ePCT Experimental Design and Analysis

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Learning goals

- Learn about cluster randomized and stepped-wedge study designs
- Recognize the analytical challenges and trade-offs of pragmatic study designs, focusing on what PIs need to know—highlighting design and analysis considerations and key decision points

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Design Considerations

Embedded Pragmatic Clinical Trials

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Important things to know

- Studies that randomize groups or deliver interventions to groups face special analytic challenges not found in traditional individually randomized trials
- Failure to address these challenges will result in an underpowered study and/or invalid inference (confidence interval too small; an inflated type 1 error rate)
- We won't advance the science by using inappropriate methods

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NIH Collaboratory ePCT: STOP CRC

- Strategies and Opportunities to Stop Colorectal Cancer in Priority Populations (STOP CRC)
- 40,000+ patients across 26 clinical sites
- Intervention
  - Health system–based program to improve CRC screening
  - Applied to clinical site → cluster randomization
- Unit of randomization: clinical site
- Two-arm cluster randomized trial (CRT)
  - Also referred to as a group-randomized trial

stop screen to prevent colon cancer

Coronado GD et al. *Contemp Clin Trials*. 2014;38(2):344-349.

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Reasons to randomize clusters instead of individuals

- Intervention targets health care units rather than individuals
  - STOP CRC: clinic-based intervention to improve screening
- Intervention targeted at individual risks "contamination"
  - Intervention spills over to members of control arm
  - For example, physicians randomized to new educational program may share knowledge with control-arm physicians in their practice
  - Contamination reduces the observed treatment effect
- Logistically easier to implement intervention by cluster

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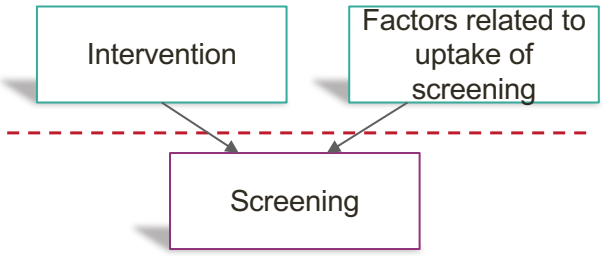
STOP CRC cluster randomization

Level 2: Randomization at the level of the clinic (ie, cluster)



Level 1: Individual-level outcomes nested within clinics

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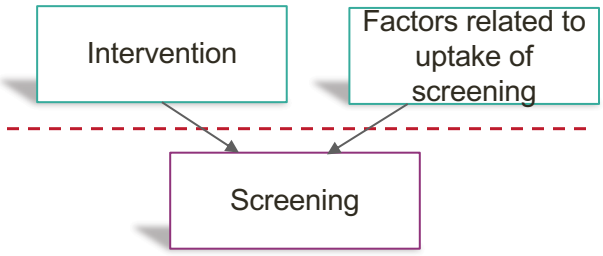
STOP CRC cluster randomization



Level 1: Individual-level outcomes nested within clinics

- Individual-level outcomes within same clinic expected to be correlated (i.e., to *cluster*)
- Reduces power to detect treatment effect if same sample size used as under individual randomization

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Understanding outcome clustering

- Consider 10 control-arm clinics (i.e., clusters)
- Each with 5 age-eligible patients: ie, who are not up to date with colorectal cancer (CRC) screening
- Binary outcome: not screened (Y/N)

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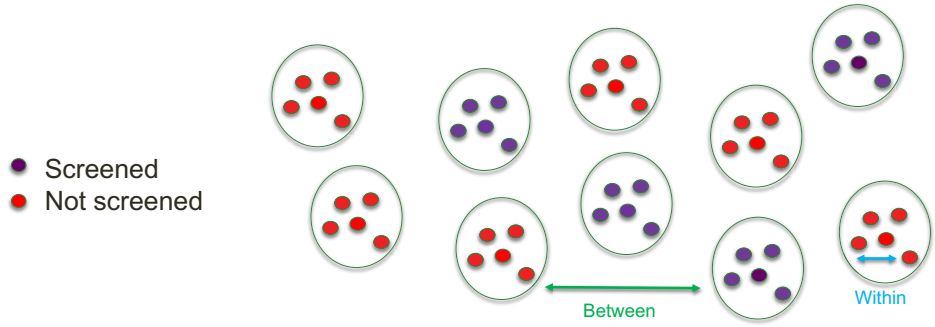
Understanding outcome clustering: complete clustering (ICC =1)



Intracluster correlation coefficient (ICC) $= \frac{\sigma_B^2}{\sigma_{\text{Total}}^2} = \frac{\sigma_B^2}{\sigma_B^2+\sigma_W^2} = \frac{\sigma_B^2}{\sigma_B^2} = 1$, because $\sigma_B^2 > 0$ & $\sigma_W^2 = 0$

σ_B^2 = between-cluster outcome variance; σ_W^2 = within-cluster outcome variance

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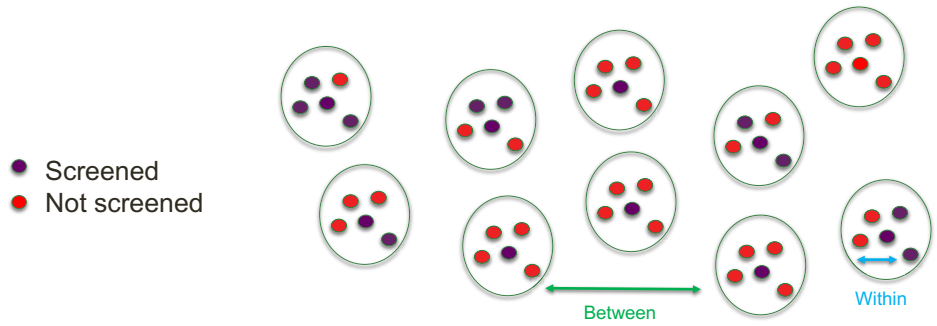
Understanding outcome clustering: some clustering (0 < ICC < 1)



ICC = $\frac{\sigma_B^2}{\sigma_B^2+\sigma_W^2}$; 0 < ICC < 1, because $\sigma_B^2 > 0$ & $\sigma_W^2 > 0$

σ_B^2 = between-cluster outcome variance; σ_W^2 = within-cluster outcome variance

