ePCT Experimental Design and Analysis

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Learning goals

- 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.

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 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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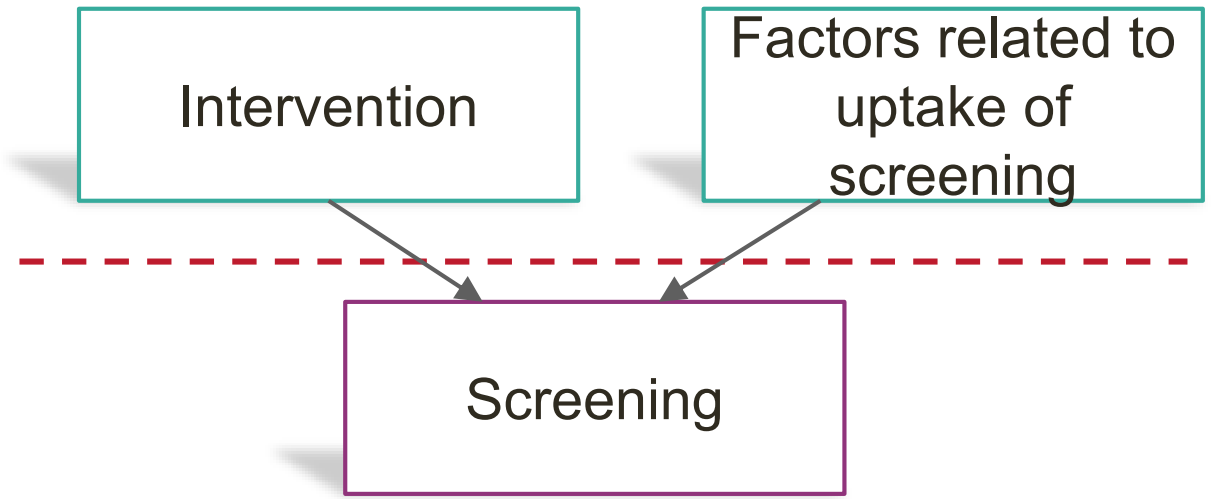
Reasons to randomize clusters instead of individuals

- 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

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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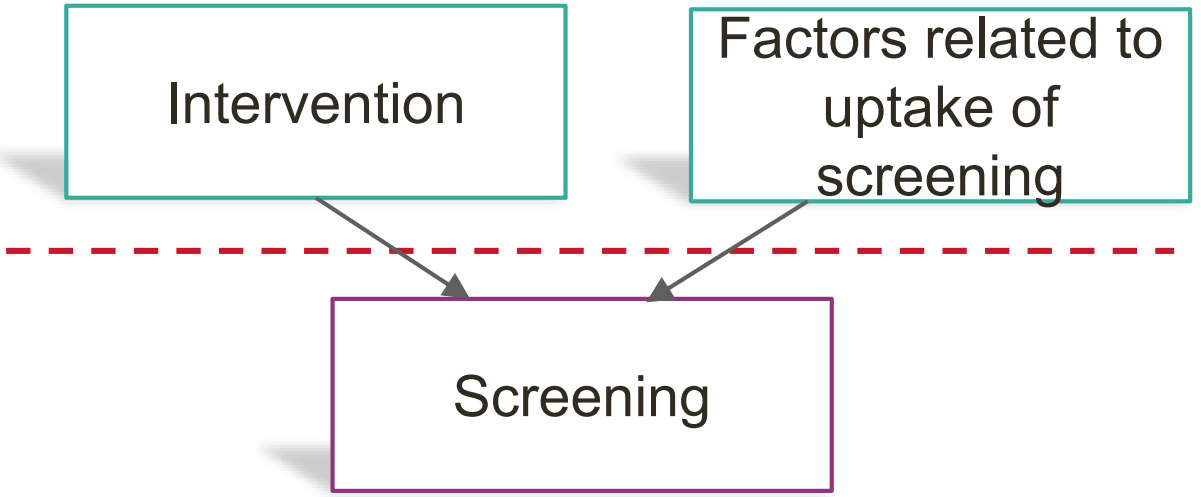
STOP CRC cluster randomization



Level 1: Individual-level outcomes nested within clinics

- Individual-level outcomes within same clinic expected to be correlated (i.e., to *cluster*)

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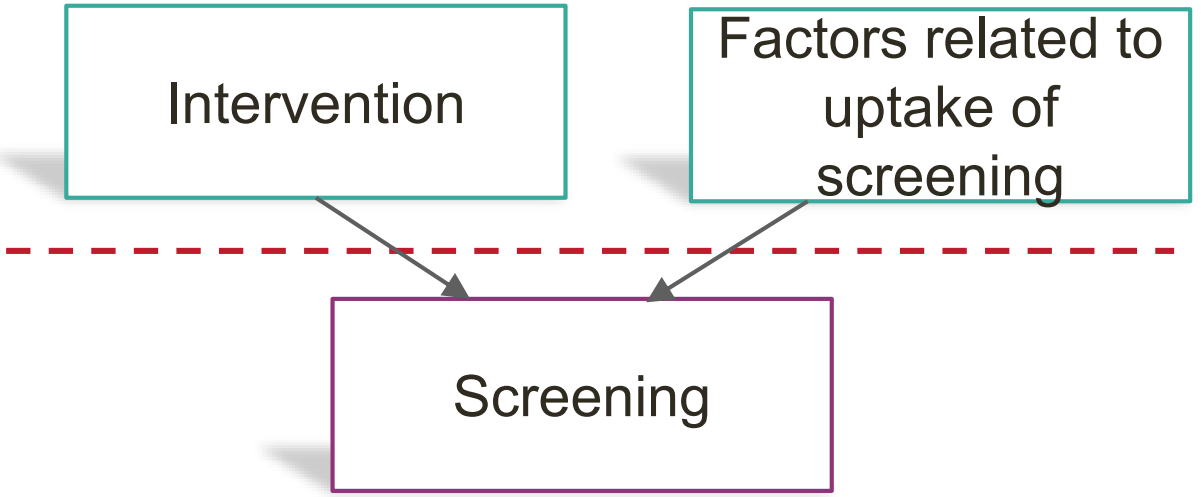
STOP CRC cluster randomization



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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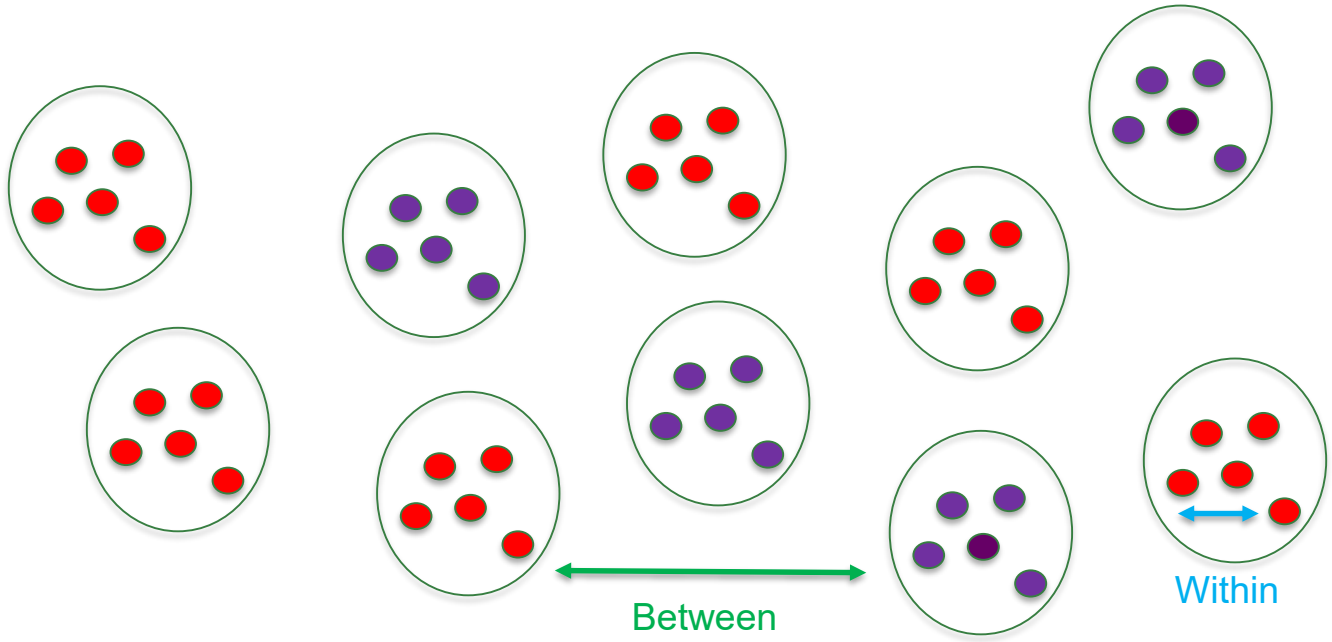
Understanding outcome clustering

