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.

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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 rates
  - Applied to clinical site → cluster randomization
- Unit of randomization: clinical site
- Two-arm cluster randomized trial (CRT)
  - Also referred to as a group-randomized or community randomized trial

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

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Reasons to randomize clusters instead of individuals

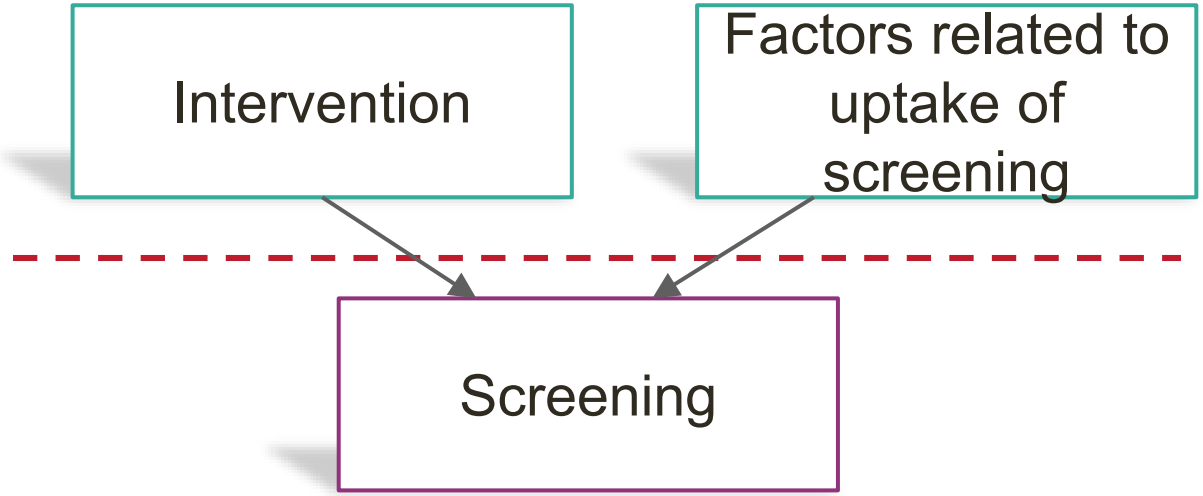
- Intervention targets health care units rather than individuals
  - STOP CRC: clinic-based intervention to improve screening

- 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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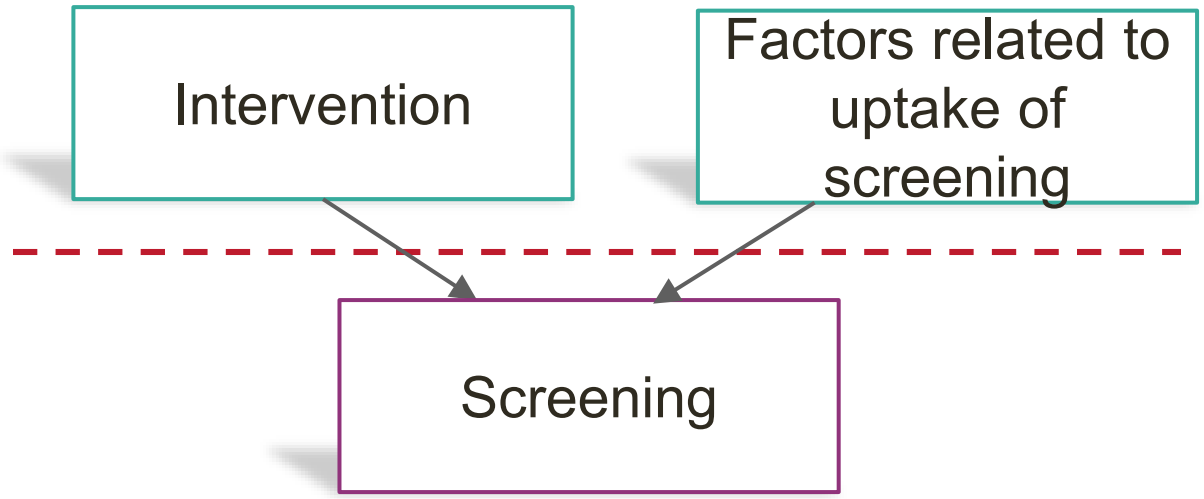
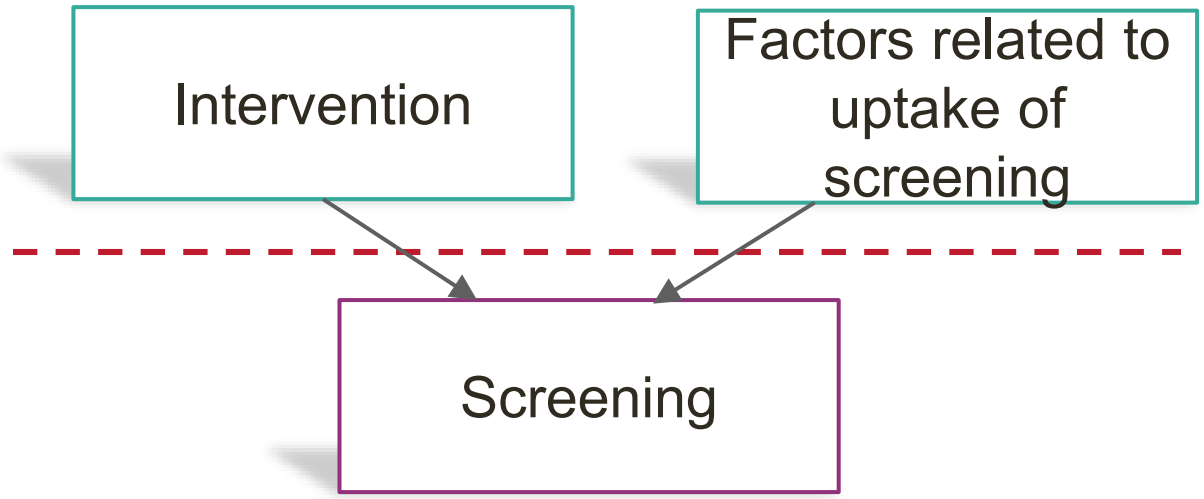
STOP CRC cluster randomization



