ePCT Experimental Design and Analysis

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NIH PRAGMATIC TRIALS COLLABORATORY
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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.

Analysis Considerations

Embedded Pragmatic Clinical Trials

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Learning goals

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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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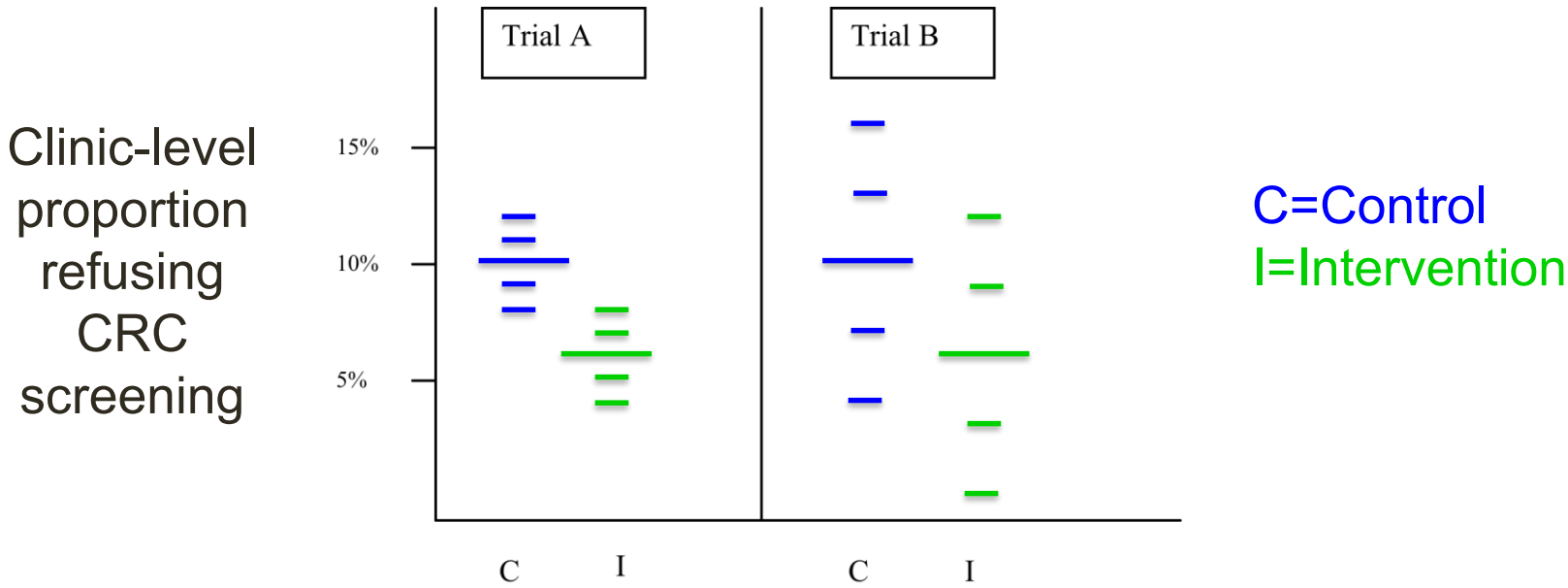
Two example CRTs inspired by STOP CRC

- 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”

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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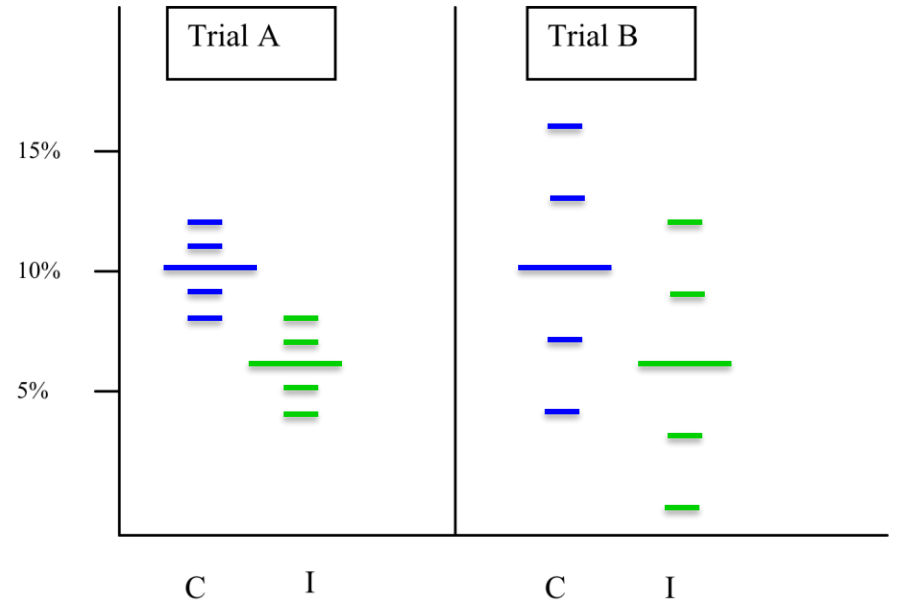
Clustering in CRTs: Implications for analysis

