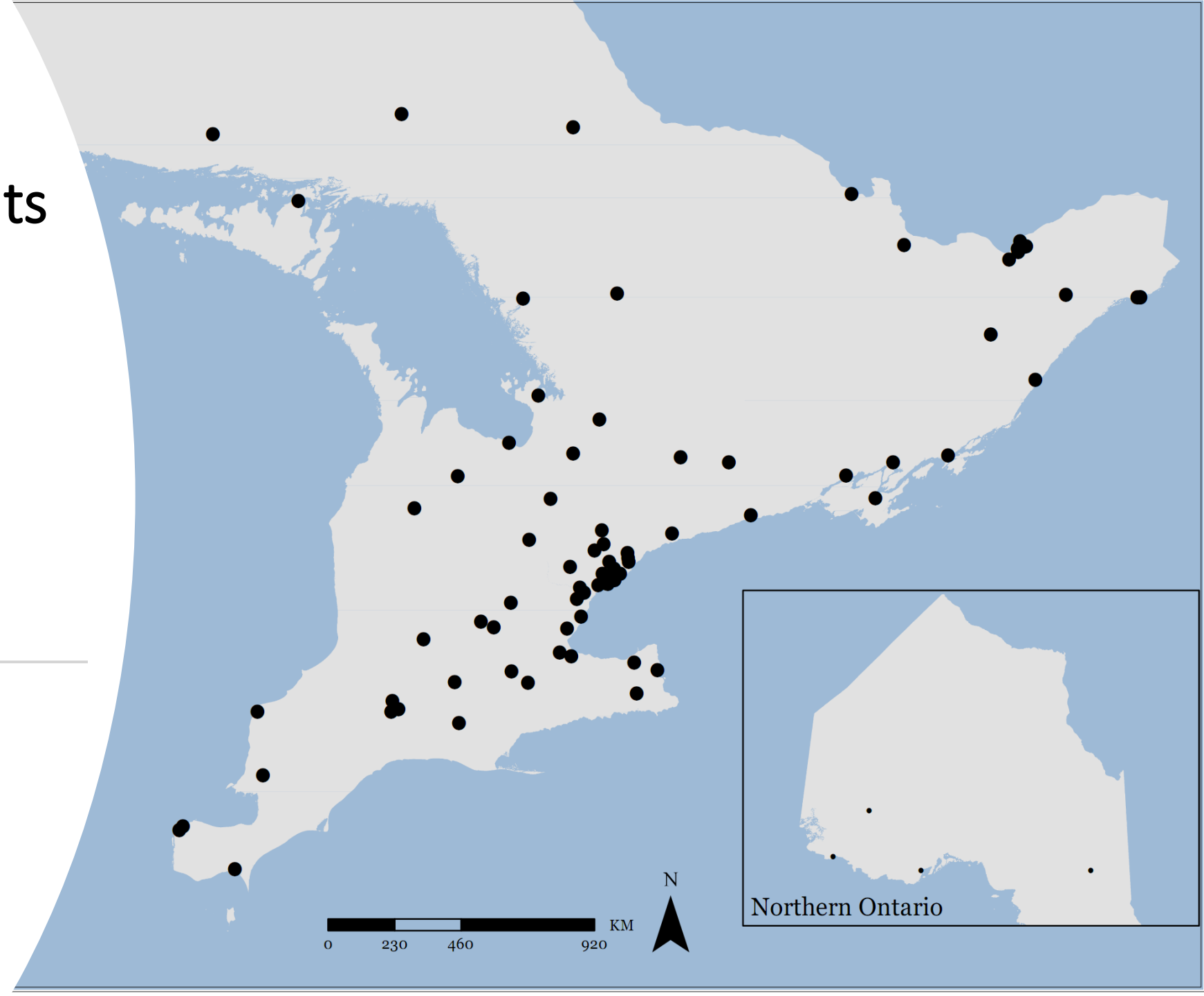
Different intentions,
design choices,
conclusions, recommendations
lead to different **usefulness for decision-making**

~ 2 million people worldwide receive ongoing hemodialysis treatments to live

84 hemodialysis units in Ontario

~8000 patients

~ 90 pts per unit



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

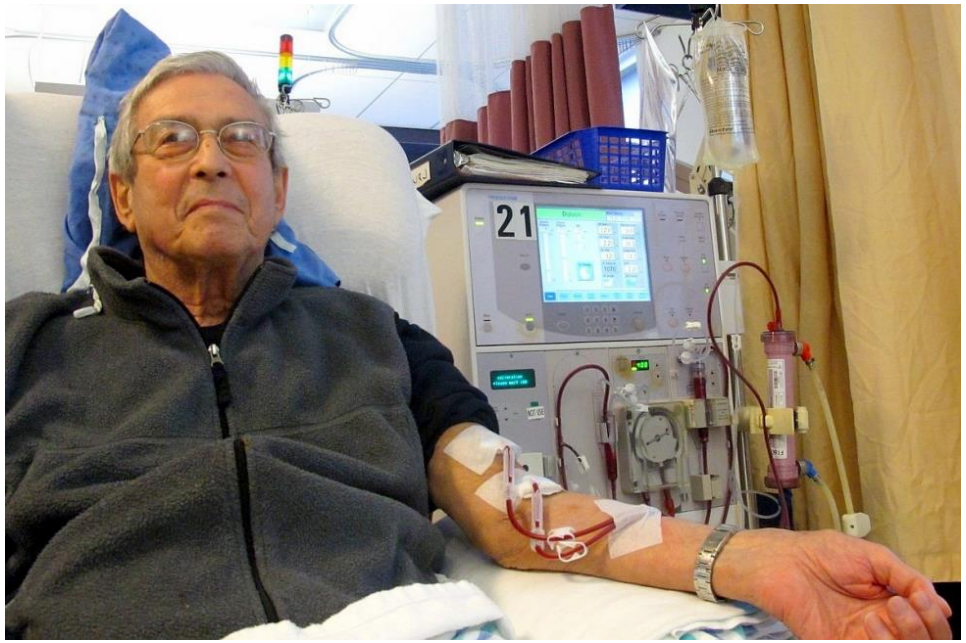


Photo by Anna Frodesiak/Wikimedia

usual temp

36.5 ° C

(97.7 ° F)

alternative approach

personalized temperature

(0.5 to 0.9°C ↓)