Level 1: Individual-level outcomes nested within clinics

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

STOP CRC cluster randomization



Level 1: Individual-level outcomes nested within clinics

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

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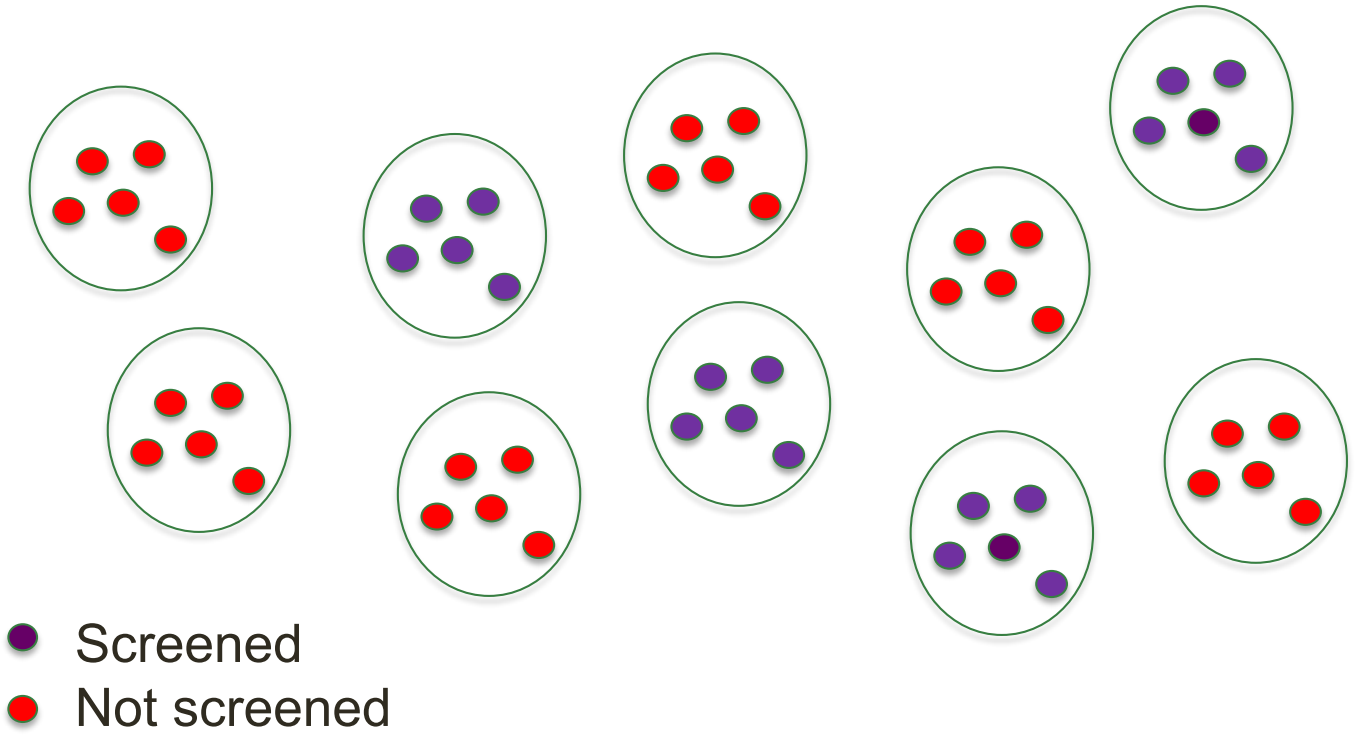
Understanding outcome clustering