- 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)

Understanding outcome clustering: complete clustering (ICC =1)

- Screened
- Not screened



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 σ_W^2 =0

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

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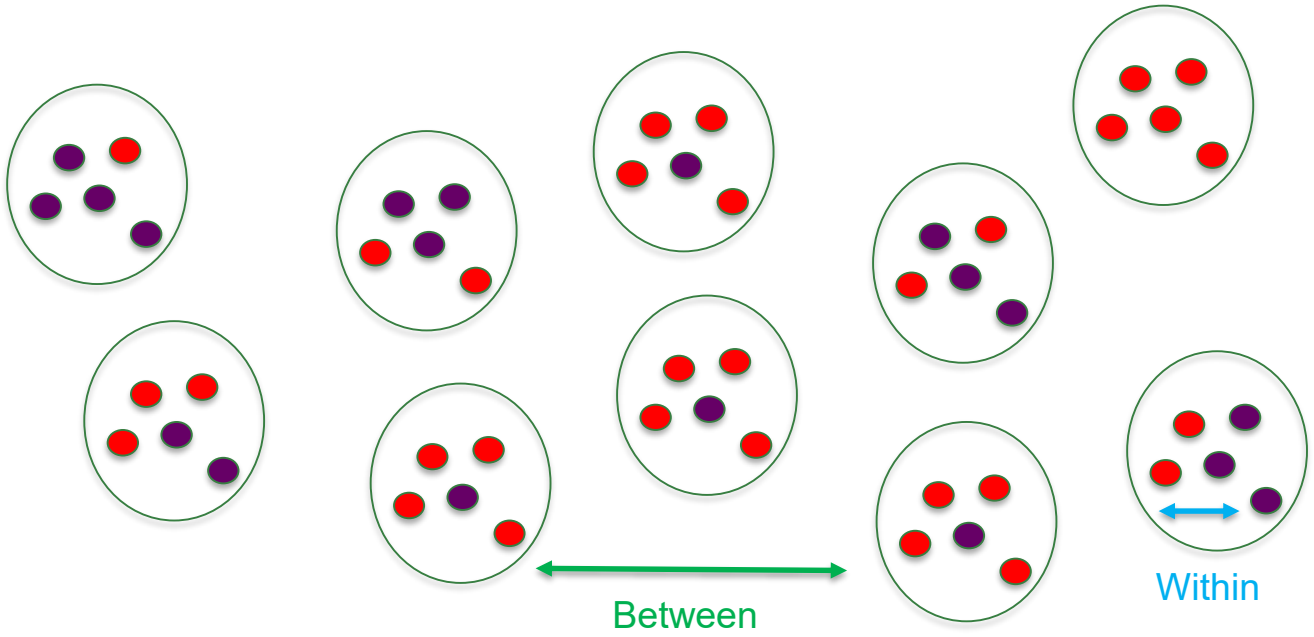
Understanding outcome clustering: some clustering (0 < ICC < 1)

- Screened
- Not screened



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

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

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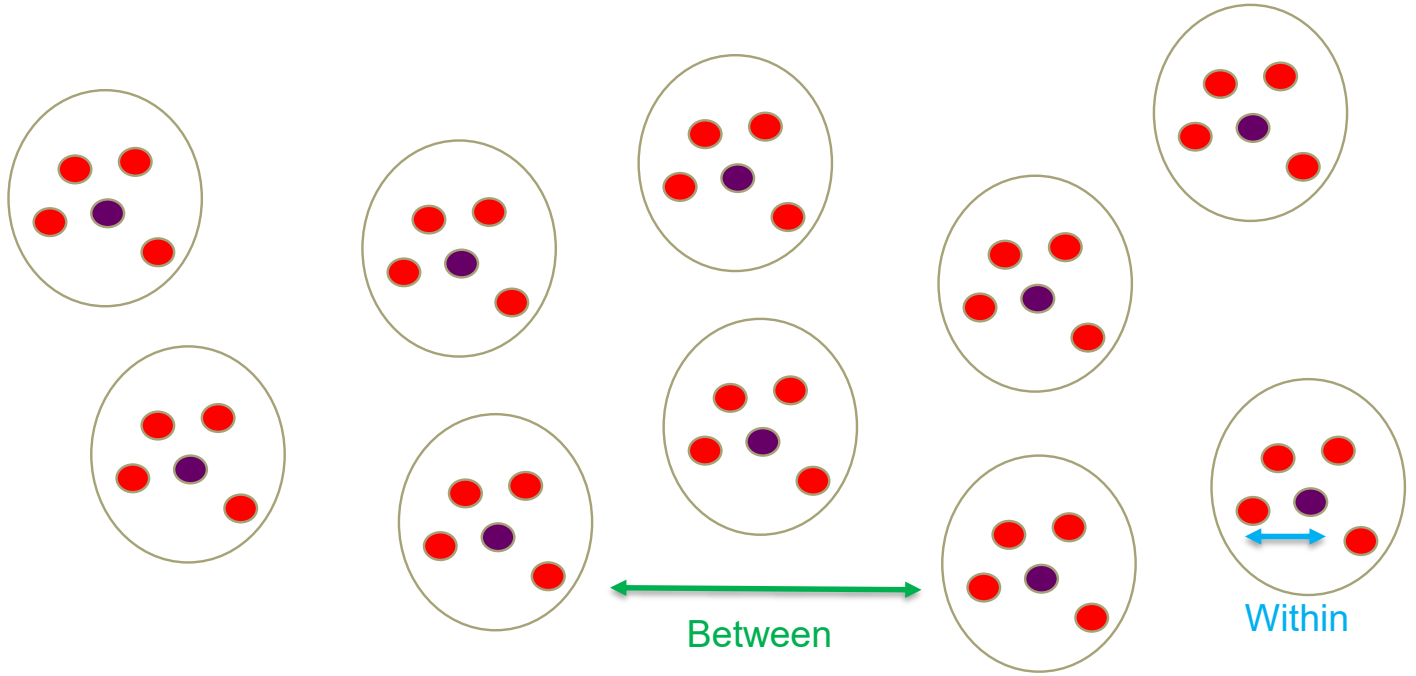
Understanding outcome clustering: no clustering (ICC=0)

- Screened
- Not screened



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

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

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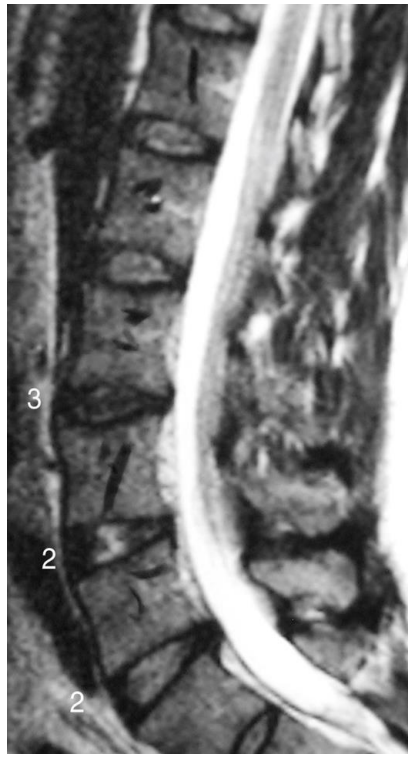
Summary of design issues for CRTs

- 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-factor 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.

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.
- Alternatives to randomized trials are available, but not included in this presentation.