A lower (vs. usual) dialysis temp beneficial in 10+ small RCTs

Less brain and heart injury seen on MRI *(McIntyre)*

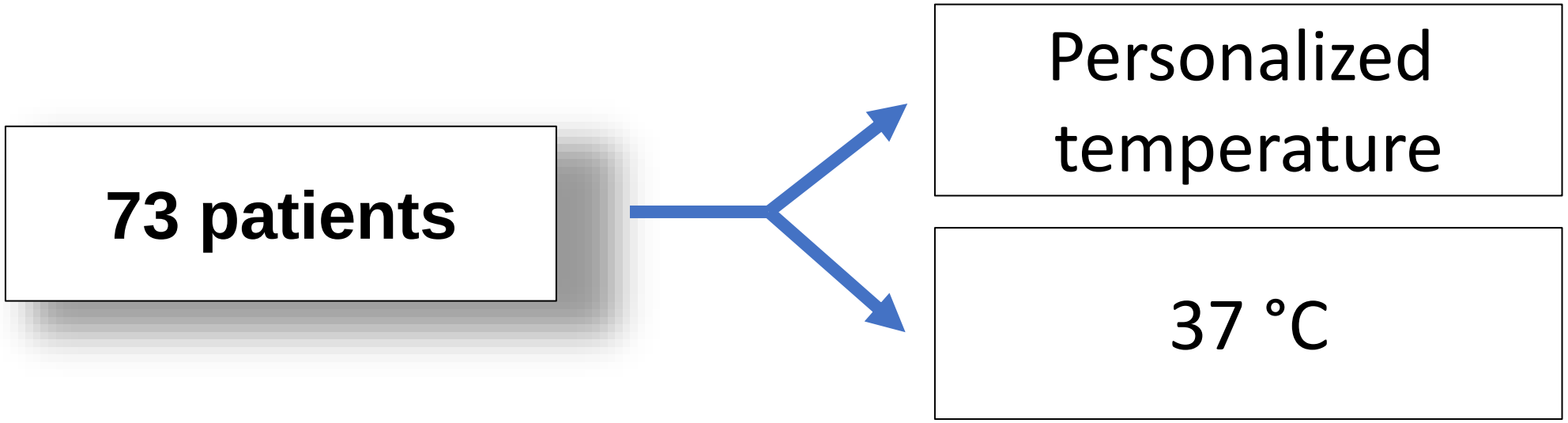
Less hypotension on hemodialysis *(↓ 70%)*

Less debilitating symptoms (fatigue, pain, dizziness)

***Potential* to ↑ survival and ↓ CV events**
(associated with ↑ survival in a cohort study)

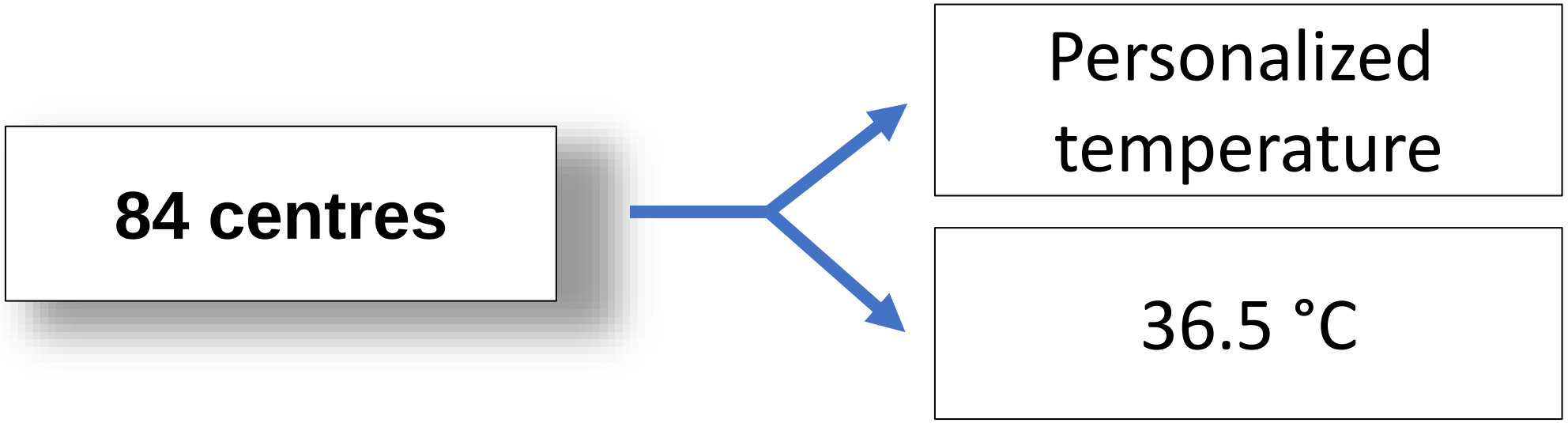
Individualized dialysis temp is well tolerated
No new cost to giving ↓ temp dialysis
May lower healthcare costs
Easy to apply worldwide

Individual-level RCT



- Patients from Nottingham UK enrolled into the trial from September 2009 and January 2013
- patients were followed for 1 year
- ~ 11,000 hemodialysis sessions in the trial
- Individual-level consent
- Trial-specific data collection
- Primary outcome was the change in the resting EF by CMR at 12 months compared with baseline
- Cardiac structure, function, and aortic distensibility were assessed by cardiac magnetic resonance imaging

MyTEMP Cluster RCT



- Centres from Ontario followed from April 2017 and March 2021
- Patients were followed from cohort entry date to a maximum of four years or death
- ~ 16,000 patients (~ 8000 entered at start of trial, ~8000 entered during trial)
- ~ 4 million hemodialysis sessions during the trial
- Patient notification with letter poster & newsletter; opt out consent to Rx
- Almost all baseline and follow-up information comes from large databases
- Primary outcome was cardiac death or hospital admission with MI, stroke or CHF

Two trials, one similar intervention, but two different intentions

Intention (individual-level RCT):

Test whether in patients who newly start chronic hemodialysis

use of personalized dialysate temperature

provides long-term cardiac protection and abrogates progressive morphologic and functional change characteristics of hemodialysis-associated cardiomyopathy