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

Understanding outcome clustering: complete clustering



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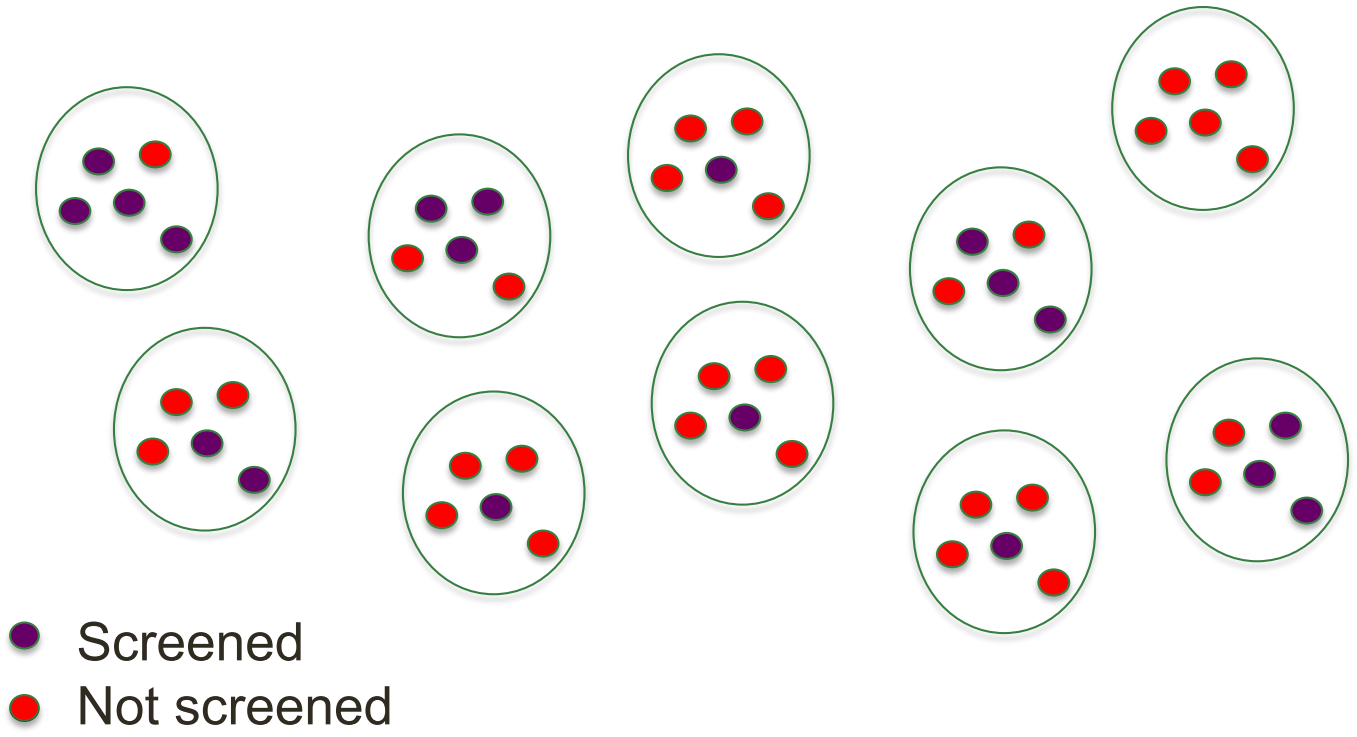
Understanding outcome clustering: some clustering



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

Summary of design issues

- All the design features common to RCTs are available to GRTs 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.