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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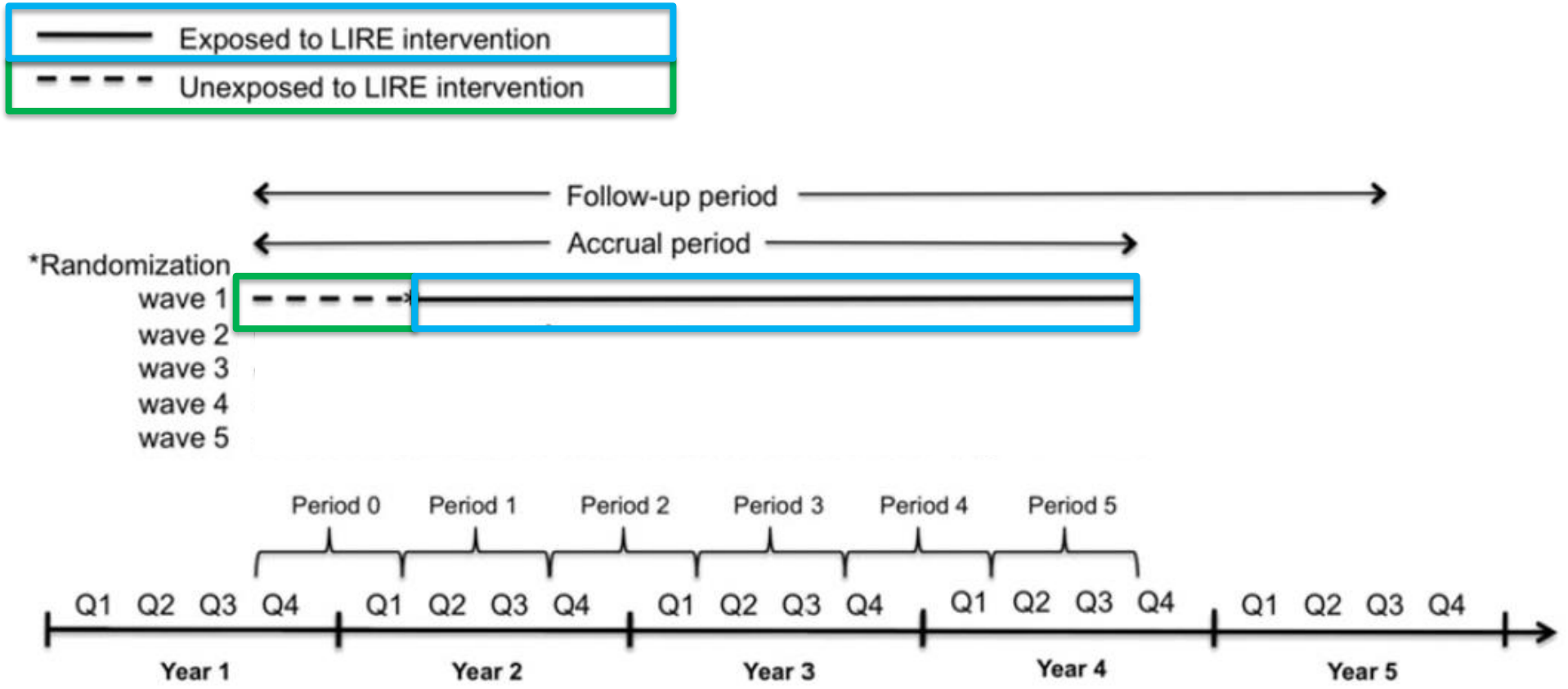
NIH Collaboratory ePCT: LIRE



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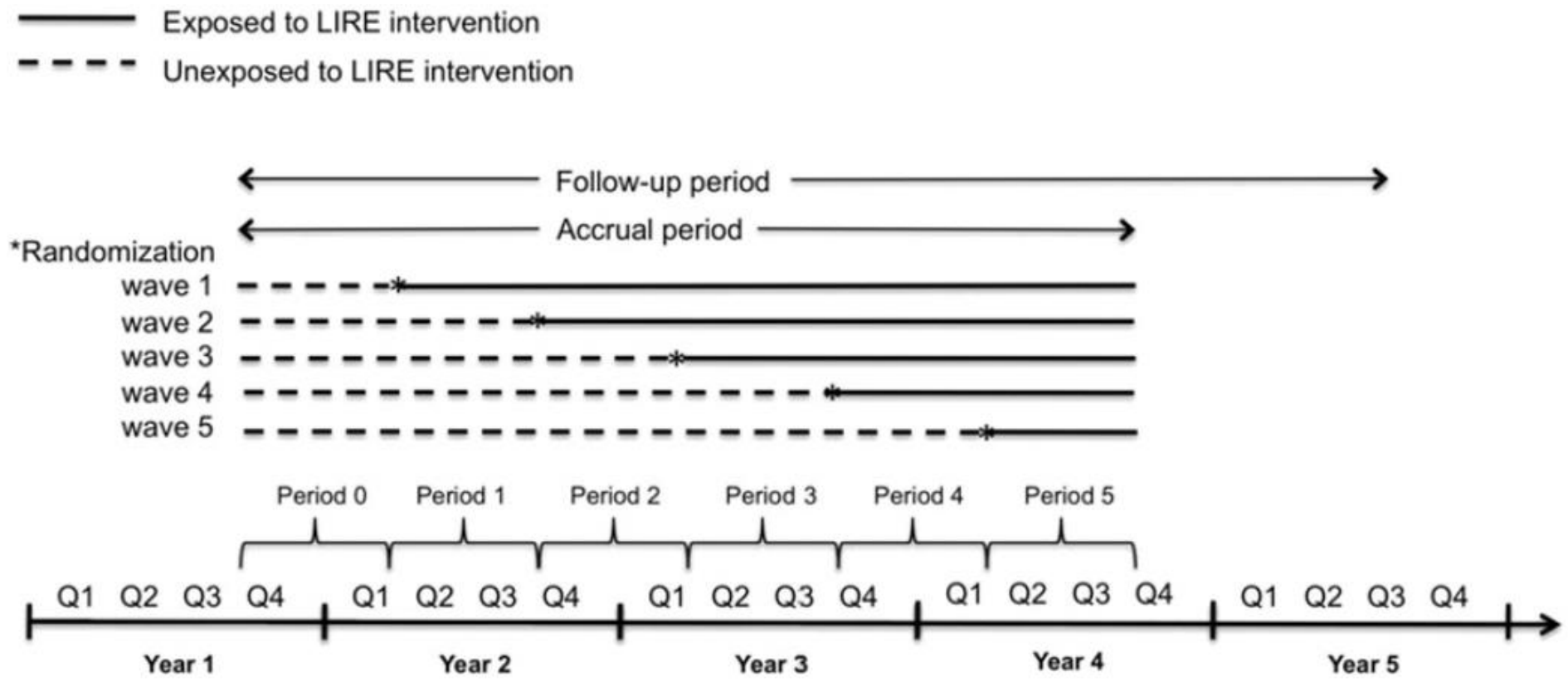
NIH Collaboratory ePCT: LIRE



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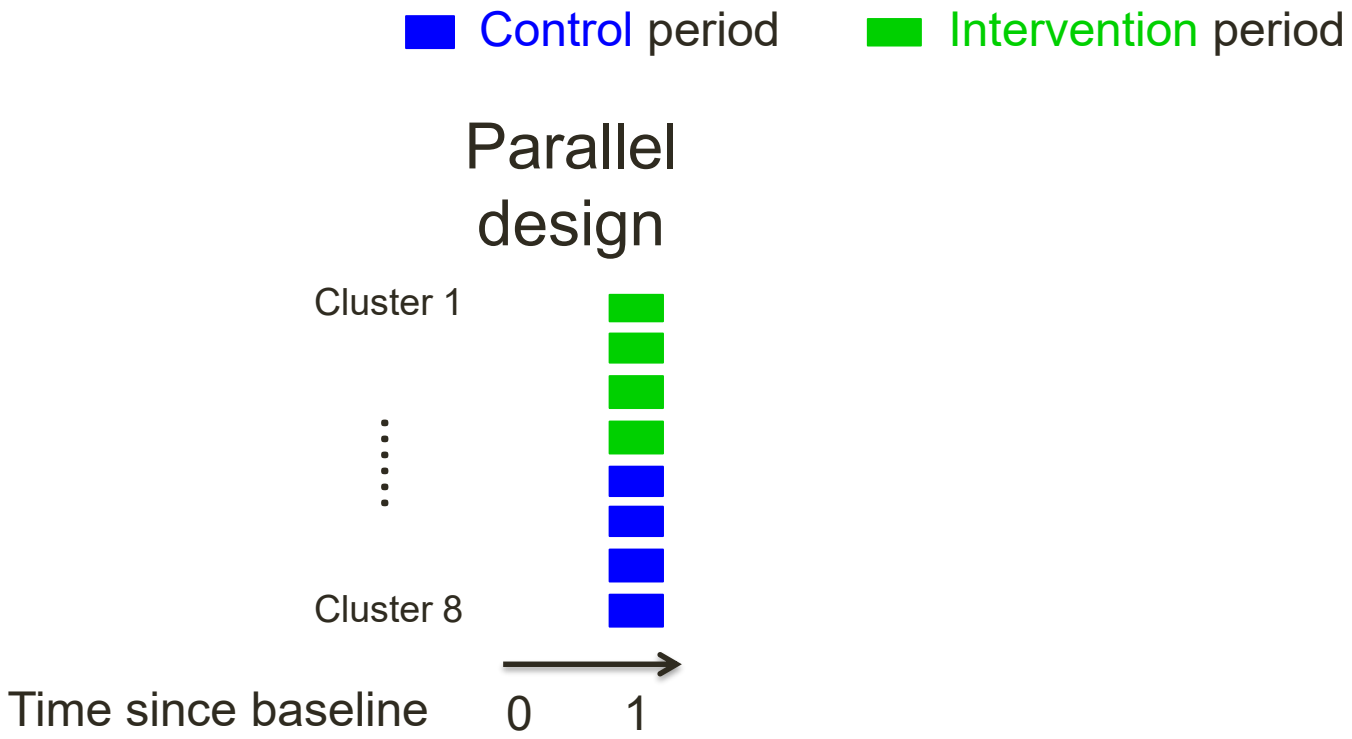
Types of CRT designs