Clinic-level proportion refusing CRC screening

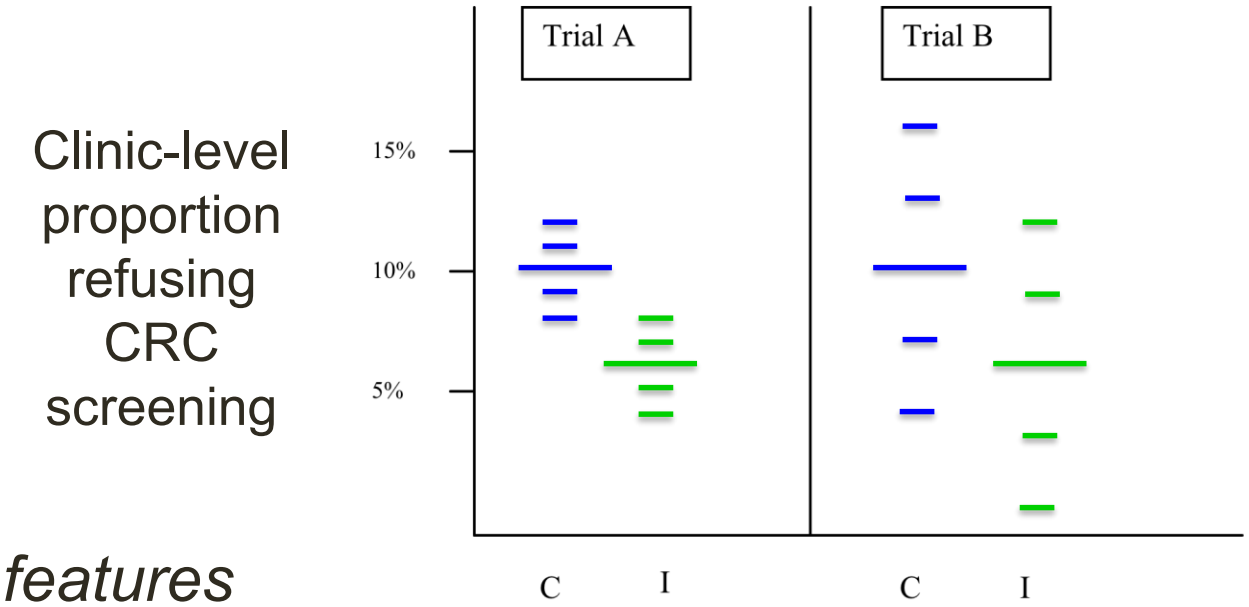


C=Control
I=Intervention

Which trial shows more evidence of benefit?

Adapted from Hayes & Moulton (2009)