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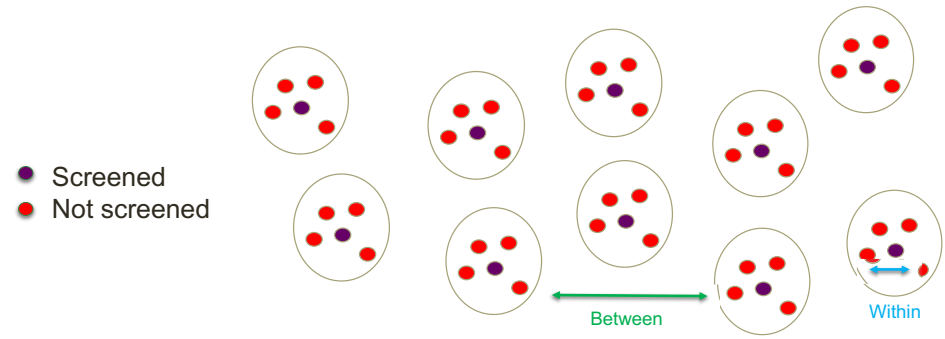
Understanding outcome clustering: no clustering (ICC=0)



ICC = $\frac{\sigma_B^2}{\sigma_B^2+\sigma_W^2}$; ICC =0 because $\sigma_B^2 = 0$ & $\sigma_W^2 > 0$

σ_B^2 = between-cluster outcome variance; σ_W^2 = within-cluster outcome variance

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Summary of design issues for CRTs

- All the design features common to RCTs are available to CRTs with the added complication of an extra level of nesting:
  - Cohort and cross-sectional designs
  - Post only, pre-post, and extended designs
  - Single-comparison designs and factorial designs
  - A priori matching or stratification
  - Constrained randomization
- The primary threats to internal and statistical validity are well known, and defenses are available.
  - Plan the study to reflect the nested design, with sufficient power for a valid analysis, and avoid threats to internal validity.

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Methods for pragmatic trials

- Pragmatic trials do not require a completely different set of research designs, measures, analytic methods, etc.
- As always, the choice of methods depends on the research question.
  - The research question dictates: the intervention, target population, and variables of interest
  - Which dictate the setting, research design, measures, and analytic methods.
- Randomized trials will provide the strongest evidence.
  - What kind of randomized trial depends on the research question and how the intervention will be delivered.

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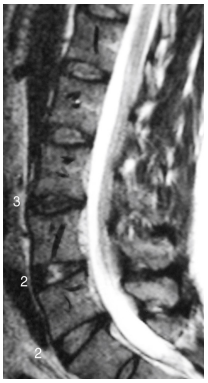
NIH Collaboratory ePCT: LIRE



- Lumbar Imaging With Reporting of Epidemiology (LIRE)
- Goal: Reduce unnecessary spine interventions by providing info on prevalence of normal findings
- Patients of 1700 PCPs across 100 clinics
- Clinic-level intervention → cluster randomization
- Unit of randomization: clinic
- Pragmatic trial
  - All clinics will eventually receive intervention
  - Stepped-wedge CRT (SW-CRT)

Jarvik JG et al. *Contemp Clin Trials*. 2015;45(Pt B):157-163.

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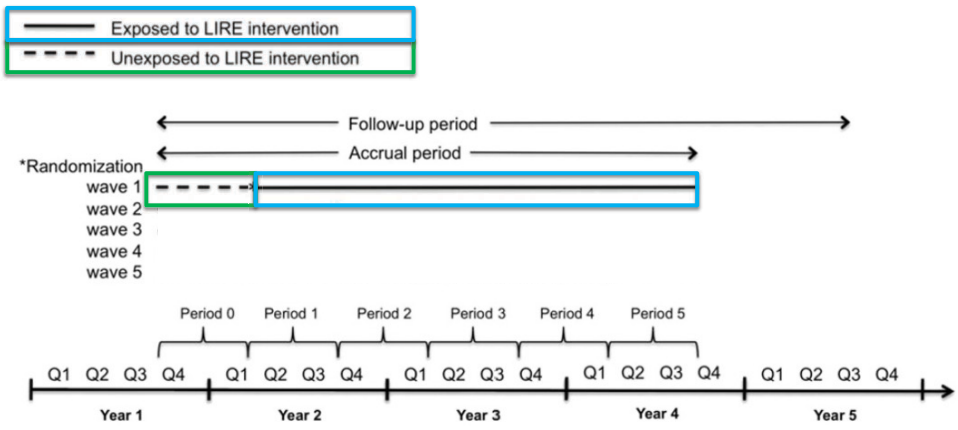
NIH Collaboratory ePCT: LIRE



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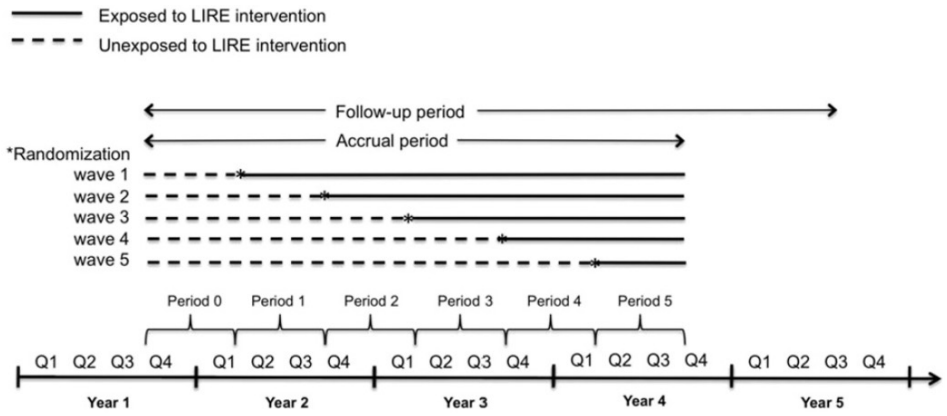

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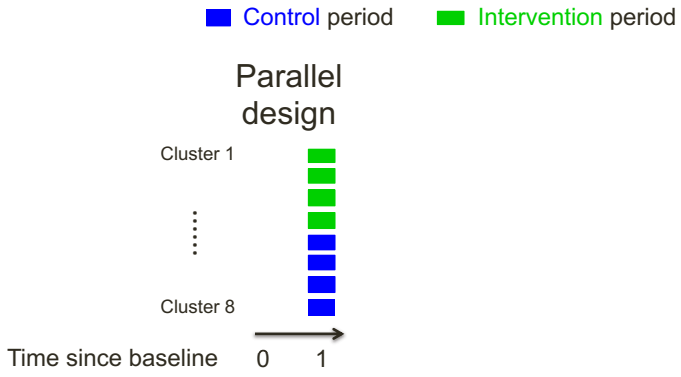
Types of CRT designs

Examples with 8 clusters: 1-year intervention



Based on: Hemming K et al. 2015. *Stat Med*. 34:181-196.