Examples with 8 clusters: 1-year intervention



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Types of CRT designs

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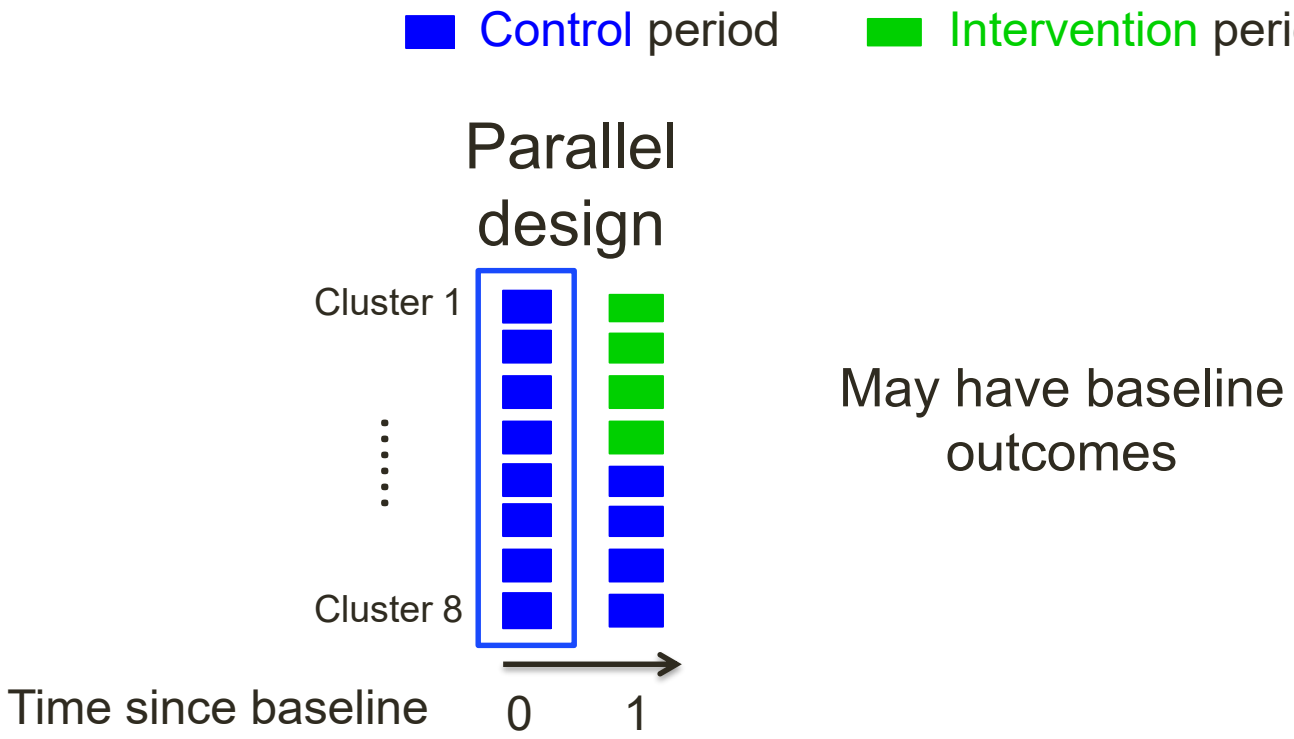

May have baseline outcomes

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

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Types of CRT designs

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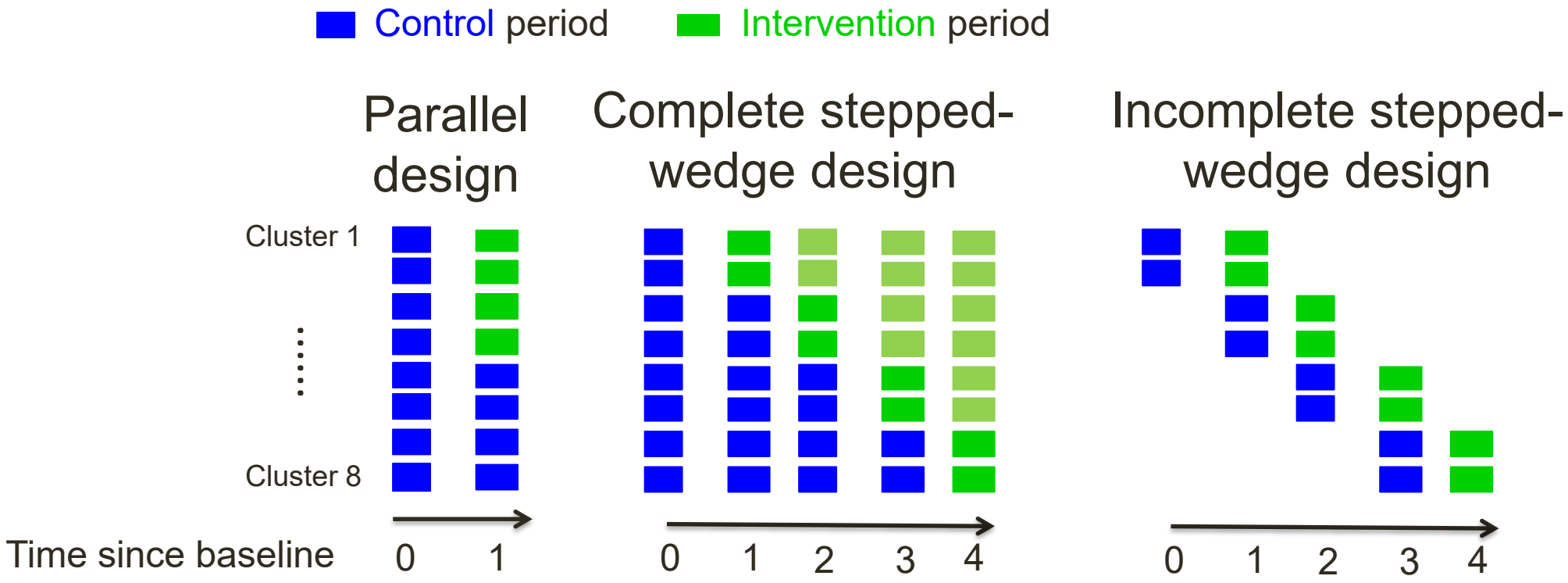

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Types of CRT designs

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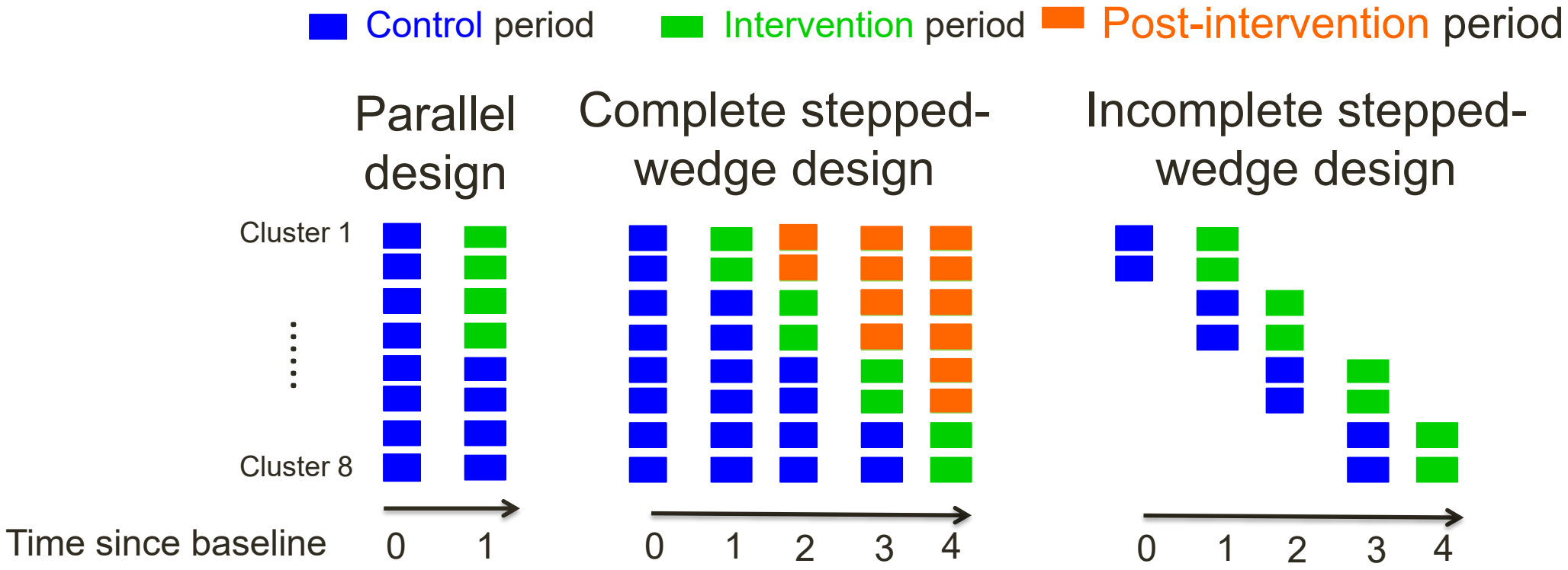

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Summary of design issues

- Many design features common to RCTs are available to SW-CRTs:
  - Cohort and cross-sectional designs
  - Single-factor 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.