Clustering in CRTs: Implications for analysis



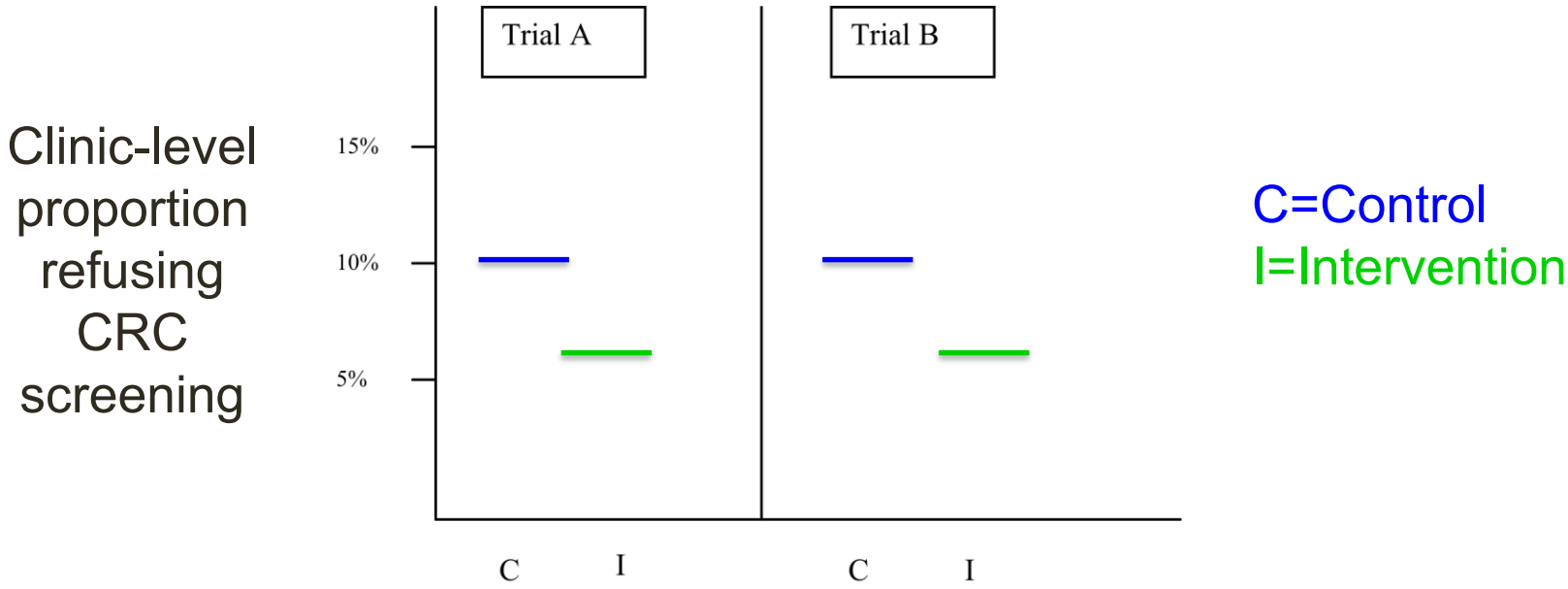
C=Control
I=Intervention

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)

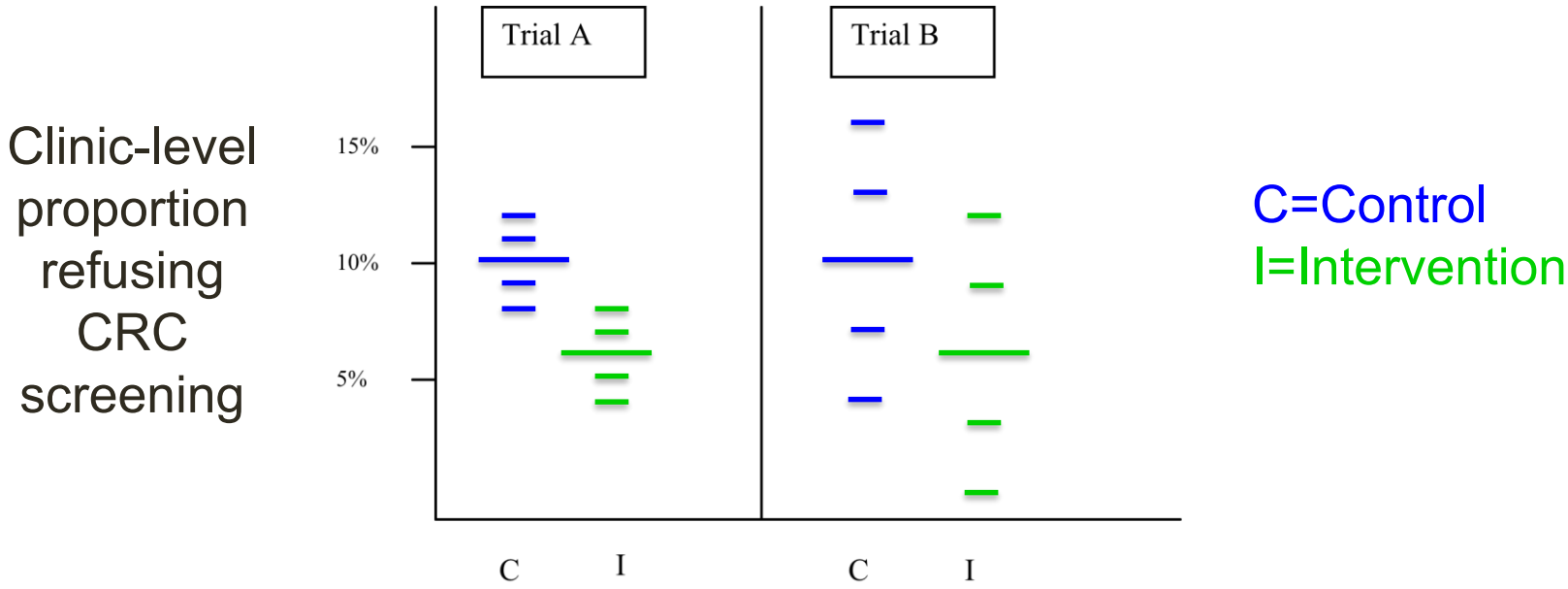
Clustering in CRTs: Implications for analysis



- 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)