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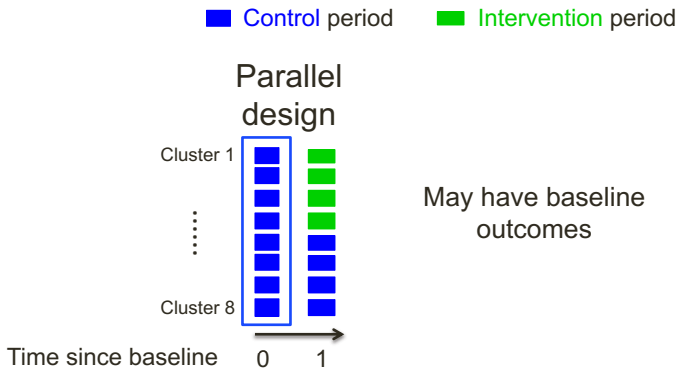

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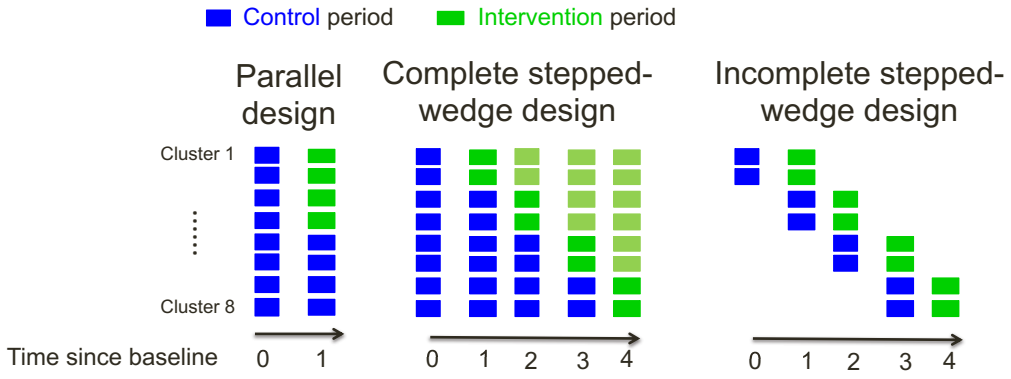

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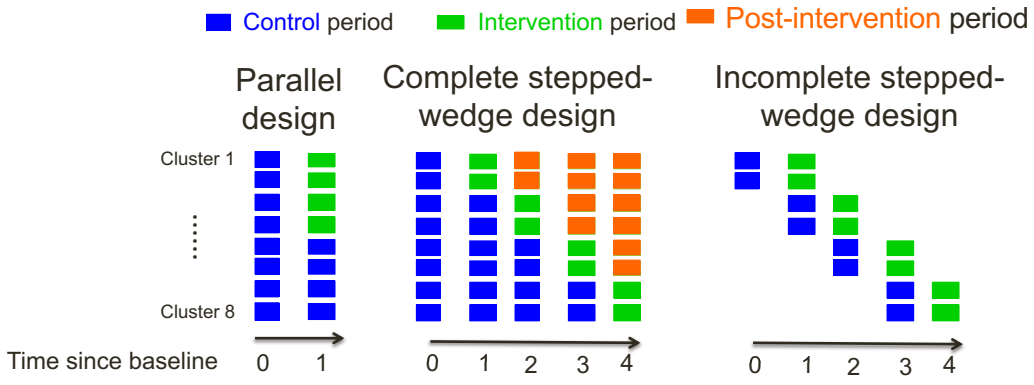

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Summary of design issues

- Many design features common to RCTs are available to SW-CRTs:
  - Cohort and cross-sectional designs
  - Single-comparison designs and factorial designs
  - A priori matching, stratification, or constrained randomization to create comparable sequences
- The primary threats to internal and statistical validity are well known, and defenses are available.
  - Plan the study to reflect the nested design, with sufficient power for a valid analysis, and avoid threats to internal validity.
- Accounting for the pattern of the intervention effect over time:
  - The common assumption of an immediate, sustained intervention effect may yield biased estimates.
  - In the absence of evidence to the contrary, it is reasonable to assume intervention effect changes with exposure time.
  - Important to define intervention effect in this case – e.g., average at one point in time, average over more than one time.

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NIH Collaboratory ePCT: OPTIMUM

Optimum
Optimizing Pain Treatment in Medical Settings Using Mindfulness

- Optimizing Pain Treatment In Medical settings Using Mindfulness (OPTIMUM)
- Goal: to reduce pain and pharmacologic medications via a group-based mindfulness-based stress reduction (MBSR) program
- Study population: individuals with chronic lower back pain
- Group-based online intervention → groups must be formed by study team
- Unit of randomization: individual → individually-randomized group treatment (IRGT) trial
- Pragmatic trial
  - Diverse settings: Safety-net hospital, FQHCs & academic hospital
  - Healthcare utilization data via EMR

Greco CM et al. *Contemp Clin Trials*. 2021;109:106545.

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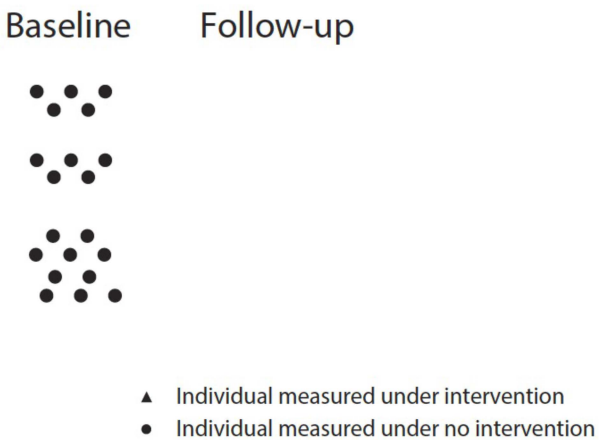
NIH Collaboratory ePCT: OPTIMUM



Extracted from Figure 1 in Turner et al. *Am J Public Health*. 2017;107(6).

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Summary of design issues

- Many design features common to RCTs are available to IRGTTs:
  - Cohort, but not easy to conceive of a cross-sectional design;
  - Single-comparison designs and factorial designs
  - A priori stratification, or other restricted randomization procedures such as minimization to create comparable treatment arms
- The primary threats to internal and statistical validity are well known, and defenses are available.
  - Plan the study to reflect the nested design, with sufficient power for a valid analysis, and avoid threats to internal validity.