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

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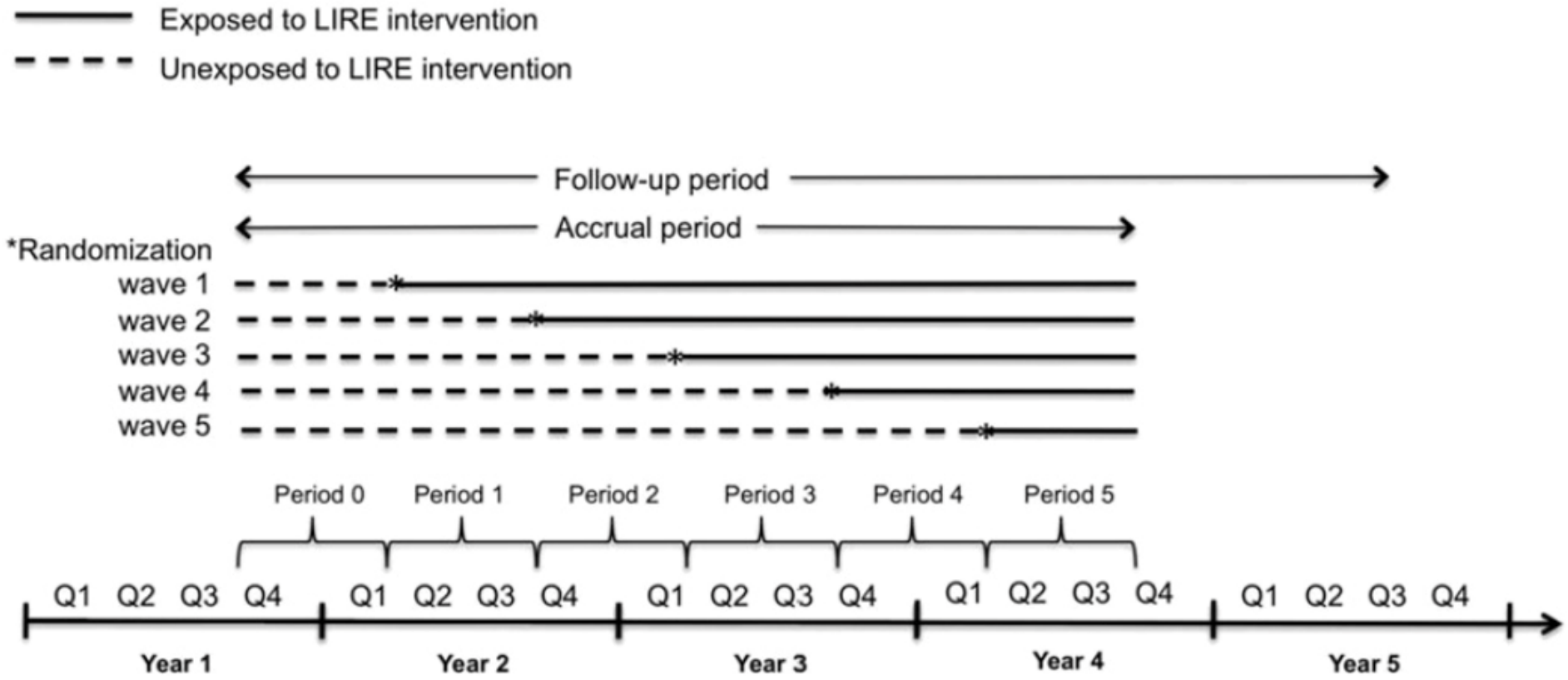
Jarvik JG et al. *Contemp Clin Trials*. 2015;45(Pt B):157-163.