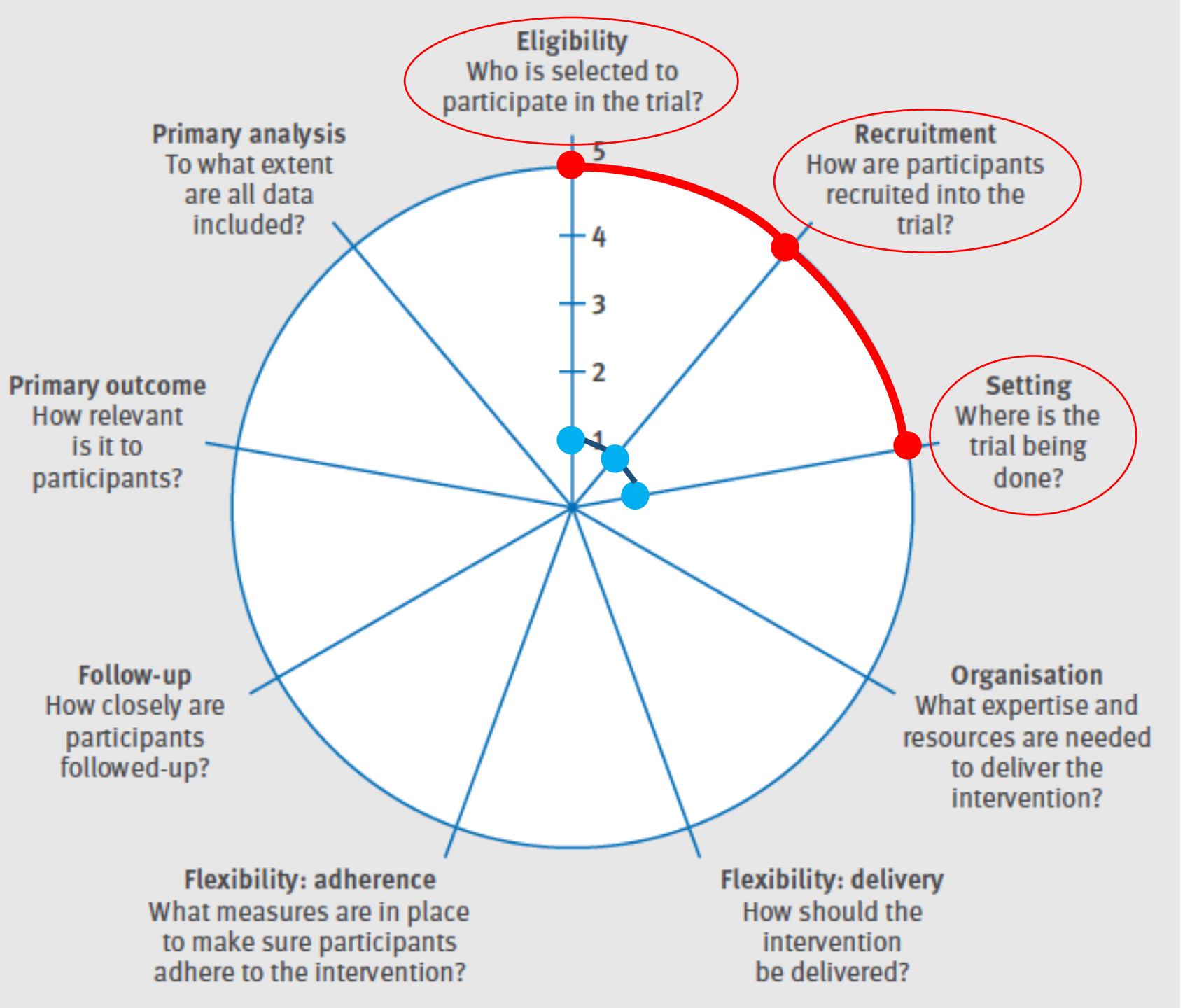
than standard dialysate temperature

CJASN August 2015, 10 (8): 1408-1417

Intention (MyTEMP cluster trial)

Test whether use of *a* centre-level protocol of personalized temperature-reduced dialysate results in a different rate of cardiovascular-related deaths or hospitalizations than a standard temperature dialysate

Can J Kidney Health Dis. 2020, 7 (1): 1-18


Eligibility
Who is selected to participate in the trial?
Recruitment
How are participants recruited into the trial?
Setting
Where is the trial being done?
Organisation
What expertise and resources are needed to deliver the intervention?
Flexibility: delivery
How should the intervention be delivered?
Flexibility: adherence
What measures are in place to make sure participants adhere to the intervention?
Follow-up
How closely are participants followed-up?
Primary outcome
How relevant is it to participants?
Primary analysis
To what extent are all data included?
5
4
3
2
1