NIH Collaboratory ePCT: OPTIMUM

- 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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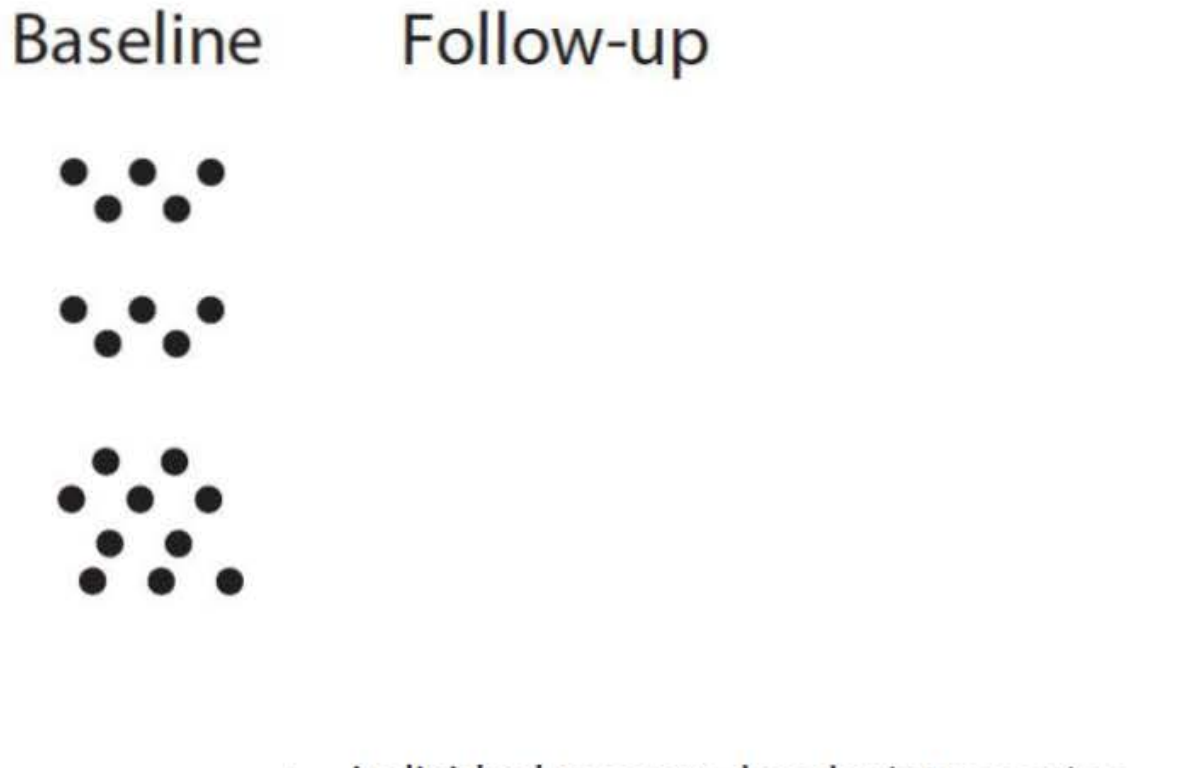
NIH Collaboratory ePCT: OPTIMUM



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-factor 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.

How to choose the right design?

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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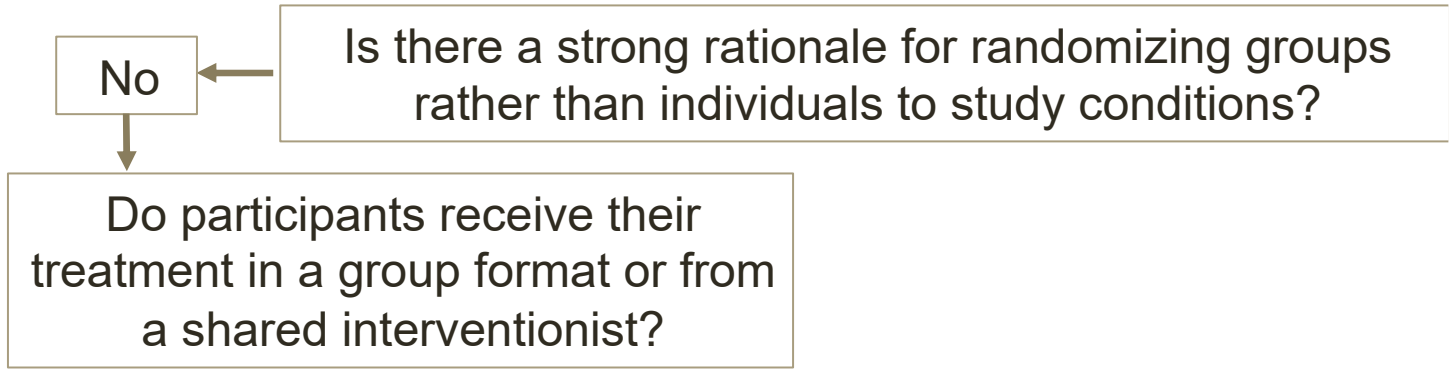
How to choose the right design?



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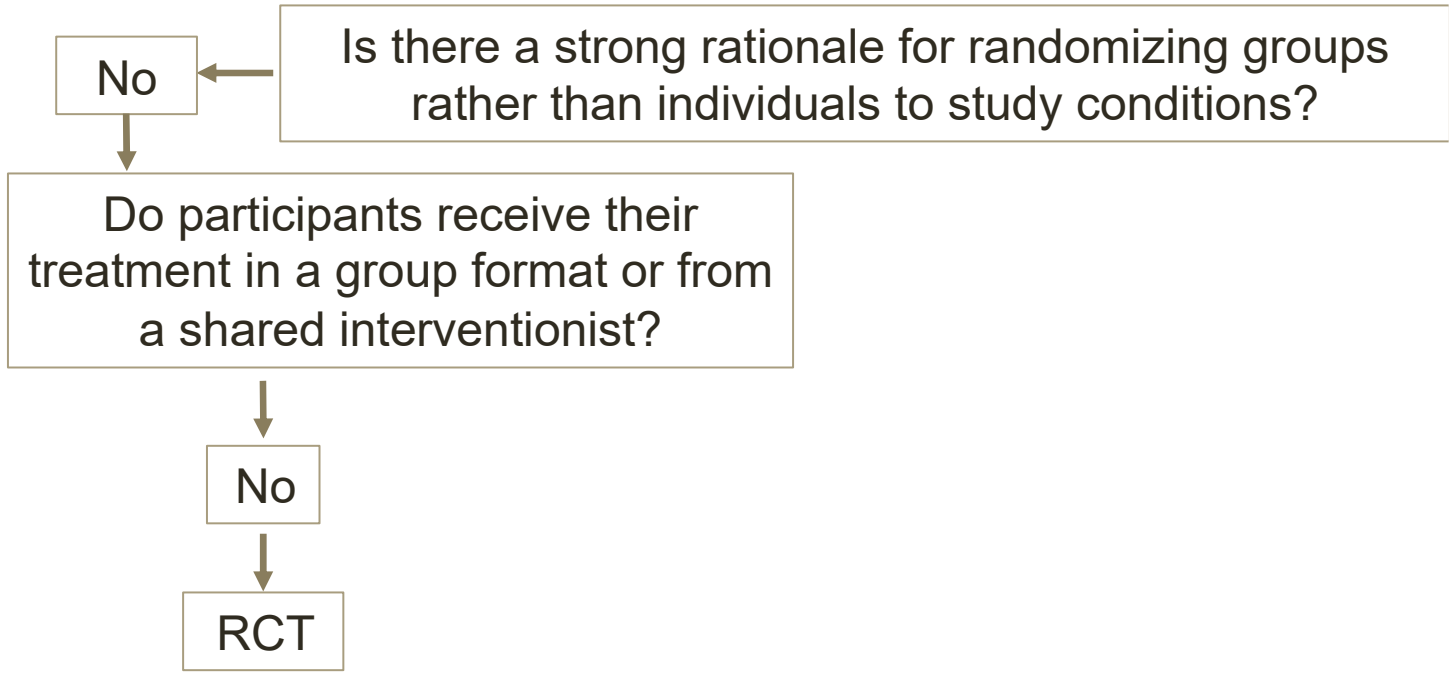