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It all starts with a clear research question…

- Population
- Intervention
- Comparison
- Outcome(s)

From: European Medicines Agency
ICH E9 (R1)

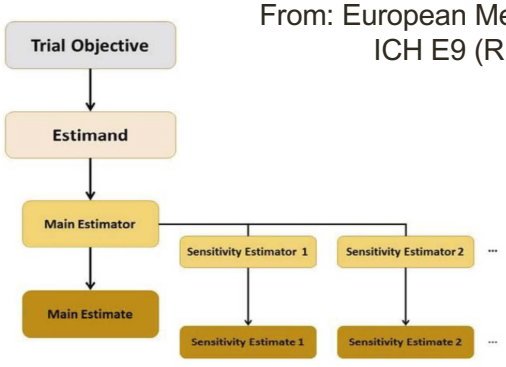

Figure 1: Aligning target of estimation, method of estimation, and sensitivity analysis, for a given trial objective

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How to choose the right design?

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How to choose the right design?

Is there a strong rationale for randomizing groups rather than individuals to study conditions?

Based on: Murray DM et al. *Ann Rev Public Health.* 2020;41: 1-19

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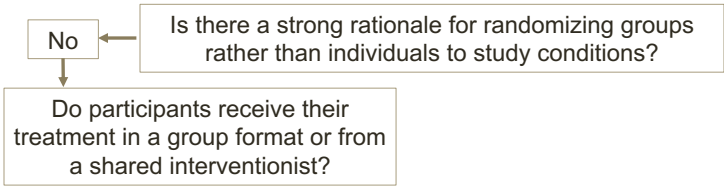

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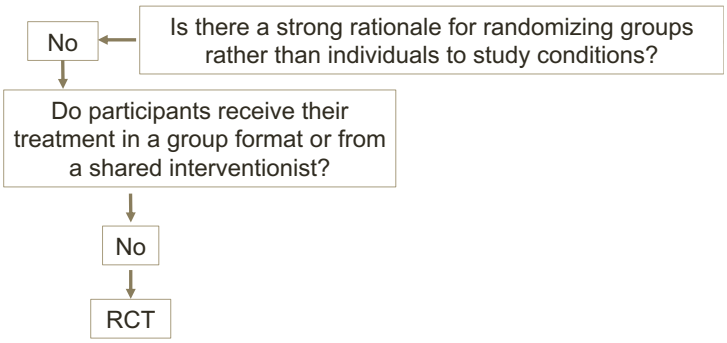

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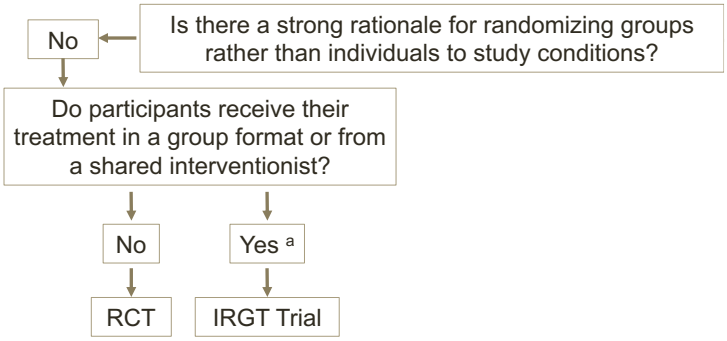

[a] If the intervention is delivered through a physical or a virtual group, or through shared interventionists who each work with multiple participants, positive ICC can develop over the course of the trial.

Based on: Murray DM et al. *Ann Rev Public Health.* 2020;41: 1-19

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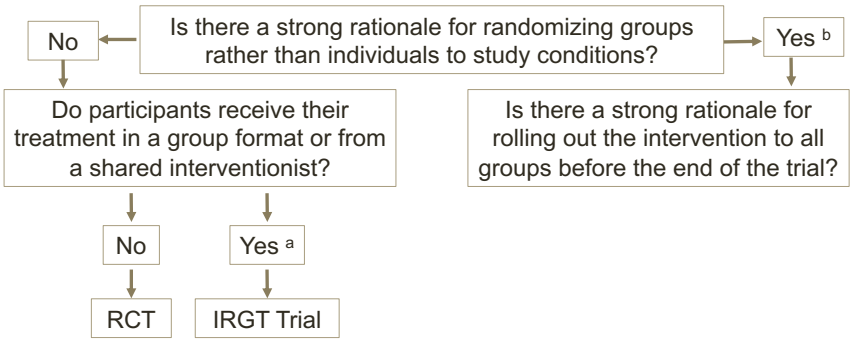

[a] If the intervention is delivered through a physical or a virtual group, or through shared interventionists who each work with multiple participants, positive ICC can develop over the course of the trial.

[b] There may be logistical reasons to randomize groups (clusters) or it may not be possible to deliver the intervention to individuals without substantial risk of contamination.

Based on: Murray DM et al. *Ann Rev Public Health.* 2020;41: 1-19

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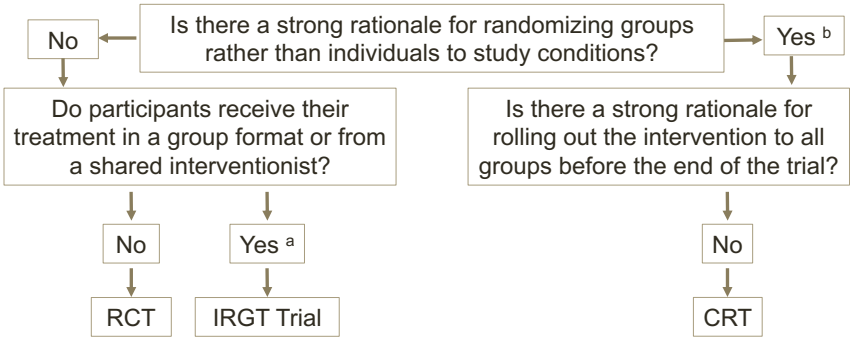

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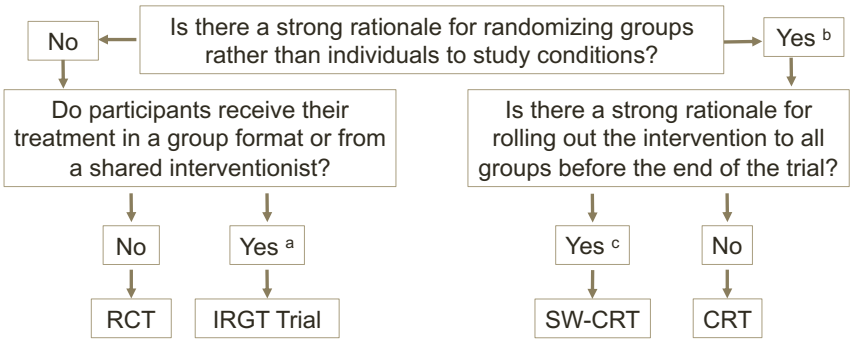

[a] If the intervention is delivered through a physical or a virtual group, or through shared interventionists who each work with multiple participants, positive ICC can develop over the course of the trial.