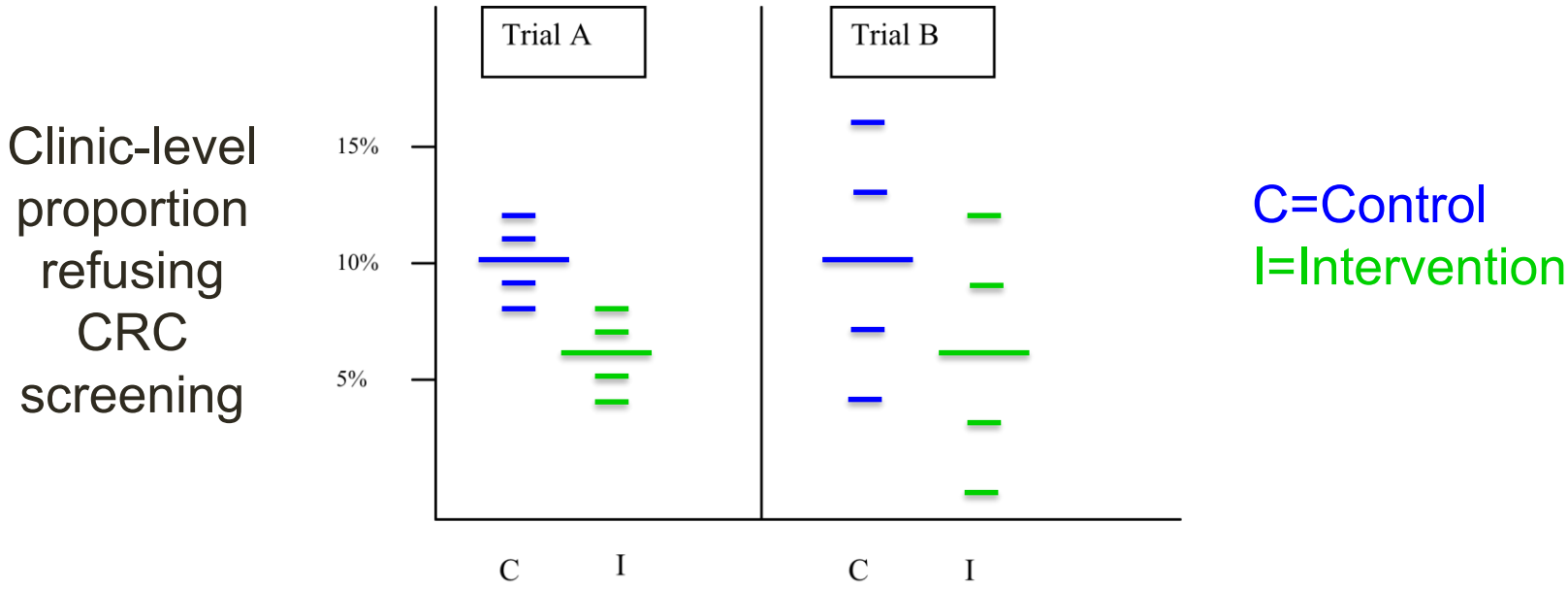
Clustering in CRTs: Implications for analysis



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

Adapted from Hayes & Moulton (2009)