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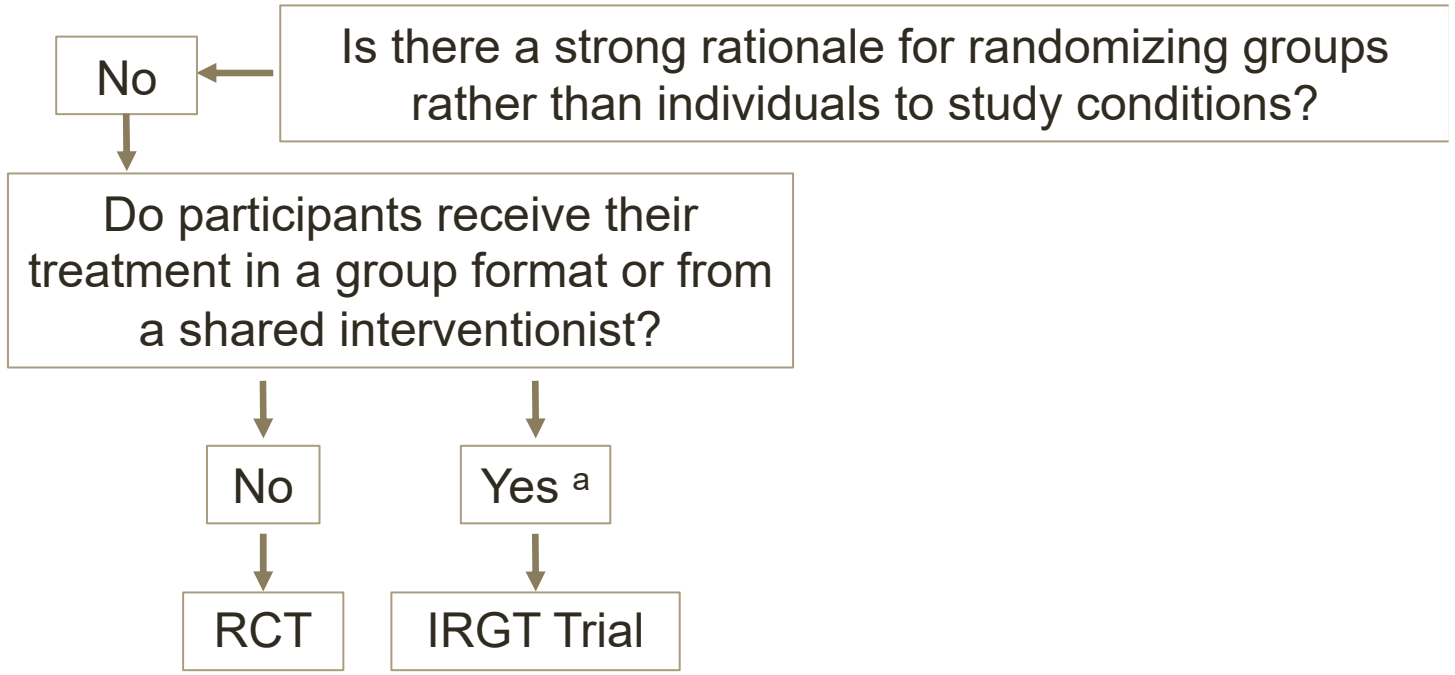

[a] If the intervention is delivered through a physical or a virtual group, or through shared interventionists who each work with multiple participants, positive ICC can develop over the course of the trial.

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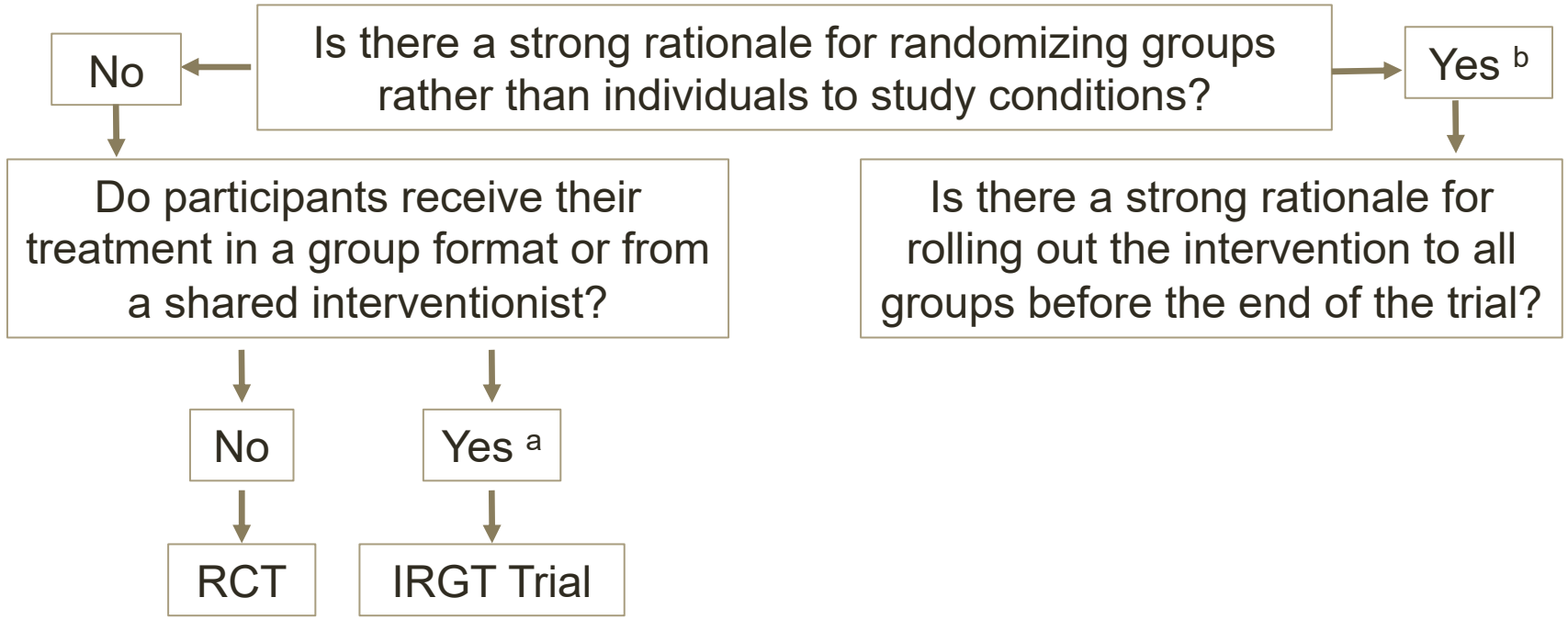

[a] If the intervention is delivered through a physical or a virtual group, or through shared interventionists who each work with multiple participants, positive ICC can develop over the course of the trial.