[b] There may be logistical reasons to randomize groups (clusters) or it may not be possible to deliver the intervention to individuals without substantial risk of contamination.

[c] There may be legitimate political or logistical reasons to roll out the intervention to all clusters.

Based on: Murray DM et al. *Ann Rev Public Health.* 2020;41: 1-19

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Implications of design choice

- Randomized controlled trials
  - Randomization usually distribute potential confounders evenly, as most RCTS have N>100
  - If well executed, confounding is usually not a concern
- Individually randomized group treatment (IRGT) trials
  - There may be less opportunity for randomization to distribute potential confounders evenly, as many IRGT Trials have N<100

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Implications of design choice

- Parallel cluster randomized trials (CRTs)
  - Most CRTs are “small”, ie, total # clusters (C) <50
  - Randomization may not evenly distribute potential confounders.
  - Confounding may be a concern in CRTs if C<50
  - Can use restricted randomization, eg, constrained randomization
- Stepped wedge CRTs
  - Clusters crossed with study condition, which minimizes confounding except, intervention effects confounded with time
  - SW-CRTs more complicated than parallel CRTs
    - Only choose when a parallel CRT not appropriate.

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The need for these designs

- An RCT is the best comparative design whenever…
  - Individual randomization possible without post-randomization interaction of participants
- An IRGT trial is the best comparative design whenever...
  - Individual randomization is possible but there are reasons to allow post-randomization interaction of participants.
- A CRT is the best comparative design whenever the investigator wants to evaluate an intervention that…
  - Cannot be delivered to individuals without risk of contamination
- An SW-CRT is an alternative to a parallel CRT if…
  - Intervention is being rolled out to all groups as part of system-wide implementation
  - Cannot implement intervention in many groups at same time
  - External events are unlikely to affect the outcomes (disruption!)

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Clustering: Impact on power

- Power and sample size
  - Account for anticipated clustering in CRTs (inc. SW-CRTs) & IRGTTs
  - Inflate RCT sample size
  - Work with statistician to do this correctly
- Use ICC for outcome
  - ICC often 0.01-0.05 in CRTs, larger in IRGT Trials
  - STOP CRC: ICC = 0.03 for primary outcome
  - OPTIMUM: ICC = 0.053 for primary outcome
  - Depends on outcome & study characteristics
  - Different outcome = different ICC, even in same CRT or IRGT Trial
  - **More than 1 ICC in longitudinal study like SW-CRT!**

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Clustering: Impact on power in STOP CRC

- "Assumed equal numbers of subjects per clinic and equal numbers of clinics (n = 13) per [arm]. In practice, the clinic sizes will not be equal, but since almost all clinics have at least **450** active age-eligible patients, we conservatively use this figure for all sites.

Source: Coronado GD et al. *Contemp Clin Trials*. 2014;38:344-9.

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Clustering: Impact on power in STOP CRC

- We based our calculations on the simple paradigm of comparing two binomial proportions with a type I error rate of 5%, and **adjusted both for intraclass correlation (ICC) and the reduced degrees-of-freedom (n = 24) for the critical values**. […] we expect the ICC to be about .03.

Source: Coronado GD et al. *Contemp Clin Trials*. 2014;38:344-9.

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Clustering: Impact on power in STOP CRC

- "Using this figure, we will have **very good power (>91%) to detect absolute differences as small as 10 percentage points** even if the FIT [fecal immunochemical testing] completion rate in the **UC arm is as high as 15%** (fecal testing rates for 2013 for usual care clinics was 10%)."

Source: Coronado GD et al. *Contemp Clin Trials*. 2014;38:344-9.

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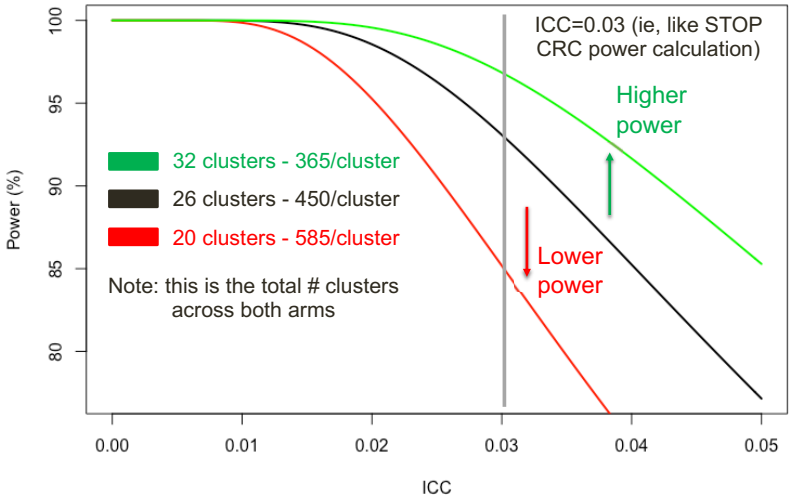

Power for parallel-arm CRT to compare two proportions of 15% vs 25% at two-tailed 5% significance (alpha) for an **overall sample of 11,700** (ie, like STOP CRC CRT)

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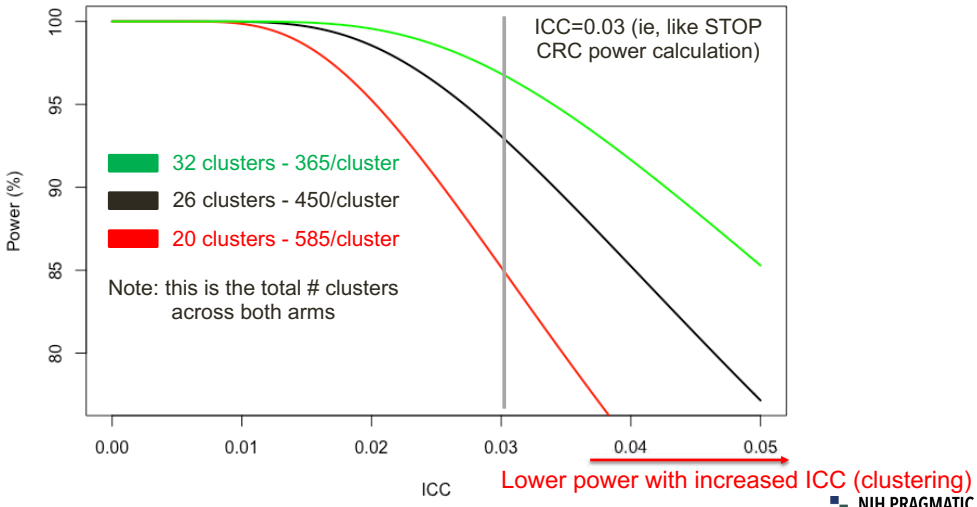