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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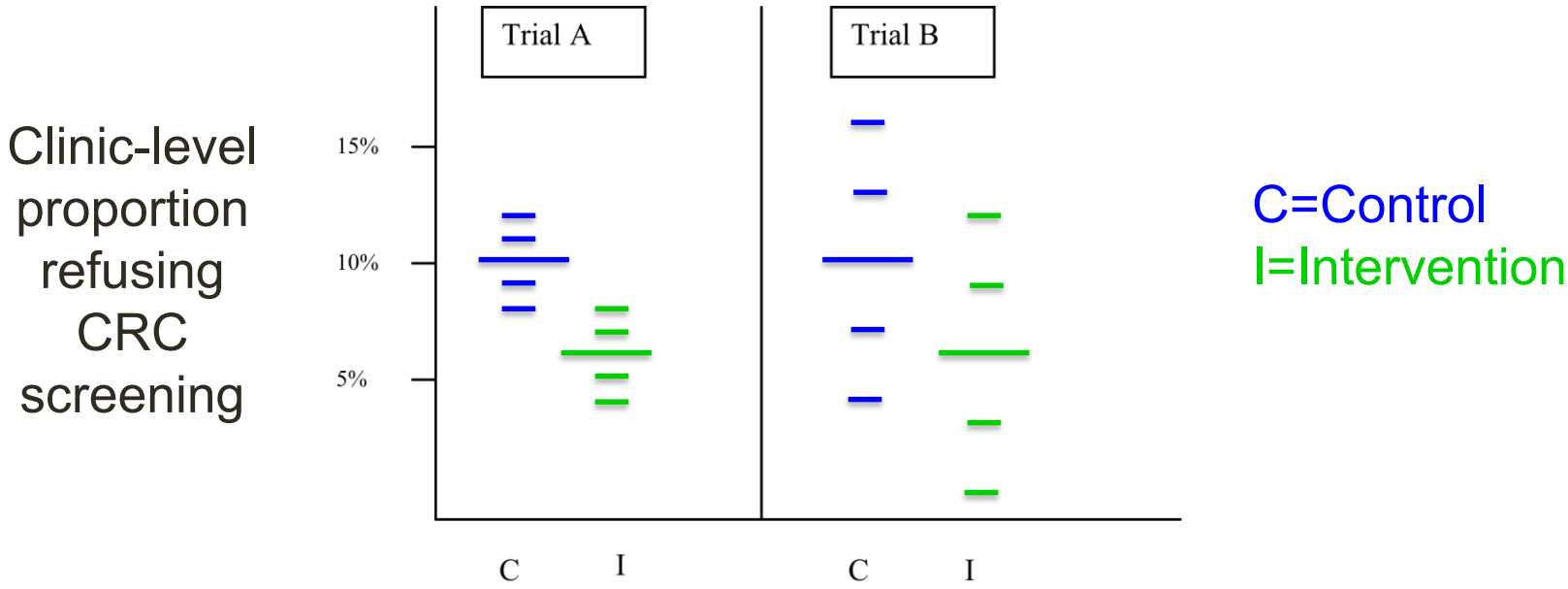
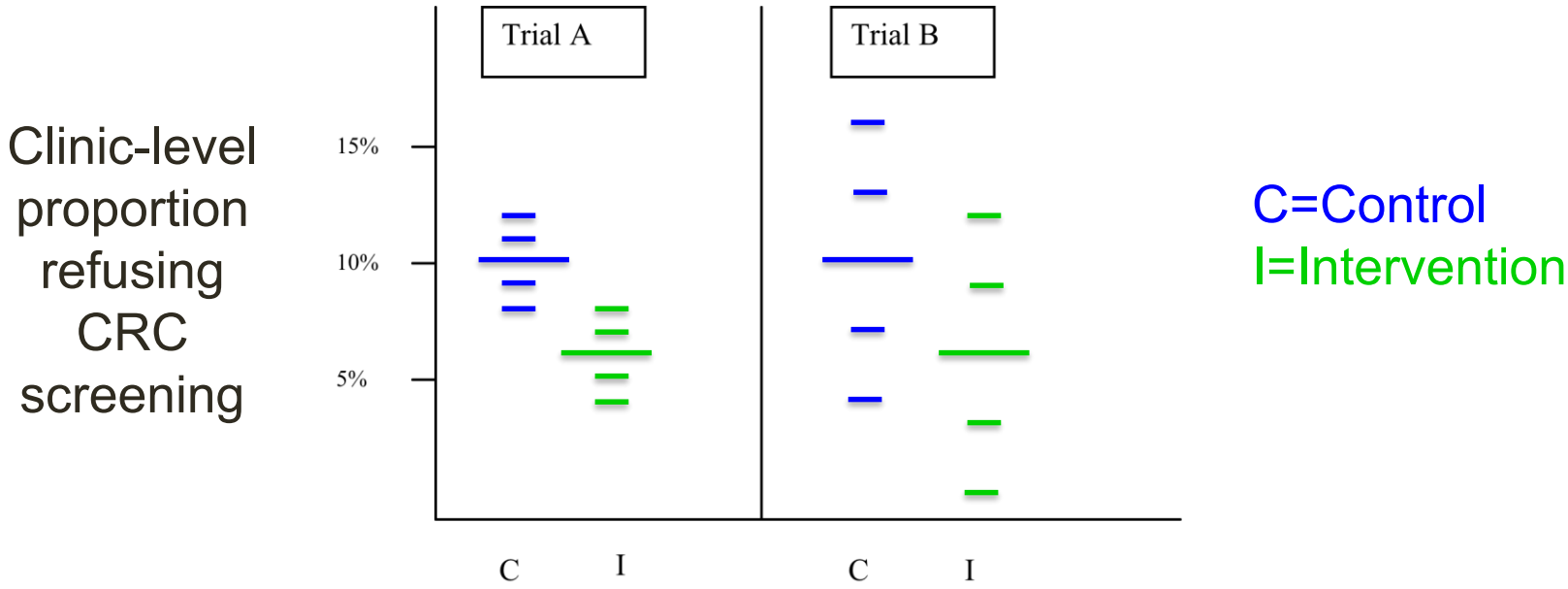
Clustering in CRTs: Implications for analysis



- 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)