NIH Collaboratory ePCT: LIRE



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

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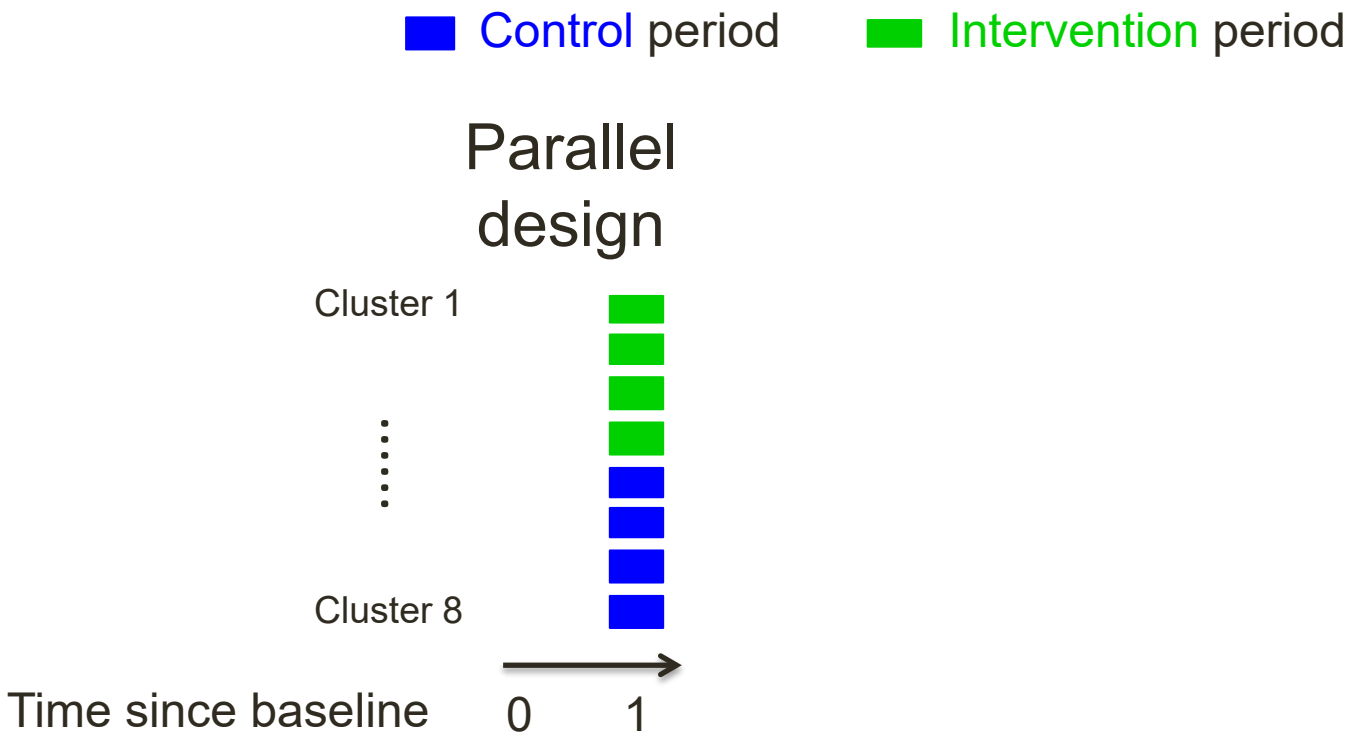
Types of CRT designs

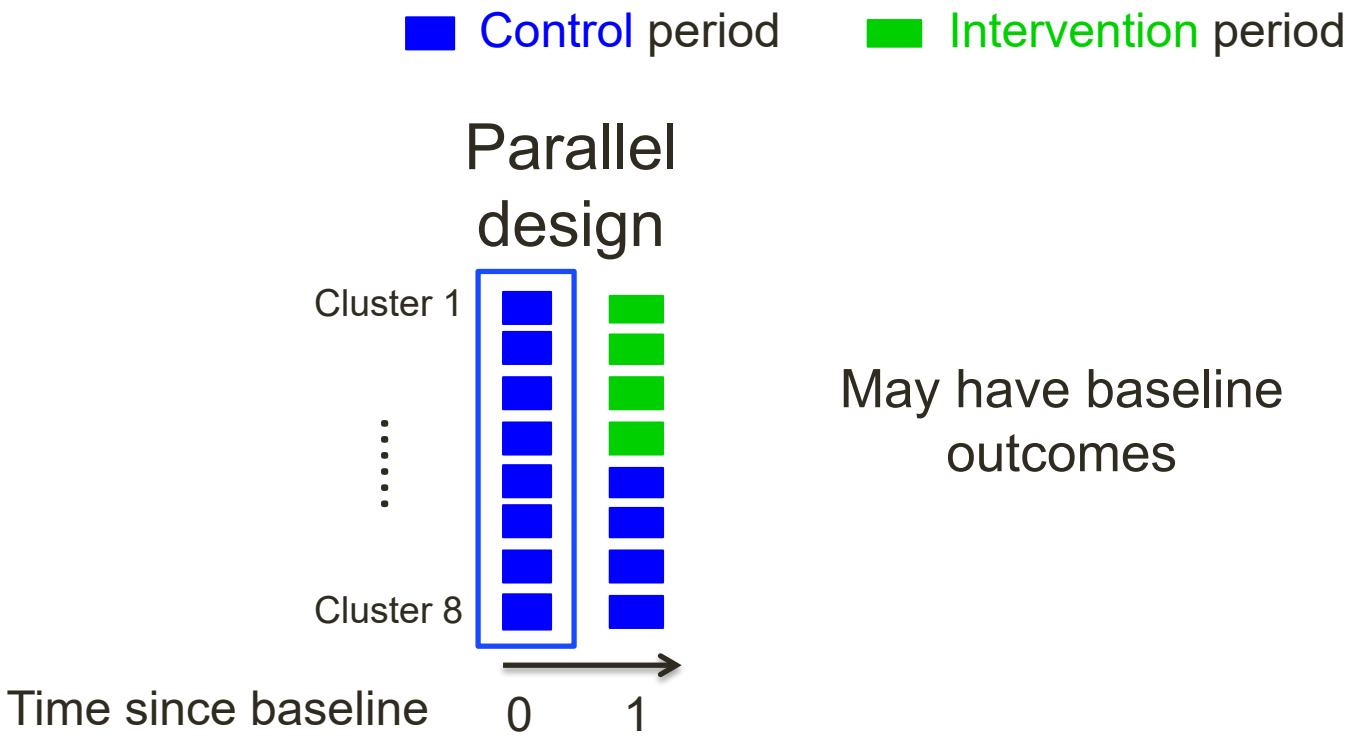
Examples with 8 clusters: 1-year intervention