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Summary: Important things to know

- Studies that randomize groups or deliver interventions to groups face special analytic challenges not found in traditional individually randomized trials
- Failure to address these challenges will result in an underpowered study and/or an inflated type 1 error rate
- We won't advance the science by using inappropriate methods

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Question & Answer

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Analysis Considerations

Embedded Pragmatic Clinical Trials

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Learning goals

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Two example CRTs inspired by STOP CRC

- 10 clinics/CRT
  - 5 intervention (I) clinics & 5 control (C) clinics
  - 100 patients/clinic
- 1000 patients per trial
  - 500 intervention vs. 500 control
- Binary outcome: “No screening within year of enrollment”

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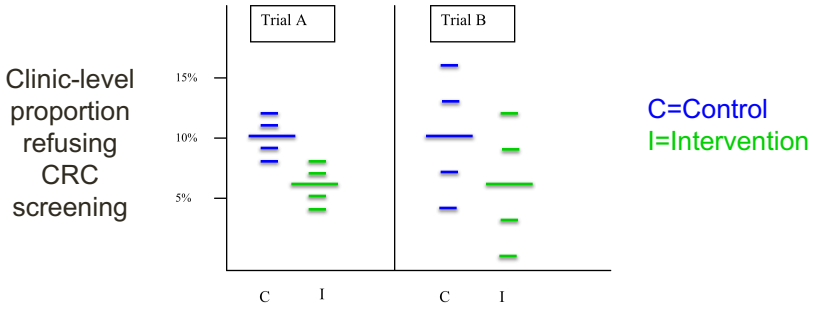
Clustering in CRTs: Implications for analysis



- 5 clinics each randomized to control and intervention
- 100 eligible participants per clinic measured

Overall screening refusal proportion in both trials: 10% vs 6%
Question: is intervention effective?

Adapted from Hayes & Moulton (2009)

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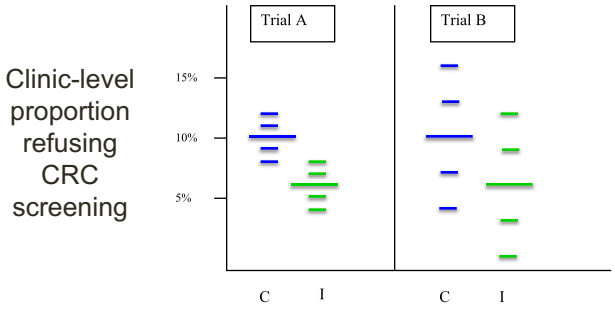

C=Control
I=Intervention

Which trial shows more evidence of benefit?

Adapted from Hayes & Moulton (2009)

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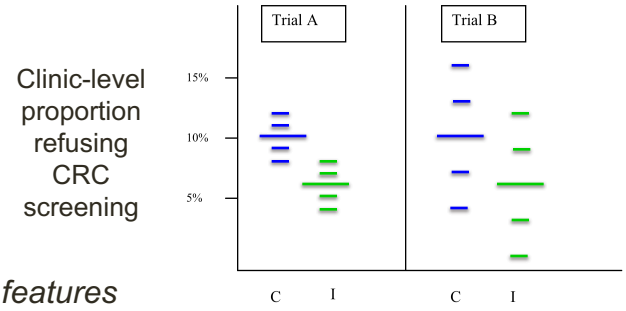

C=Control
I=Intervention

Study features

- Trial A:
  - Lower between-clinic variability (ie, less clustering)
  - Little overlap of I & C clinic-level proportions
- Trial B: overlap of intervention (I) & control (C) clinic-level proportions

Adapted from Hayes & Moulton (2009)

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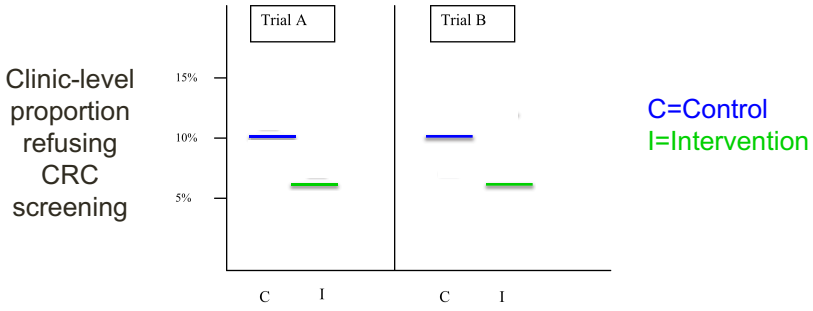

- If ignore clustering: p-value = **0.02** for both trials
- Comparison of 10% (50/500) vs 6% (30/500) by chi-sq. test

Adapted from Hayes & Moulton (2009)

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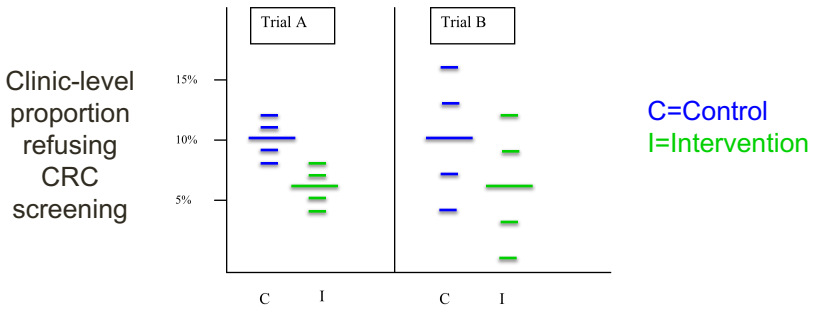
Clustering in CRTs: Implications for analysis



- Trial B p-value accounting for clustered design = ?
- If ignore clustering: p-value = **0.02**

Adapted from Hayes & Moulton (2009)