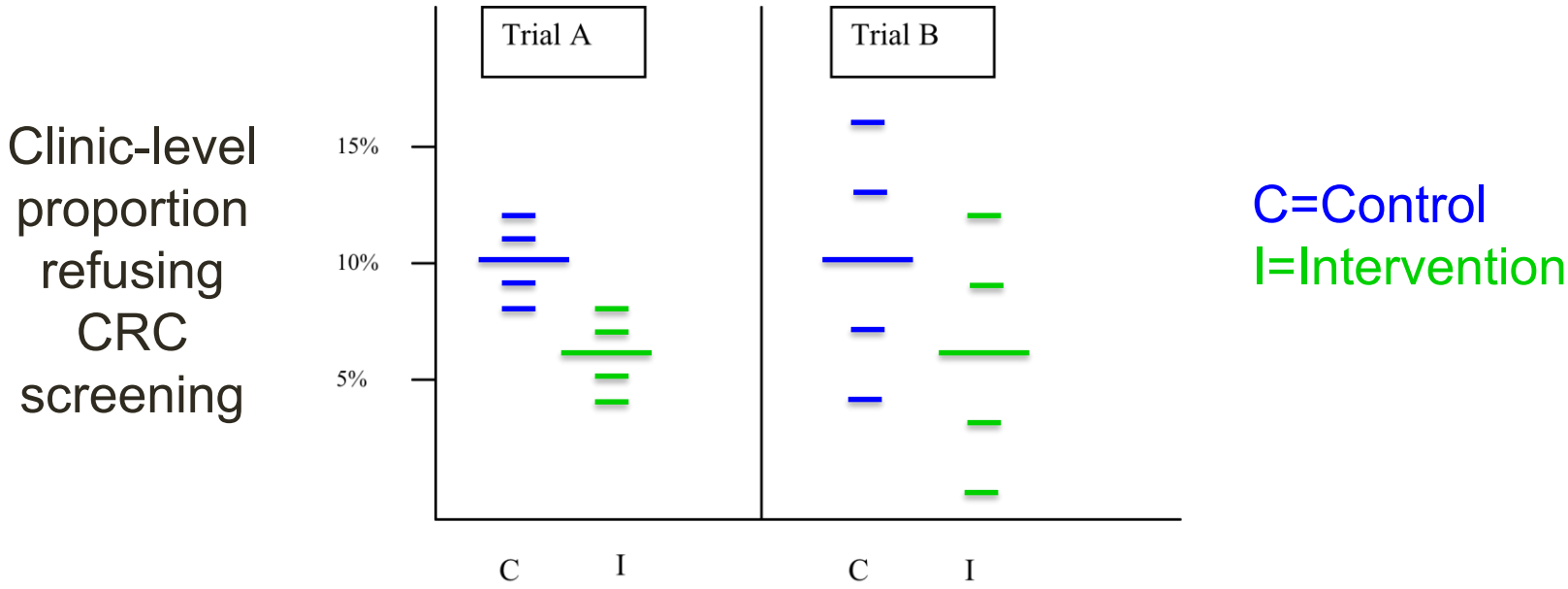
Clustering in CRTs: Implications for analysis



- 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)

Clustering in CRTs: Implications for analysis



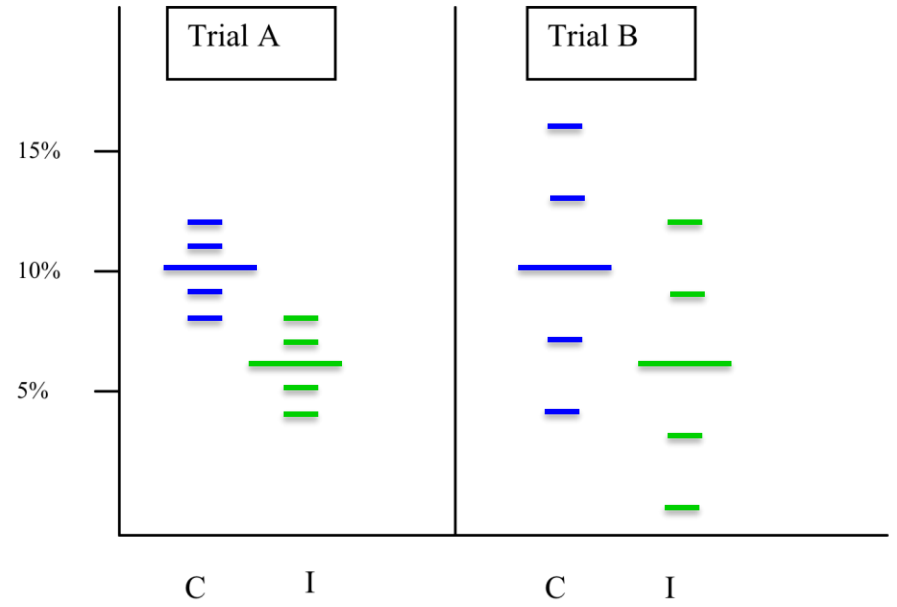
- Trial A p-value accounting for clustered design* = **0.01**
- Trial B p-value accounting for clustered design* = **0.17**

*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)

Clustering in CRTs: Implications for analysis

Clinic-level proportion refusing CRC screening



C=Control
I=Intervention

- 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)

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 conclusions from each trial
  - Between-cluster variability (& clustering) in Trial A < Trial B
  - P-value Trial A < P-value Trial B
  - Important: if incorrectly ignore clustered design, could claim ‘significant’ when not (eg, Trial B)

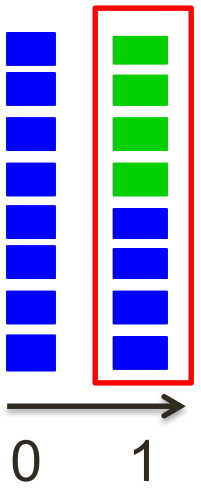
Analysis of CRTs, including SW-CRTs

- 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 ensure properly account for clustering