Based on: Hemming K, Lilford R, Girling AJ. 2015. Stepped-wedge cluster randomised controlled trials: a generic framework including parallel and multiple-level designs. Stat Med. 34:181-196. doi:10.1002/sim.6325. PMID: 25346484

Types of CRT designs

Examples with 8 clusters: 1-year intervention



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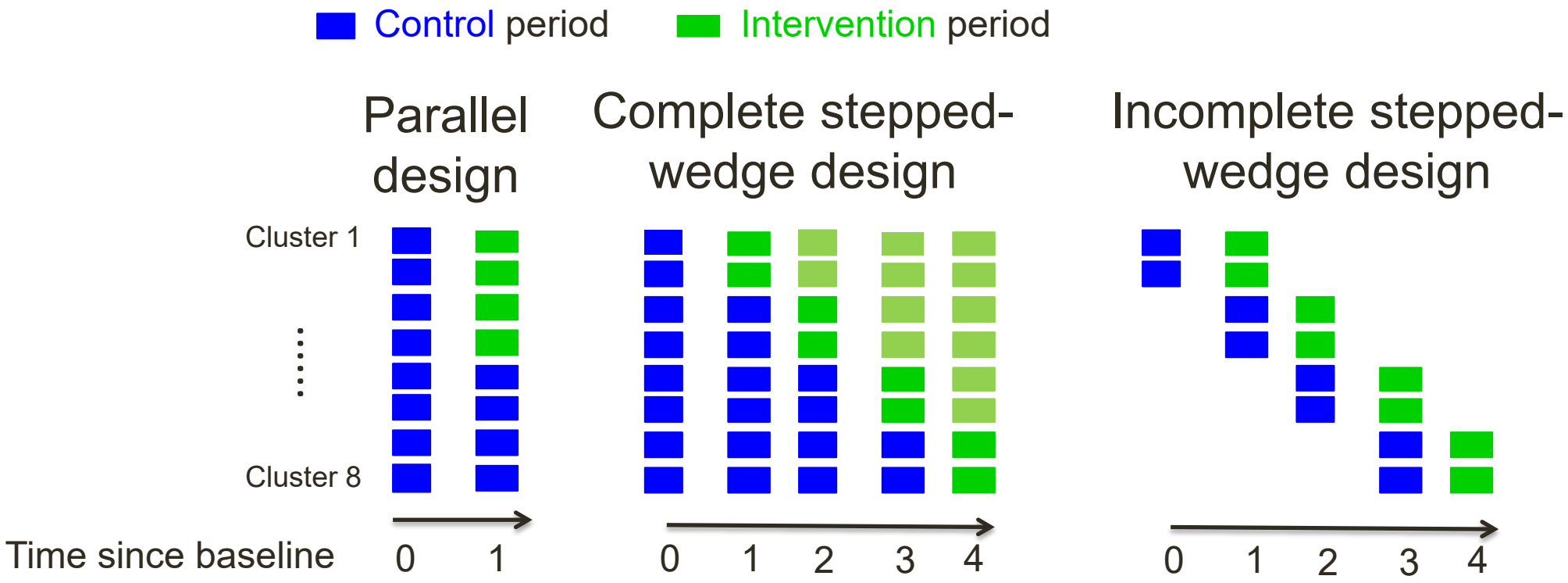
Types of CRT designs