Population

Included

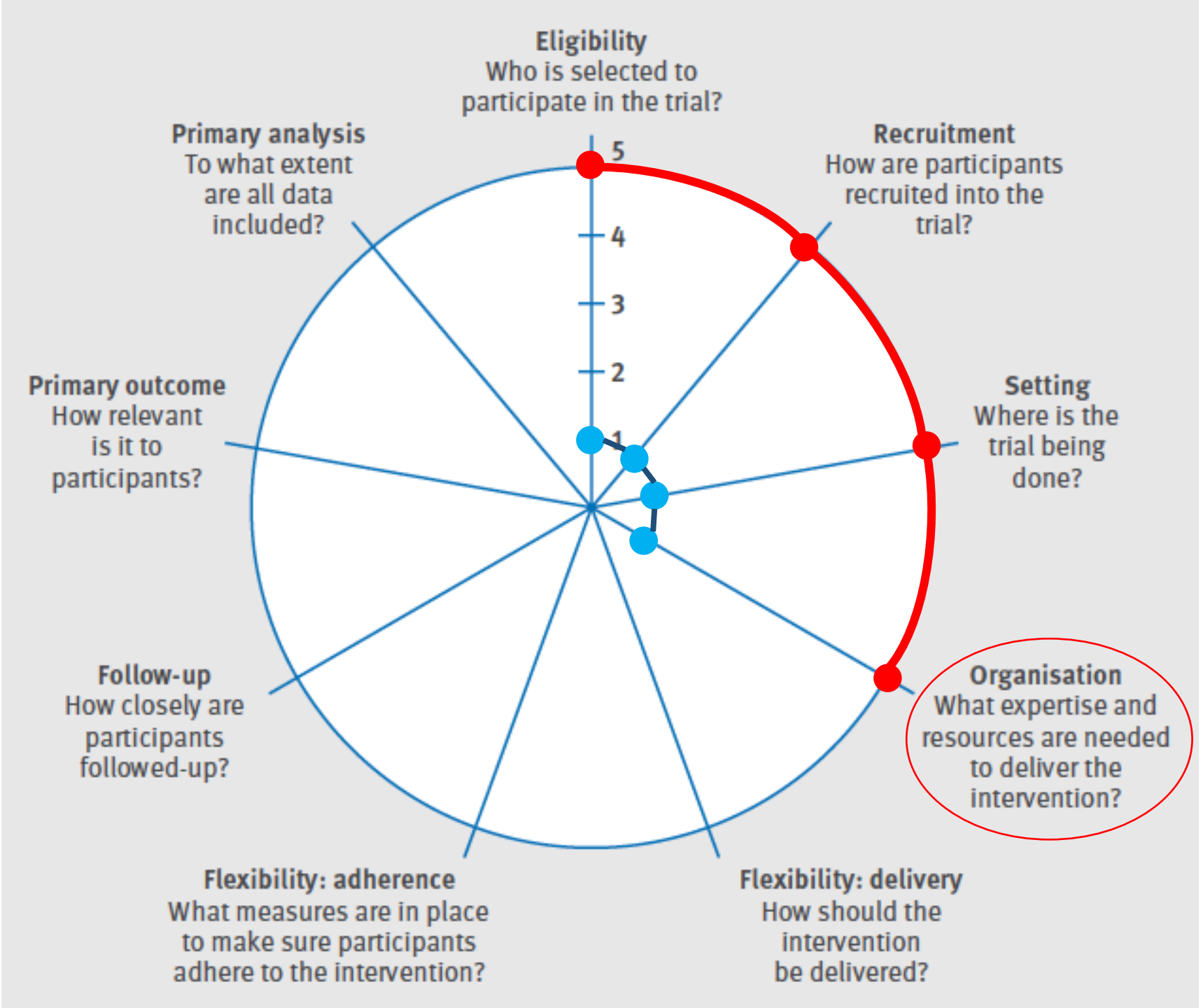
- ≥16 years of age
- Within 180 days of starting in-center HD treatment three times per week
- Capacity to consent.

Excluded

- Inability to tolerate cardiac magnetic resonance imaging
- Pregnant or lactating women,
- New York Heart Association grade IV heart failure