Analysis of CRTs, including SW-CRTs

Parallel design

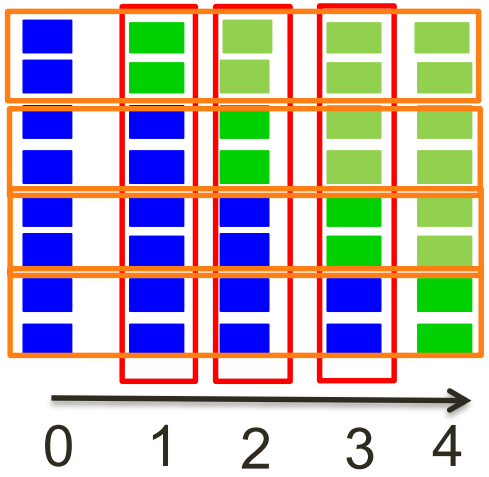
Estimated (primarily) using between-cluster ie, **vertical** information



Time since baseline

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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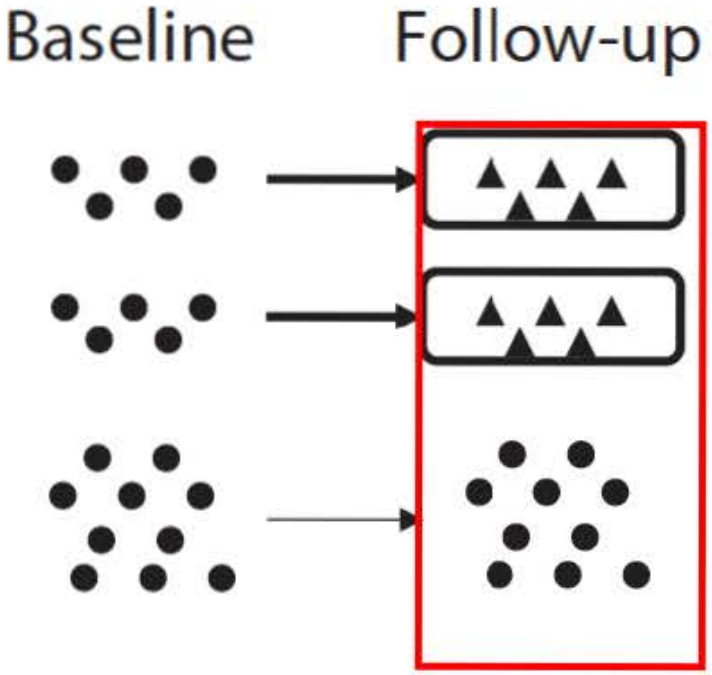
Analysis of IRGT trials



▲ Individual measured under intervention
● Individual measured under no intervention

Parallel design

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

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 ensure properly account for clustering

Analysis of CRTs, SW-CRTs, and IRGTTs

- Clustering must be accounted for in analysis
- Challenges in “small” trials (# clusters < 50)
  - Limited degrees of freedom (df) for testing intervention as df driven by # clusters (i.e. groups)
  - Use t-test not Z-test & calculate correct df
  - Intervention effect SE may be under-estimated
    - Can correct e.g. finite-sample bias corrections for GEE
  - Ignore either penalty (df & SEs) leads 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 ensure properly account for clustering

Analysis of CRTs, SW-CRTs, and IRGTTs

- May need to account for complex clustering structures
  - Different clustering (ICC) in two conditions
  - Repeated measures on same individuals, if cohort
  - Decay/change in pairwise correlations over time (eg, SW-CRT)
- Other considerations
  - May need non-constant intervention effect if multiple follow-up time points (eg, like in SW-CRT)

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
  - Potential confounding & effect modification

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

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

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.

It all starts with a clear research question…

- Population
- Intervention
- Comparison
- Outcome(s)

From: European Medicines Agency
ICH E9 (R1)

