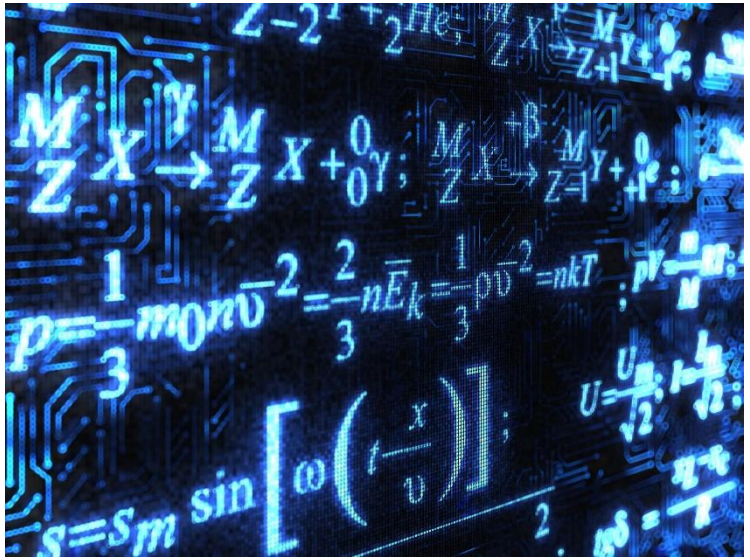
Methods

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

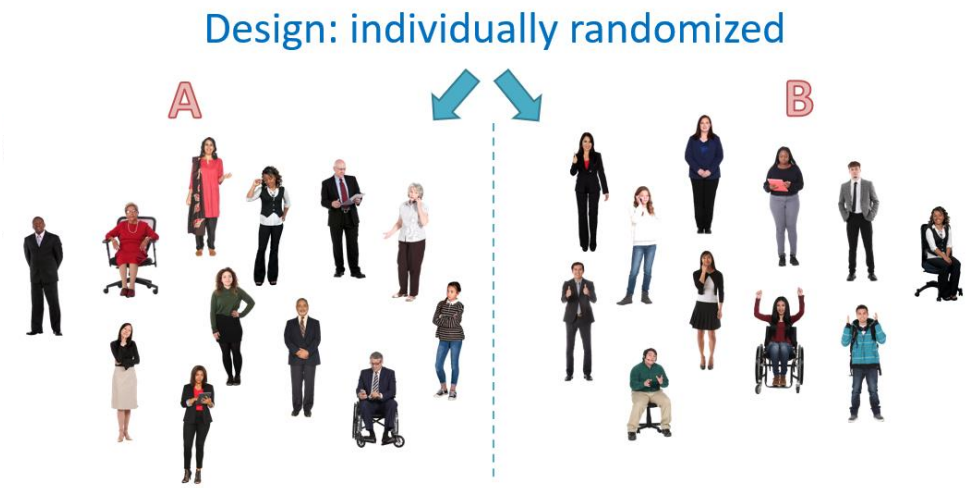
Considerations

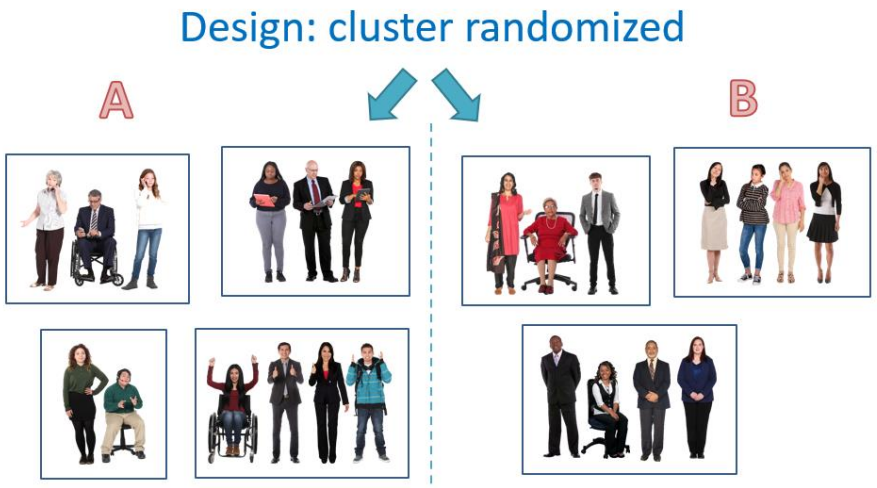


- Design:
  - Cluster-Randomized Trial
  - Covariate-constraint randomization
- Objective: to examine the effect of the intervention on
  1. a composite outcome of cardiovascular-related death or major cardiovascular-related hospitalization
  2. the mean drop in intradialytic systolic blood pressure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