Included

- Medical director had to agree for their centre(s) to be randomized to either trial arm
- A centre had to care for at least 15 adult (≥18 years) patients on conventional in-centre hemodialysis
- All patients in each centre received the allocated centre treatment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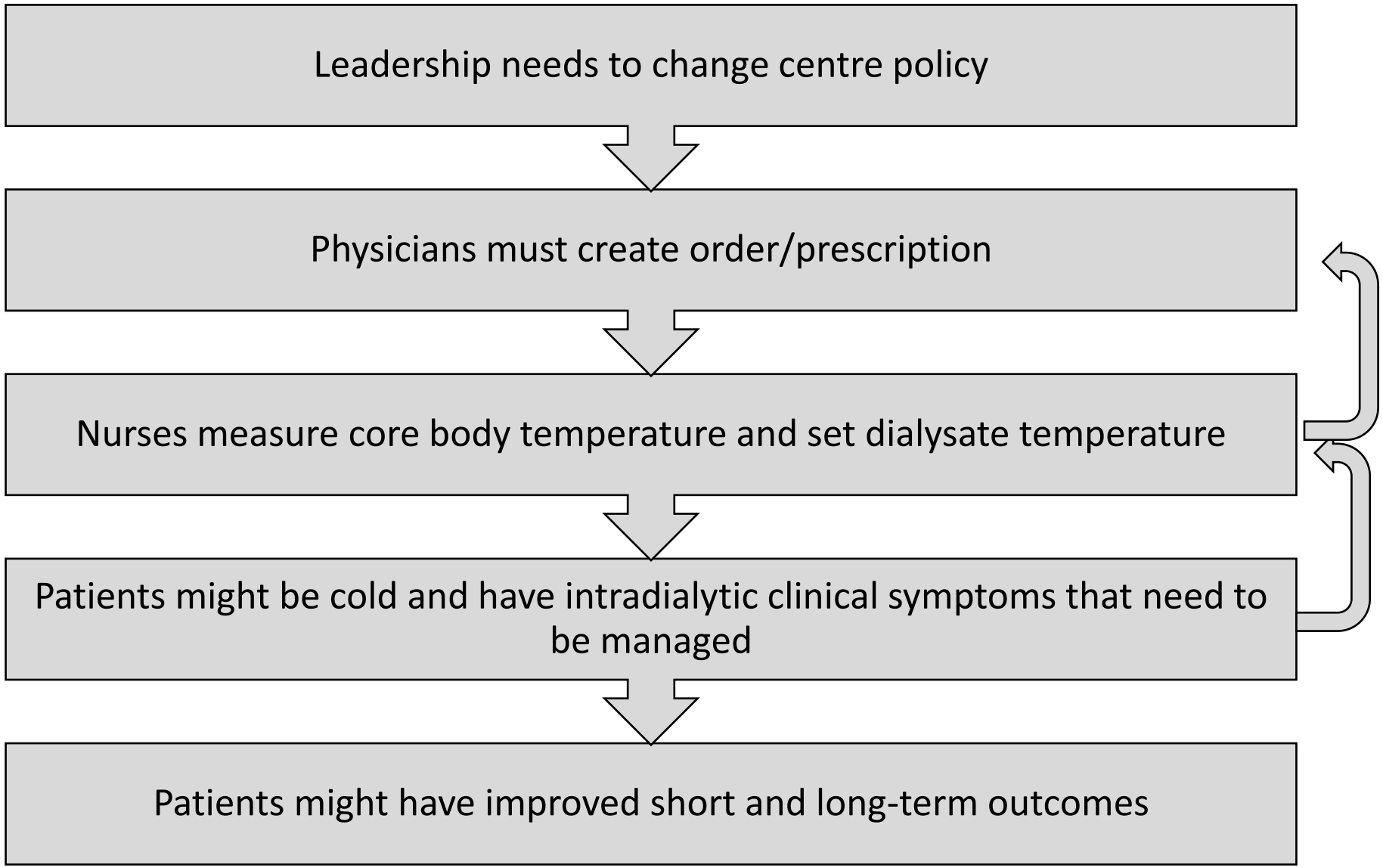
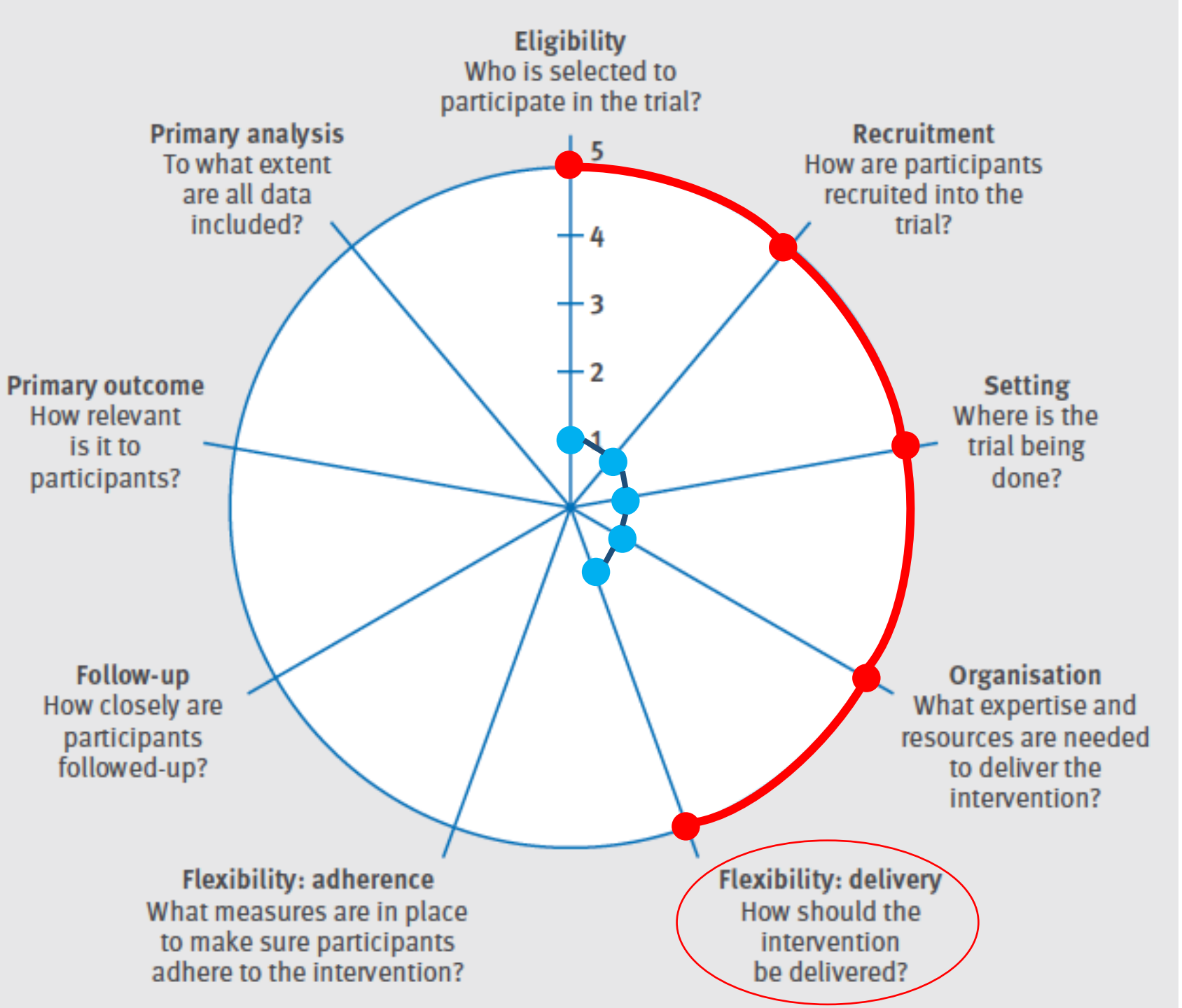
Prescribing and setting the dialysate temperature