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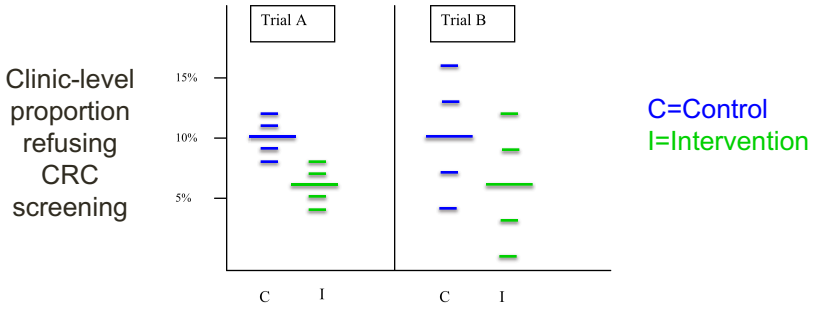
Clustering in CRTs: Implications for analysis



- Trial B p-value accounting for clustered design = **0.17**
- If ignore clustering: p-value = **0.02**

Adapted from Hayes & Moulton (2009)

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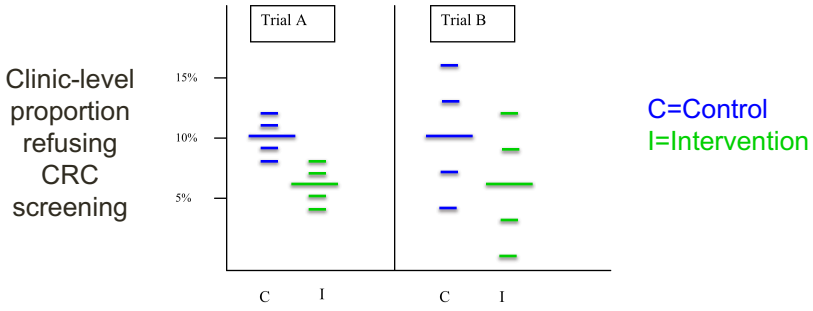
Clustering in CRTs: Implications for analysis



- Trial A p-value accounting for clustered design = **?**
- Trial B p-value accounting for clustered design = **0.17**
- If ignore clustering: p-value = **0.02**

Adapted from Hayes & Moulton (2009)

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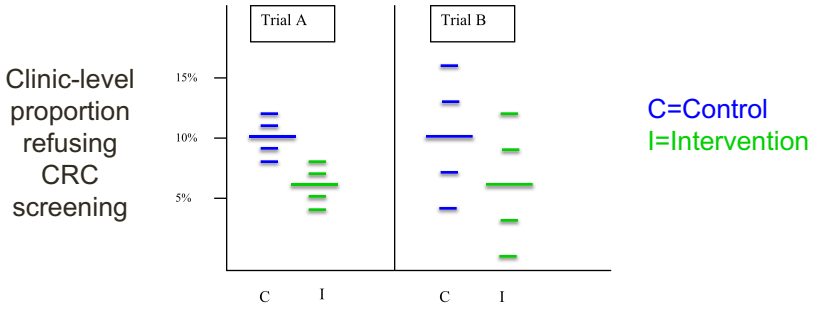
Clustering in CRTs: Implications for analysis



- Trial A p-value accounting for clustered design = **0.01**
- Trial B p-value accounting for clustered design = **0.17**
- If ignore clustering: p-value = **0.02**

Adapted from Hayes & Moulton (2009)

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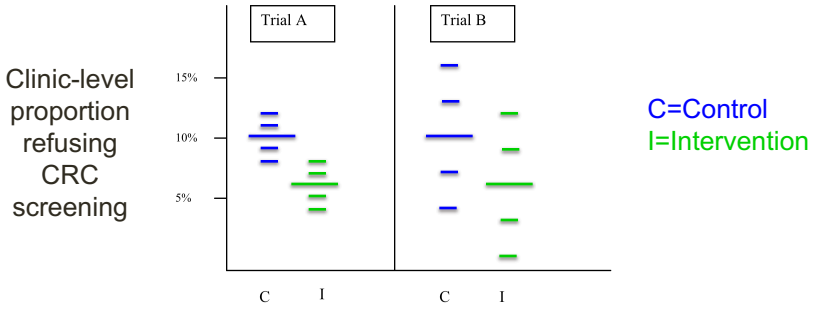
Clustering in CRTs: Implications for analysis



- Trial A p-value accounting for clustered design* = **0.01**
- Trial B p-value accounting for clustered design* = **0.17**

*By using a cluster-level analysis where the 10 cluster-level proportions (5 per arm) are treated as continuous variables and analyzed with Wilcoxon rank sum test

Adapted from Hayes & Moulton (2009)

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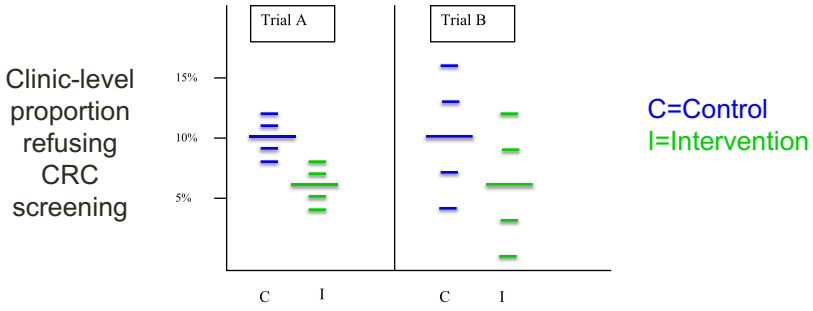
Clustering in CRTs: Implications for analysis



- Trial A p-value accounting for clustered design* = **0.004**
- Trial B p-value accounting for clustered design* = **0.22**

*Alternative cluster-level analysis using t-test, which has stronger assumptions (ie, normality of cluster-specific prevalence) than the Wilcoxon rank sum test

Adapted from Hayes & Moulton (2009)

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Summary: Analysis of two example CRTs

- Two example trials
  - Analyzed with cluster-level analysis
  - Overall sample size (# clinics/trial) =10
  - Both trials had same signal (10% vs 6%)
  - Totally different hypothesis testing results (and confidence intervals) from each trial
  - Between-cluster variability (& clustering) in Trial A < Trial B
  - Important: if incorrectly ignore clustered design, could claim ‘significant’ when not (eg, Trial B)

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Analysis of CRTs, including SW-CRTs

- Regression analysis more common than cluster-level analysis
- Analyze individual-level data
  - eg, data from 1000 participants/trial not only one proportion/clinic
- Methods to account for clustering
  - Random effects / mixed effects models
  - Generalized estimating equations (GEE)
- If SW-CRT, **must** account for time
- Work with statistician to properly account for clustering

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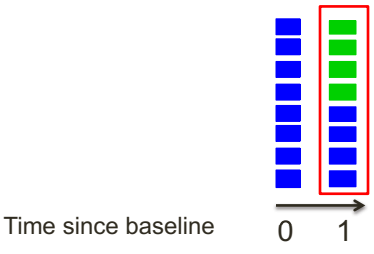
Analysis of CRTs, including SW-CRTs

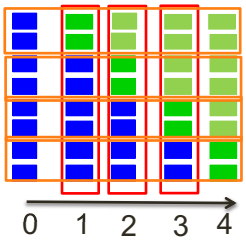
Parallel design

Estimated (primarily) using between-cluster ie, **vertical** information



Complete SW design

Estimated using both **vertical** & **horizontal** (ie, within-cluster) information



Control period Intervention period

Based on: Hemming K et al. 2015. *Stat Med*. 34:181-196.