Examples with 8 clusters: 1-year intervention



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Summary of design issues

- Many of the design features common to RCTs are available to SW-GRTs:
  - 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.

Challenges of pragmatic study design

- Trade-offs in flexibility, adherence, and generalizability are inevitable
- Implementation by healthcare system staff, not research staff
- New staff workflow and responsibility acknowledged
- Triage or case selection by healthcare system staff using existing structures with some modification

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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 group randomized designs are simple and powerful, but still need to address “clustering” for design and analysis.

It all starts with a clear research question…

- Population
- Intervention
- Comparison
- Outcome(s)

From: European Medicines Agency
ICH E9 (R1)

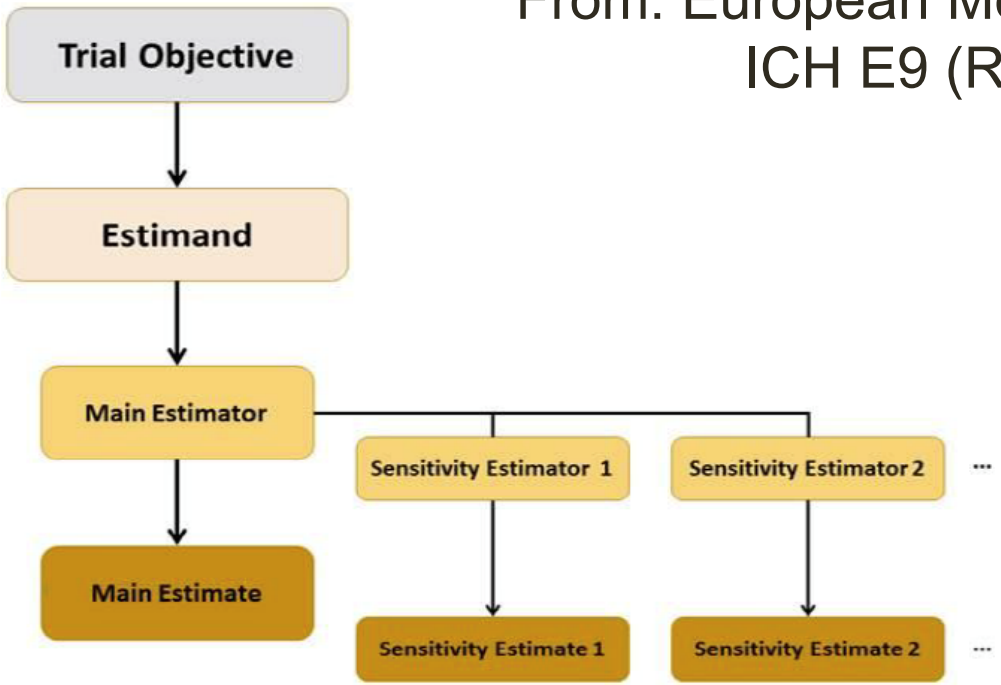

Figure 1: Aligning target of estimation, method of estimation, and sensitivity analysis, for a given trial objective