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Intervention

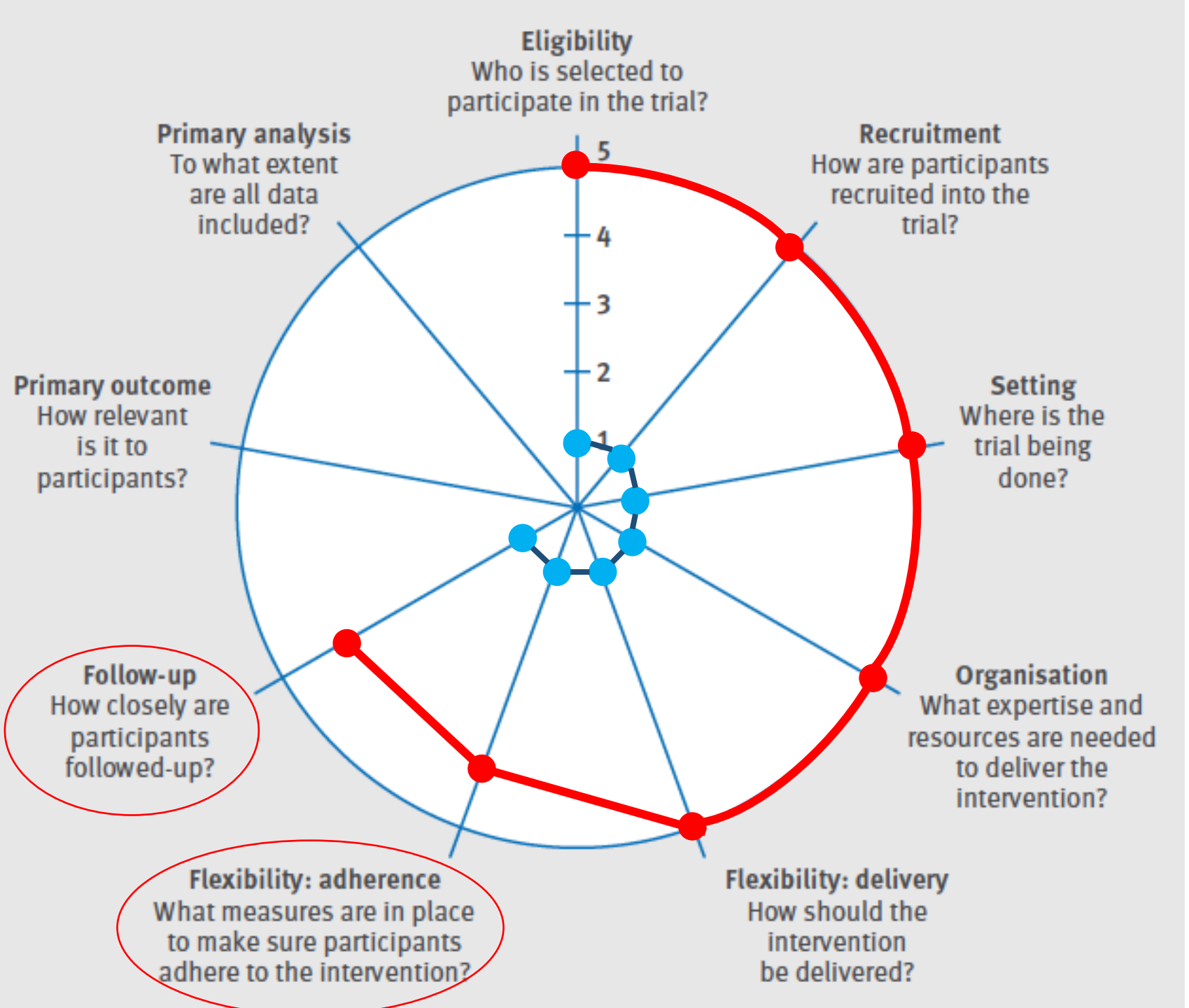
Patient temperature – 0.5 °C

Patient temperature – 0.5 to 0.9 °C

Control

37 °C or 98.6°F

36.5 °C or 97.7°F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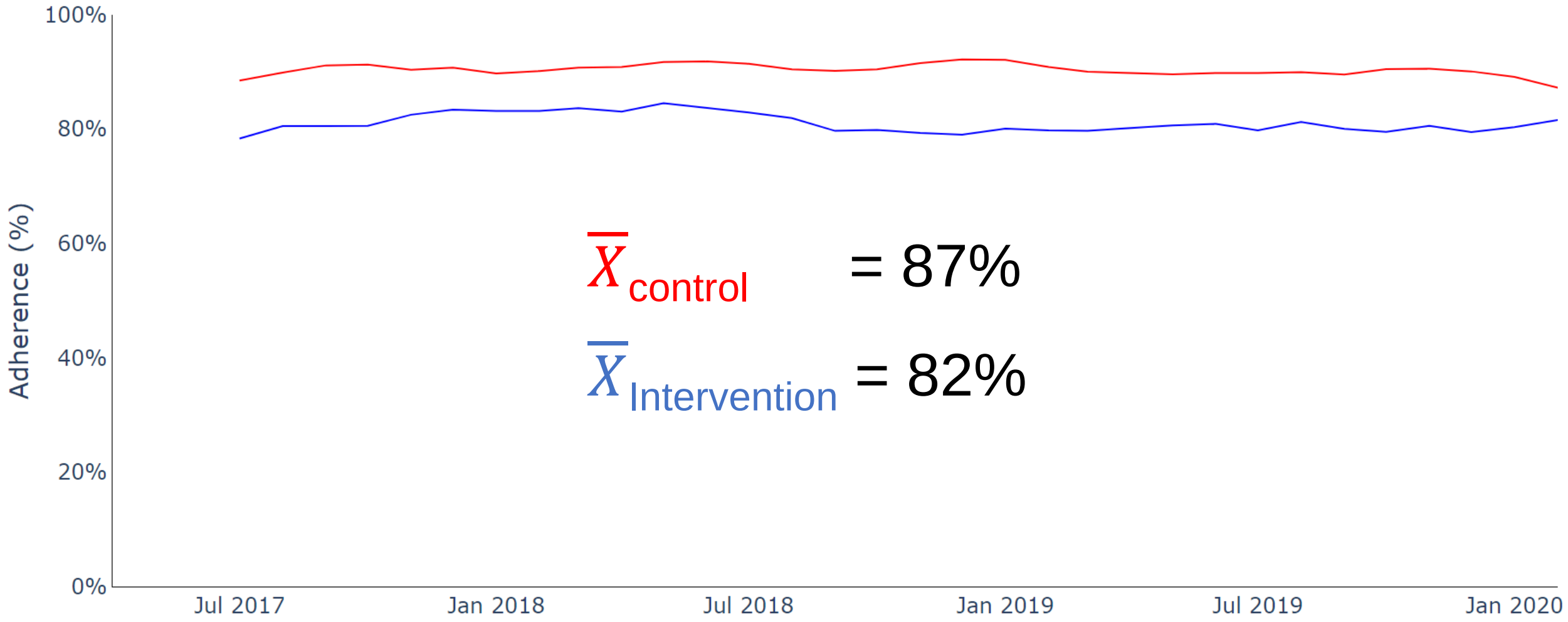
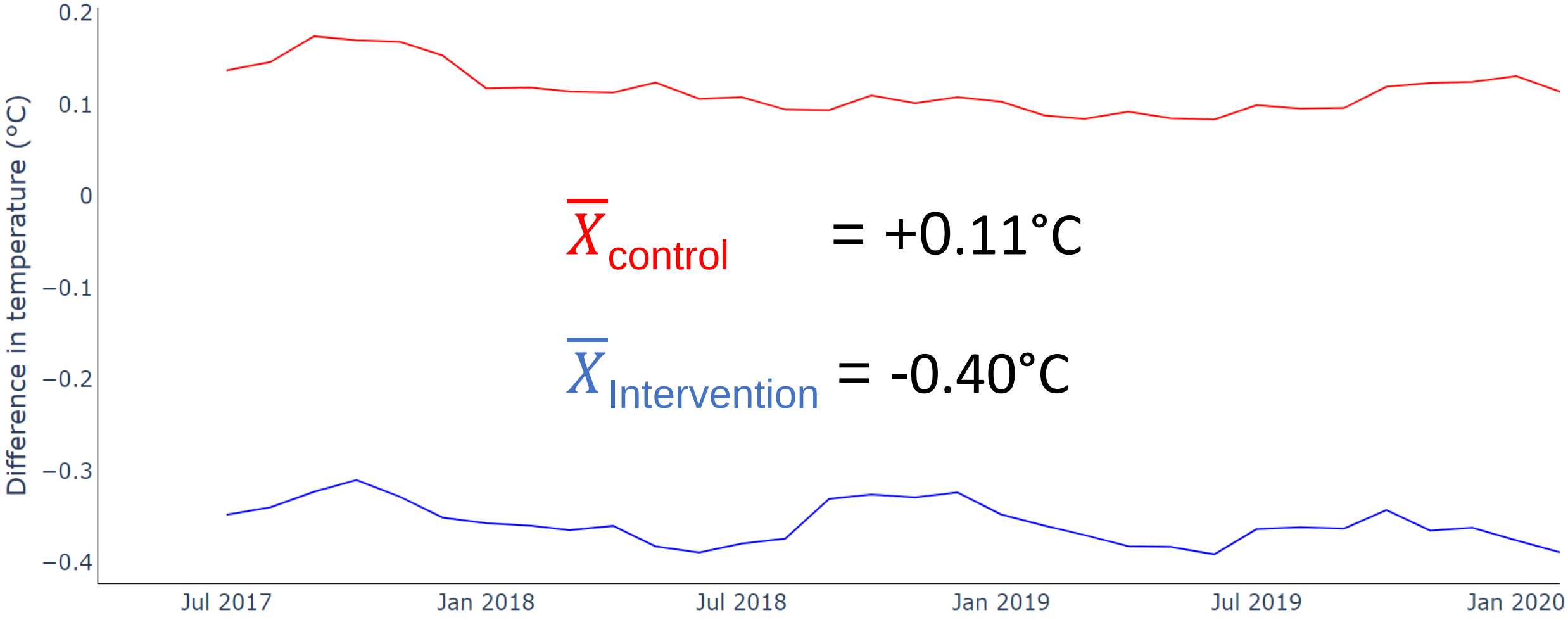
Adherence to the assigned centre protocol