[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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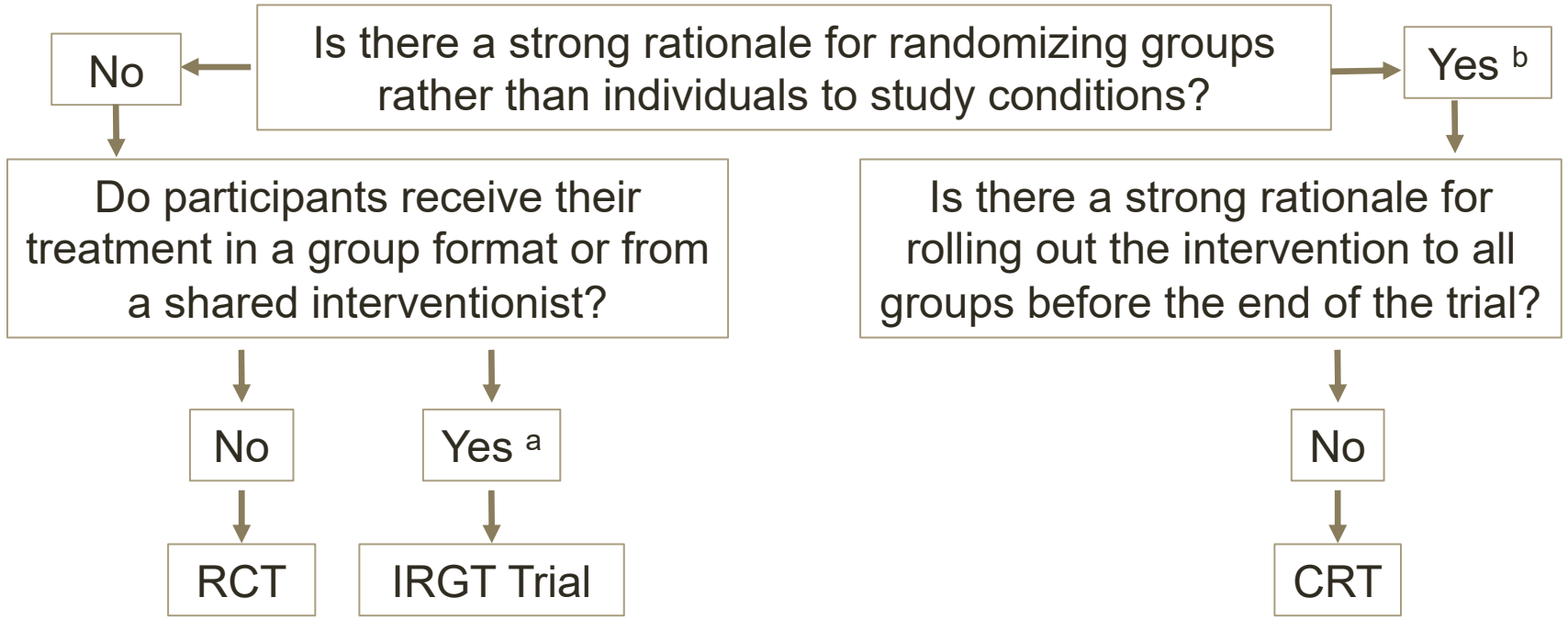

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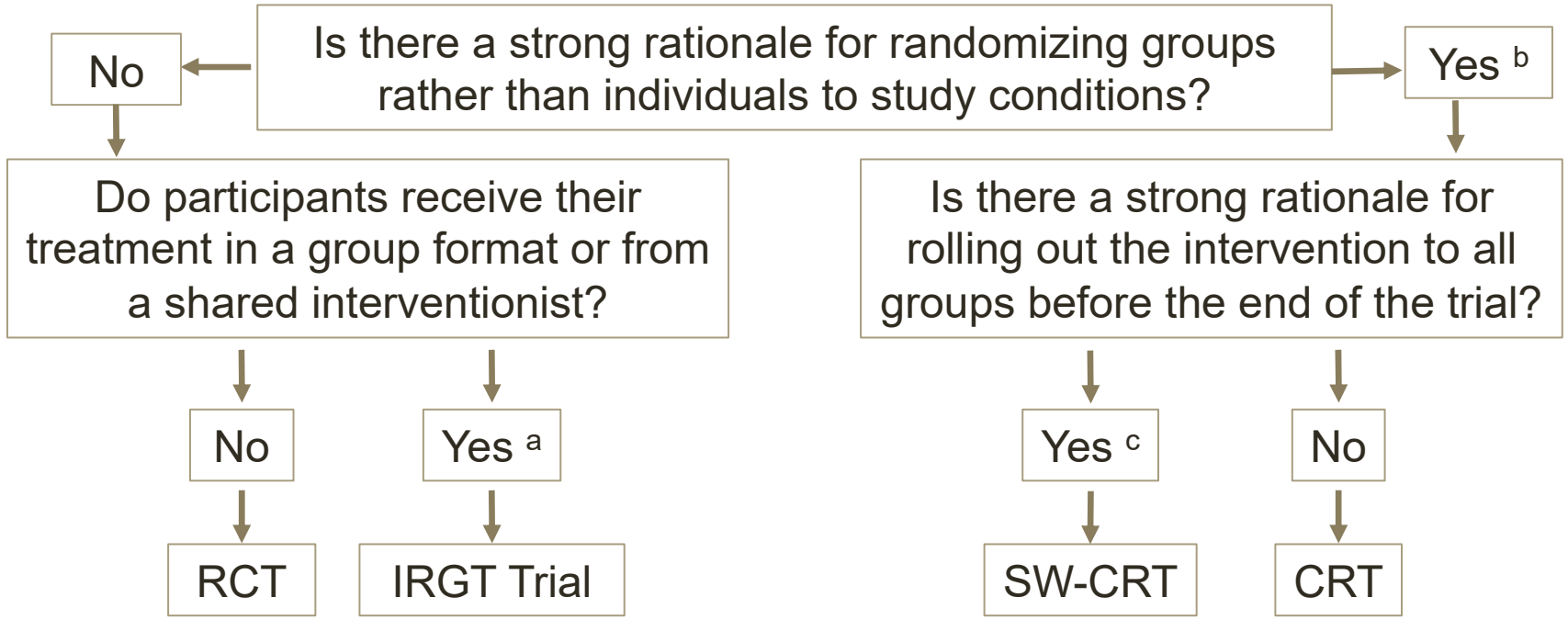

[a] If the intervention is delivered through a physical or a virtual group, or through shared interventionists who each work with multiple participants, positive ICC can develop over the course of the trial.

[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
  - Confounding can be more of a concern in IRGT Trials than in RCTs

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 is 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 less rigorous than parallel CRTs
    - Only choose when a parallel CRT not appropriate.

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 ibeing 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

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!**

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.

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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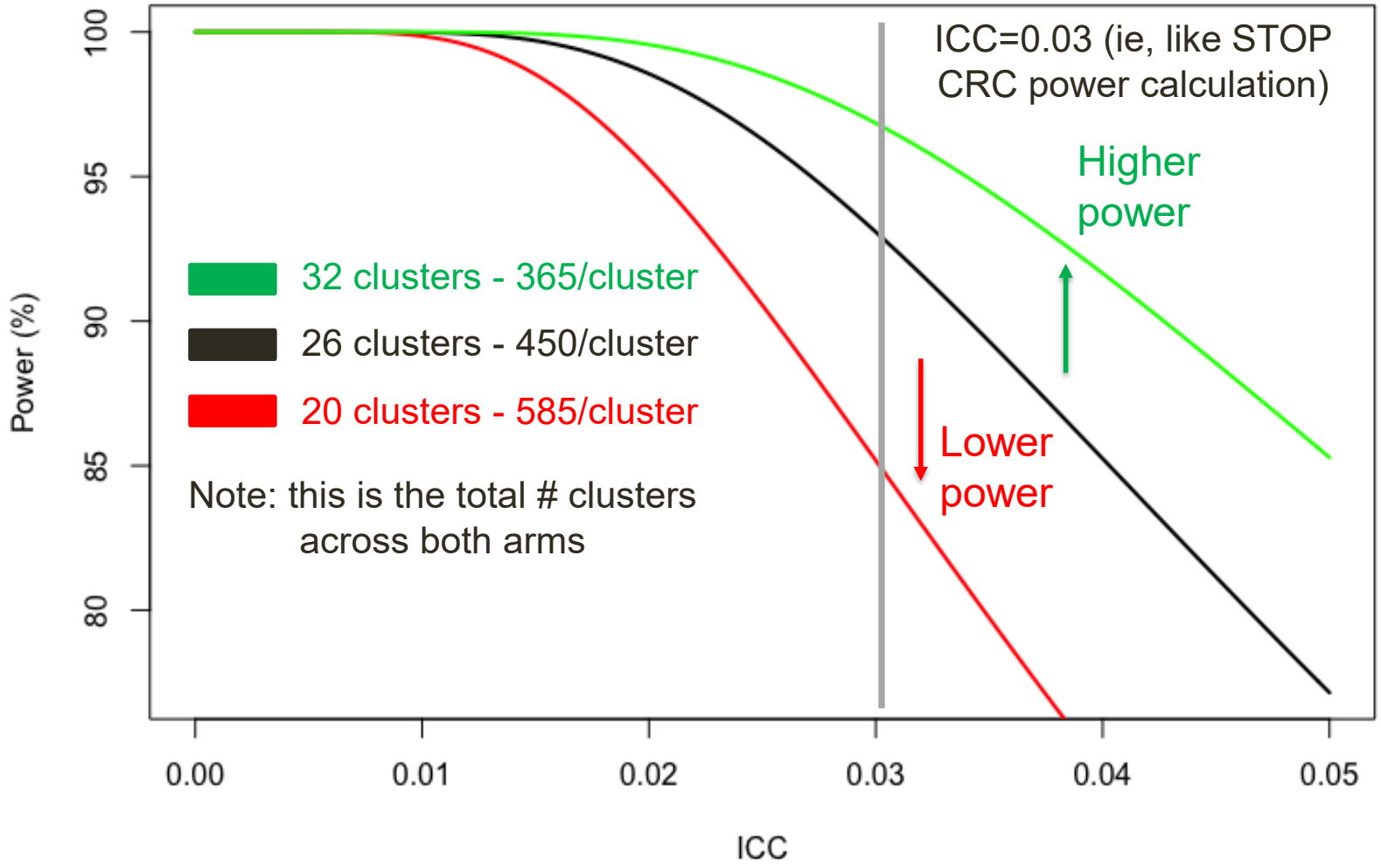
Clustering: Impact on power in STOP CRC