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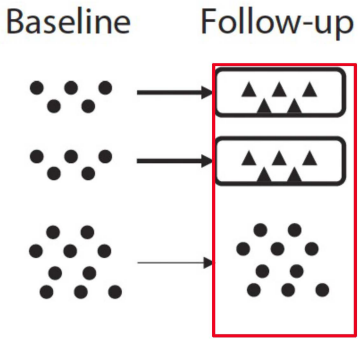
Analysis of IRGT trials



Parallel design

Estimated (primarily) using between-individual ie, **vertical** information

▲ Individual measured under intervention
● Individual measured under no intervention

Extracted from Figure 1 in Turner et al. *Am J Public Health*. 2017;107(6).

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Analysis of IRGT trials

- Analyze individual-level data accounting for clustering
  - Random effects / mixed effects models
  - Generalized estimating equations (GEE)
- Considerations on clustering
  - Clustering in both arms: if both conditions group-based & may need different degree of clustering in two arms
  - Clustering in intervention arm only: if intervention group-based but control condition not
- Work with statistician to properly account for clustering

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Analysis of CRTs, SW-CRTs, and IRGTTs

- Clustering must be accounted for in analysis
- Challenges in “small” trials (# clusters < 50)
  - Intervention effect SE may be under-estimated
    - Can correct e.g. finite-sample bias corrections for GEE
  - Ignoring can lead to inflated Type I error
    - Type I error rate may be 30-50% in a CRT, even with small ICC
    - Type I error rate may be 15-25% in an IRGTT, even with small ICC
- Work with statistician to properly account for clustering

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Strategies to protect the analysis

Avoid model misspecification

- Plan analysis
  - To reflect the study design
  - Around the primary endpoints
- Anticipate
  - All sources of random variation
  - Patterns of over-time correlation
  - Pattern of the intervention effect over time
    - Important with repeated measures designs, e.g. SW-CRTs

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Strategies to protect the analysis

Avoid low power

- Use strong interventions with good reach
- Maintain reliability of intervention implementation
- Use more & smaller groups not few large groups
- For SW-CRTs, use more steps
- Use regression adjustment
  - For covariates to reduce variance & intraclass correlation
  - In SW-CRTs, to adjust for calendar time

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NIH Collaboratory: examples of analytic challenges and trade-offs

- Stepped wedge designs “roll out” over time and are more susceptible to disruption!
- Parallel cluster randomized designs are simple and powerful, but still need to address “clustering” for design and analysis.
- Individually randomized group treatment trial designs have benefits of individual-level randomization, but still need to address “clustering” for design and analysis.

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It all starts with a clear research question…

- Population
- Intervention
- Comparison
- Outcome(s)

From: European Medicines Agency
ICH E9 (R1)

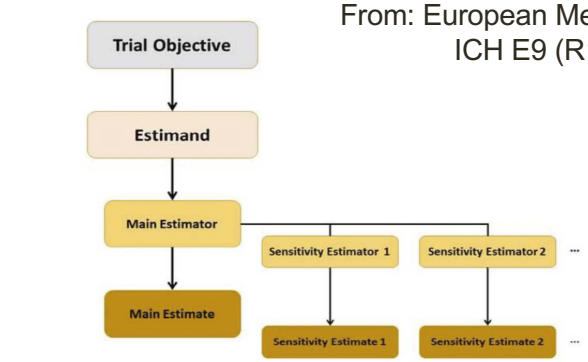

Figure 1: Aligning target of estimation, method of estimation, and sensitivity analysis, for a given trial objective

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Summary: Important things to know

- Studies that randomize groups or deliver interventions to groups face special analytic challenges not found in traditional individually randomized trials
- Failure to address these challenges will result in an underpowered study and/or an inflated type 1 error rate
- We won't advance the science by using inappropriate methods

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Resource: The Living Textbook

Visit the Living Textbook of Pragmatic Clinical Trials at
www.rethinkingclinicaltrials.org

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NIH resources

- Pragmatic and Group-Randomized Trials in Public Health and Medicine
  - https://prevention.nih.gov/grt
  - 7-part online course on GRTs and IRGTs
- Mind the Gap Webinars
  - https://prevention.nih.gov/education-training/methods-mind-gap
    - Toward Causal Inference in Cluster Randomized Trials: Estimands and Reflection on Current Practice (Fan Li, November 3, 2022)
    - An Introduction to Cross-classified, Multiple Membership, and Dynamic Group Multilevel Models (Don Hedeker, October 20, 2022)
    - Robust Inference for Stepped Wedge Designs (Jim Hughes, May 17, 2022)
- Research Methods Resources Website
  - https://researchmethodsresources.nih.gov/
  - Material on GRTs, IRGTs, SWGRTs and a sample size calculator for each

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Recommended reading

- Murray DM et al. Essential ingredients and innovations in the design and analysis of group-randomized trials. Ann Rev Public Health. 2020;41:1-19
- Hemming K, Taljaard M. Reflection on modern methods: When is a stepped-wedge cluster randomized trial a good study design choice? Int J Epidemiol. 2020. PMID: 32386407.
- Hemming K, Taljaard M. Key considerations for designing, conducting and analysing a cluster randomized trial. Int J Epidemiol. 2023. PMID: 37203433.
- Hughes JP et al. Sample size calculations for stepped wedge designs with treatment effects that may change with the duration of time under intervention. Prev Sci. 2023. PMID: 37728810.
- Kenny A et al. Analysis of stepped wedge cluster randomized trials in the presence of a time-varying treatment effect. Stat Med. 2022. PMID: 35774016.
- Kahan BC et al. Estimands in cluster-randomized trials: Choosing analyses that answer the right question. Int J Epidemiol. 2022. PMID: 35834775.
- Brown CH et al. Accounting for context in randomized trials after assignment. Prev Sci. 2022. PMID: 36083435.

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Question & Answer

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