$\overline{X}_{control}$ = 87%

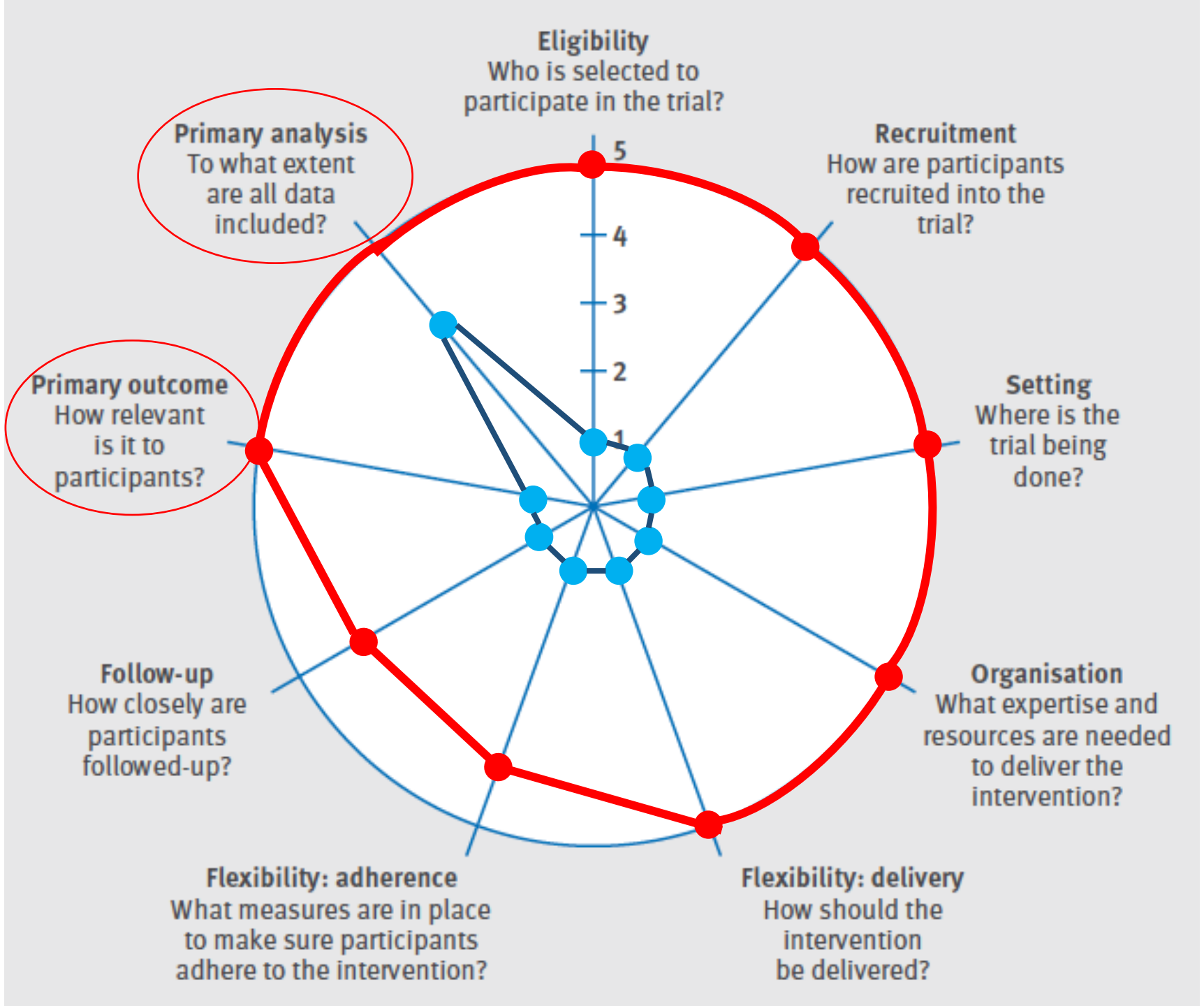
$\overline{X}_{Intervention}$ = 82%

Difference in dialysate from body temperature



$\overline{X}_{control}$ = +0.11°C

$\overline{X}_{Intervention}$ = -0.40°C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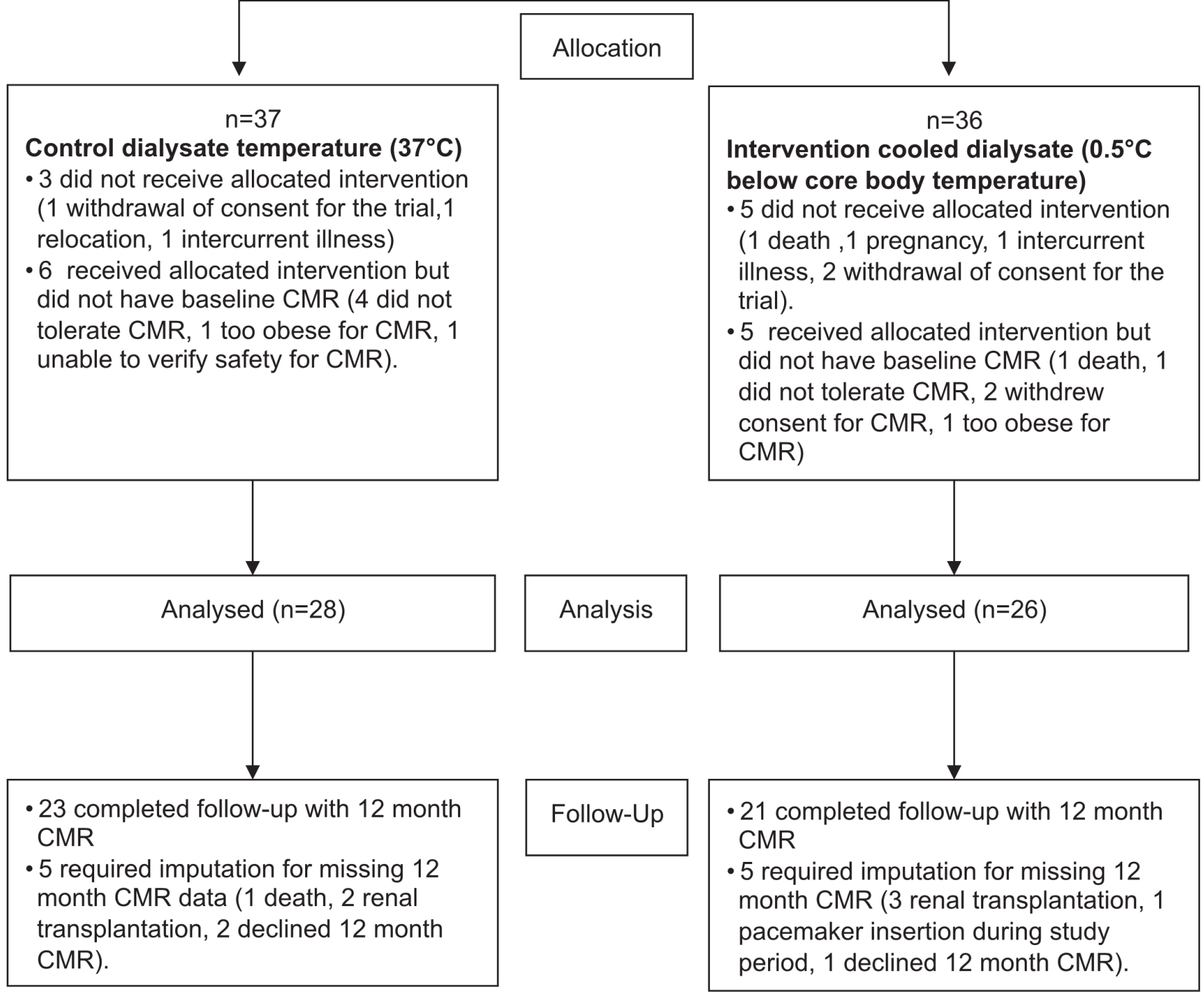
Primary outcome & analysis

- Change in the resting ejection fraction
- Intention-to-treat approach
- Multiple imputation of missing follow-up CMR data

- Composite of cardiovascular-related mortality or hospitalization for ischemic stroke, myocardial infarction, or heart failure
- Intention-to-treat approach with an open cohort
- The hazard ratio of time-to-first event
- Patient-level analyses
- Accounting for clustering at the centre level
- Patients censored when they:
  - Emigrate from the province
  - Die due to a non-CV cause


Allocation
n=37
Control dialysate temperature (37°C)
• 3 did not receive allocated intervention (1 withdrawal of consent for the trial,1 relocation, 1 intercurrent illness)
• 6 received allocated intervention but did not have baseline CMR (4 did not tolerate CMR, 1 too obese for CMR, 1 unable to verify safety for CMR).
n=36
Intervention cooled dialysate (0.5°C below core body temperature)
• 5 did not receive allocated intervention (1 death ,1 pregnancy, 1 intercurrent illness, 2 withdrawal of consent for the trial).
• 5 received allocated intervention but did not have baseline CMR (1 death, 1 did not tolerate CMR, 2 withdrew consent for CMR, 1 too obese for CMR)