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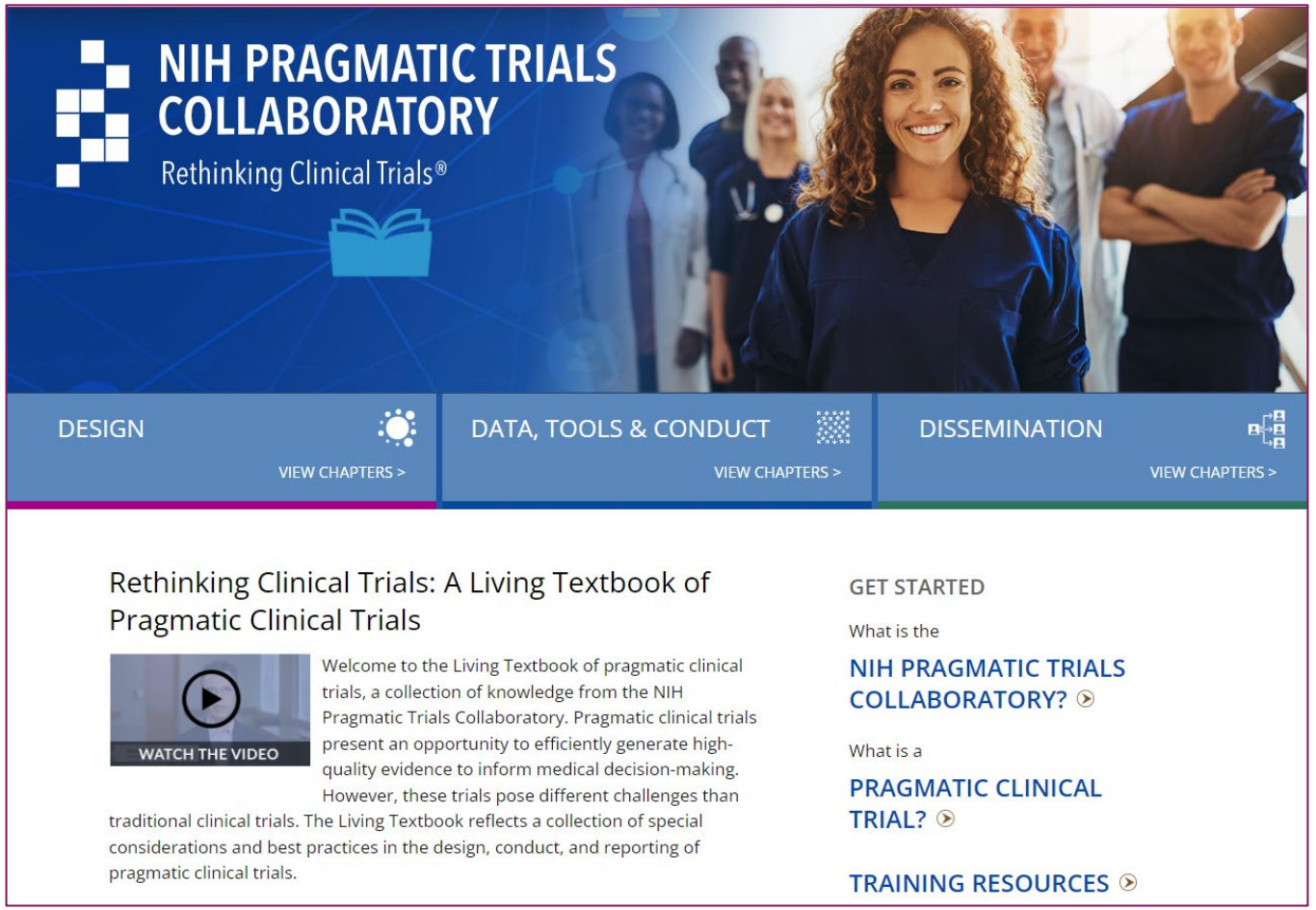
Resource: The Living Textbook

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
    - SW-GRTs for Disease Prevention Research (Monica Taljaard, July 11, 2018)
    - Design and Analysis of IRGTs in Public Health (Sherri Pals, April 24, 2017)
    - Research Methods Resources for Clinical Trials Involving Groups or Clusters (David Murray, December 13, 2017)

- Research Methods Resources Website
  - https://researchmethodsresources.nih.gov/
  - Material on GRTs and IRGTs and a sample size calculator for GRTs

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Resources

- Recommended reading:
  - Turner EL, Li F, Gallis JA, Prague M, Murray DM. Review of recent methodological developments in group-randomized trials: Part 1-design. Am J Public Health. 2017;107:907-915.
  - Turner EL, Prague M, Gallis JA, Li F, Murray DM. Review of recent methodological developments in group-randomized trials: Part 2-analysis. Am J Public Health. 2017;107:1078-1086.
  - Hemming K, Taljaard M, McKenzie JE, et al. Reporting of stepped wedge cluster randomised trials: extension of the CONSORT 2010 statement with explanation and elaboration. BMJ. 2018;363:k1614.
  - Murray DM, Pals SL, George SM, et al. Design and analysis of group-randomized trials in cancer: A review of current practices. Prev Med. 2018;111: 241-247.