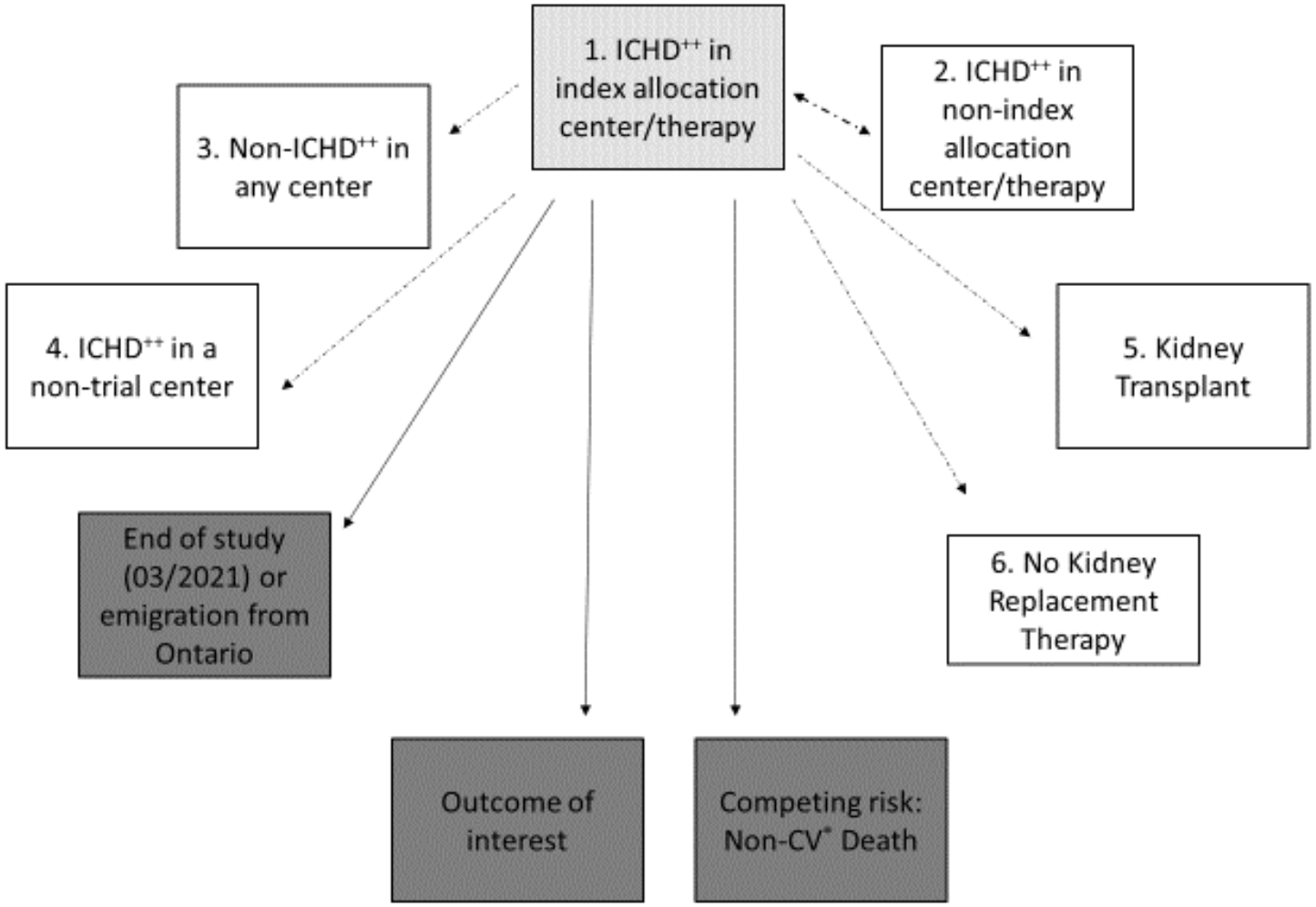
Review Stat Med. 2017 Apr 15;36(8):1203-1209. doi: 10.1002/sim.7215. Epub 2017 Jan 19.

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



Key Secondary Outcome

- The mean drop in patients' intradialytic systolic blood pressure
  - collected deidentified information on 15 randomly sampled haemodialysis treatments from each centre each month
  - Assessed 5 definitions
  - Considerations:
    - Correlation of outcomes within clusters (i.e., within dialysis centres)
    - Correlation of repeated measures (i.e., over time)
    - No individual-level identifiers
    - Between-group mean differences

Key Secondary Analysis

- Unadjusted linear mixed model on the **cluster-period summaries**, accounting for the repeated measures <u>over time</u> at the cluster level
- Explored different correlation structures overtime

$$\begin{bmatrix} \sigma^2+\sigma_1^2 & \sigma_1^2 & \sigma_1^2 & \sigma_1^2 \\ \sigma_1^2 & \sigma^2+\sigma_1^2 & \sigma_1^2 & \sigma_1^2 \\ \sigma_1^2 & \sigma_1^2 & \sigma^2+\sigma_1^2 & \sigma_1^2 \\ \sigma_1^2 & \sigma_1^2 & \sigma_1^2 & \sigma^2+\sigma_1^2 \end{bmatrix}$$

Compound symmetry

$$\begin{bmatrix} \sigma_A^2 & 0 & 0 & 0 \\ 0 & \sigma_B^2 & 0 & 0 \\ 0 & 0 & \sigma_{AB}^2 & 0 \\ 0 & 0 & 0 & \sigma_{AB}^2 \end{bmatrix}$$

Variance components
(assumed independence)

$$\sigma^2 \begin{bmatrix} 1 & \rho & \rho^2 & \rho^3 \\ \rho & 1 & \rho & \rho^2 \\ \rho^2 & \rho & 1 & \rho \\ \rho^3 & \rho^2 & \rho & 1 \end{bmatrix}$$

Auto-regressive (1)

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