Analysed (n=28)
Analysis
Analysed (n=26)
• 23 completed follow-up with 12 month CMR
• 5 required imputation for missing 12 month CMR data (1 death, 2 renal transplantation, 2 declined 12 month CMR).
Follow-Up
• 21 completed follow-up with 12 month CMR
• 5 required imputation for missing 12 month CMR (3 renal transplantation, 1 pacemaker insertion during study period, 1 declined 12 month CMR).

Primary outcome & analysis

- Change in the resting ejection fraction
- Intention-to-treat approach
- Multiple imputation of missing follow-up CMR data

- Composite of cardiovascular-related mortality or hospitalization for ischemic stroke, myocardial infarction, or heart failure
- Intention-to-treat approach with an open cohort
- The hazard ratio of time-to-first event
- Patient-level analyses
- Accounting for clustering at the centre level
- Patients censored when they:
  - Emigrate from the province
  - Die due to a non-CV cause

Summary

- We intentionally designed the MyTEMP trial to be highly pragmatic and flexible

- The hemodialysis is a setting is well suited for pragmatic cluster trials because:
  - frequent and predictable patient encounters
  - highly granular and uniform data collection
  - use of electronic data systems, and
  - delivery of care by a small number of provider organizations

- The use of pragmatic clinical trials can fill the large gaps in our knowledge about caring for patients receiving hemodialysis

Thank you

Presenters:

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Amit Garg (amit.garg@lhsc.on.ca)