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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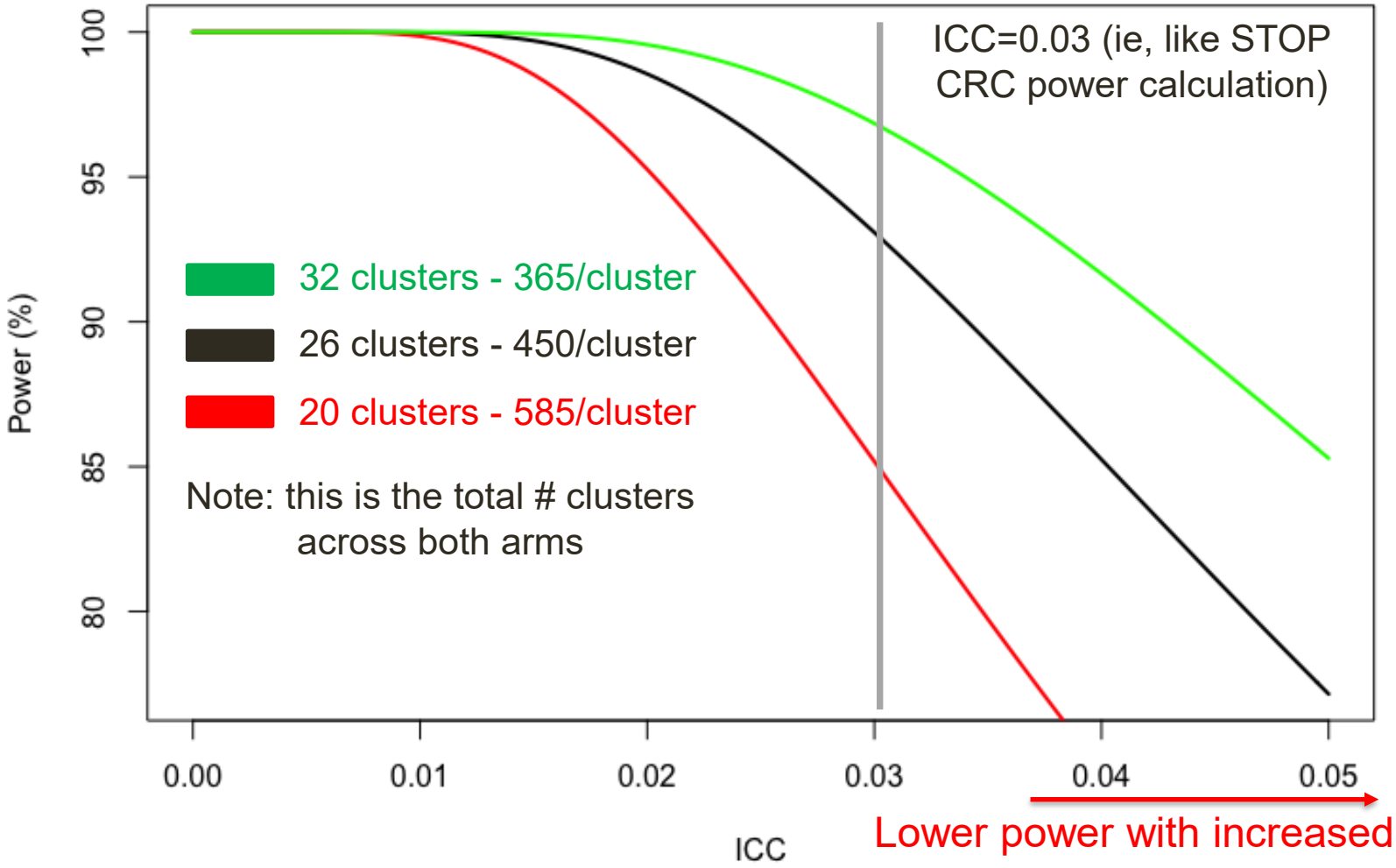
Clustering: Impact on power in STOP CRC



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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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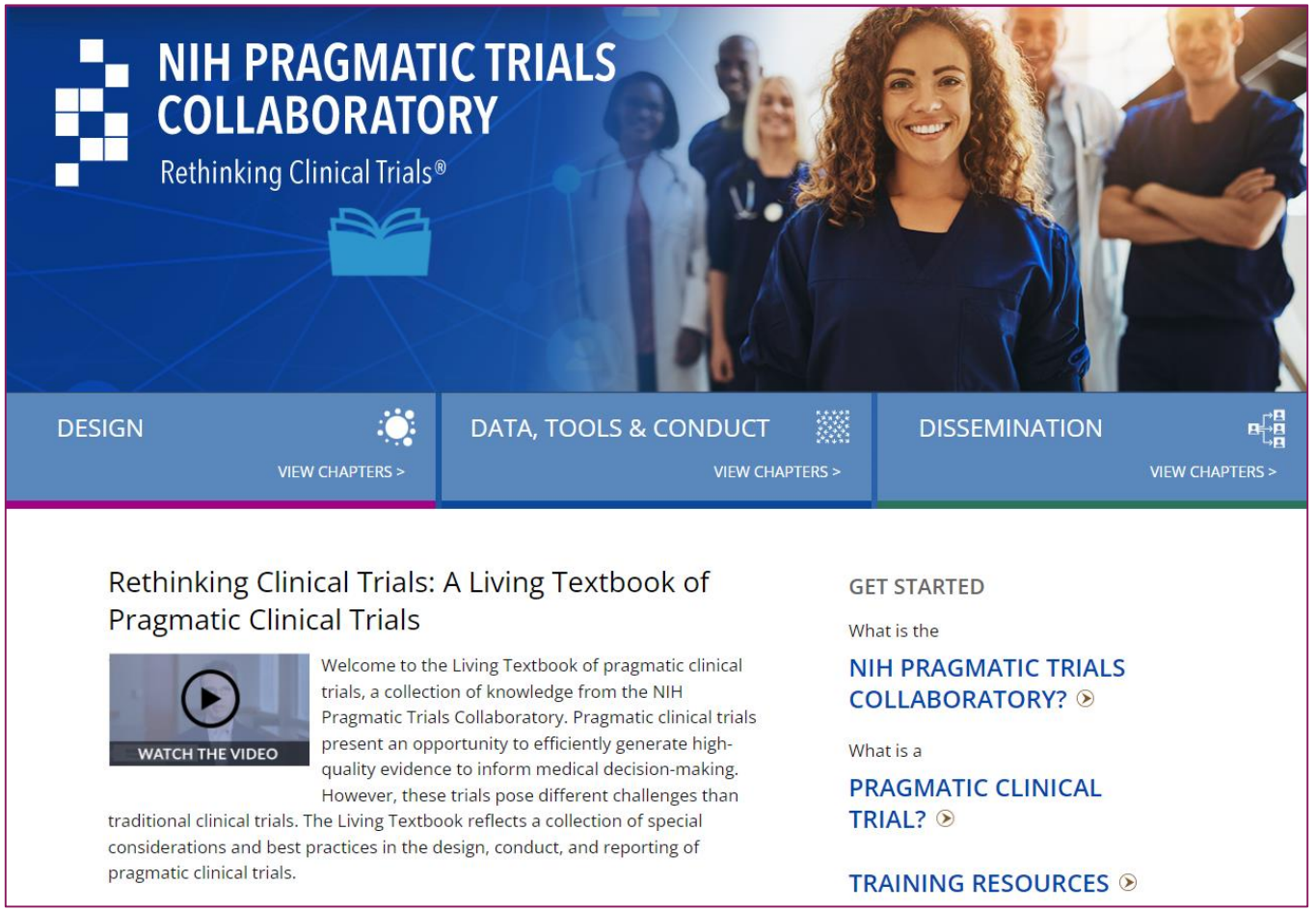
Resource: The Living Textbook

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

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
- 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.
- Maleyeff L et al. Assessing exposure-time treatment effect heterogeneity in stepped-wedge cluster randomized trials. Biometrics. 2022. Epub 2022/11/24. PMID: 36416302.
- Brown CH et al. Accounting for Context in Randomized Trials after Assignment. Prevention science : the official journal of the Society for Prevention Research. 2022. PMID: 36083435.