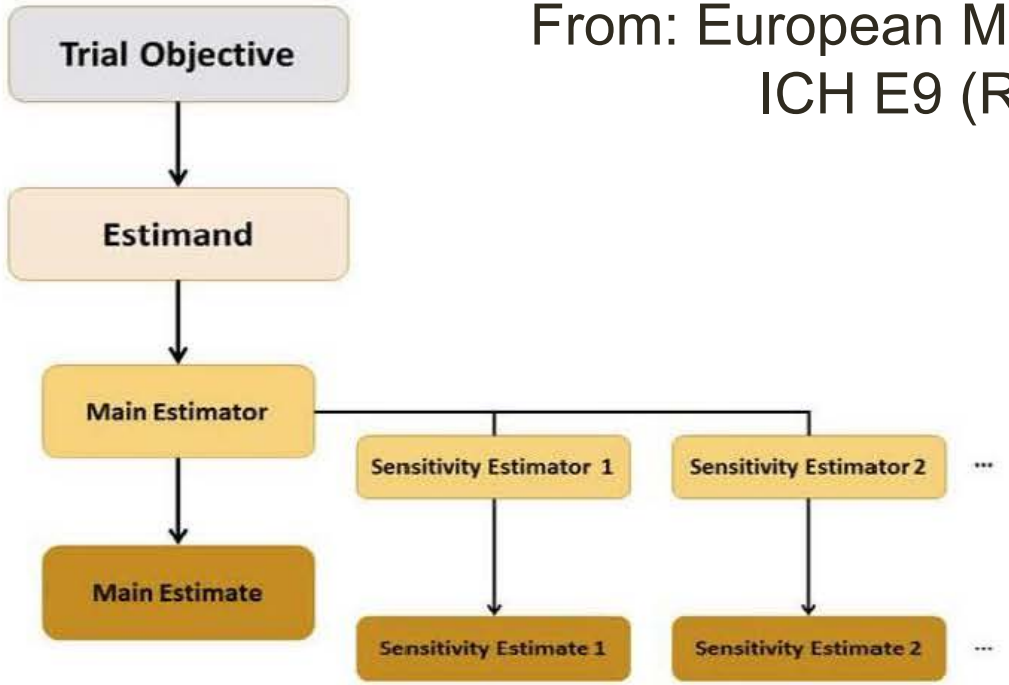

Figure 1: Aligning target of estimation, method of estimation, and sensitivity analysis, for a given trial objective

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Summary: Important things to know

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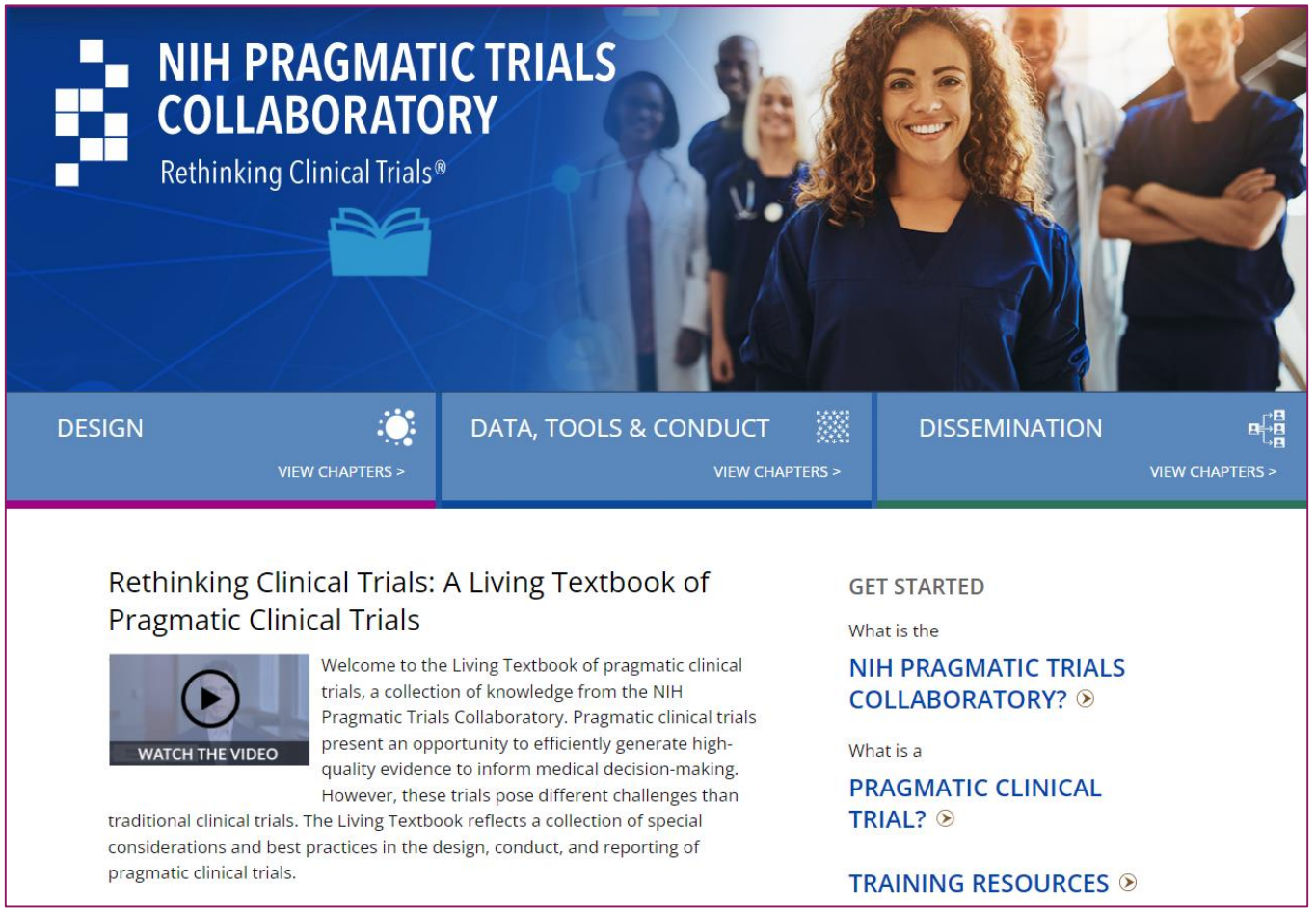
Resource: The Living Textbook

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.