Design & Analysis Considerations

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NIH PRAGMATIC TRIALS COLLABORATORY
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Learning goals

- Identify common experimental designs and randomization schemes pragmatic trials
- Discuss design and analytic considerations for trials with both effectiveness and implementation outcomes
- Understand the importance of monitoring adherence and fidelity

Design Considerations

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Three kinds of randomized trials

- Traditional randomized controlled trials (RCTs)
- Individual randomized group treatment (IRGT) trials
- Cluster randomized trial (CRTs)
  - Parallel CRT
  - Stepped-wedge CRT

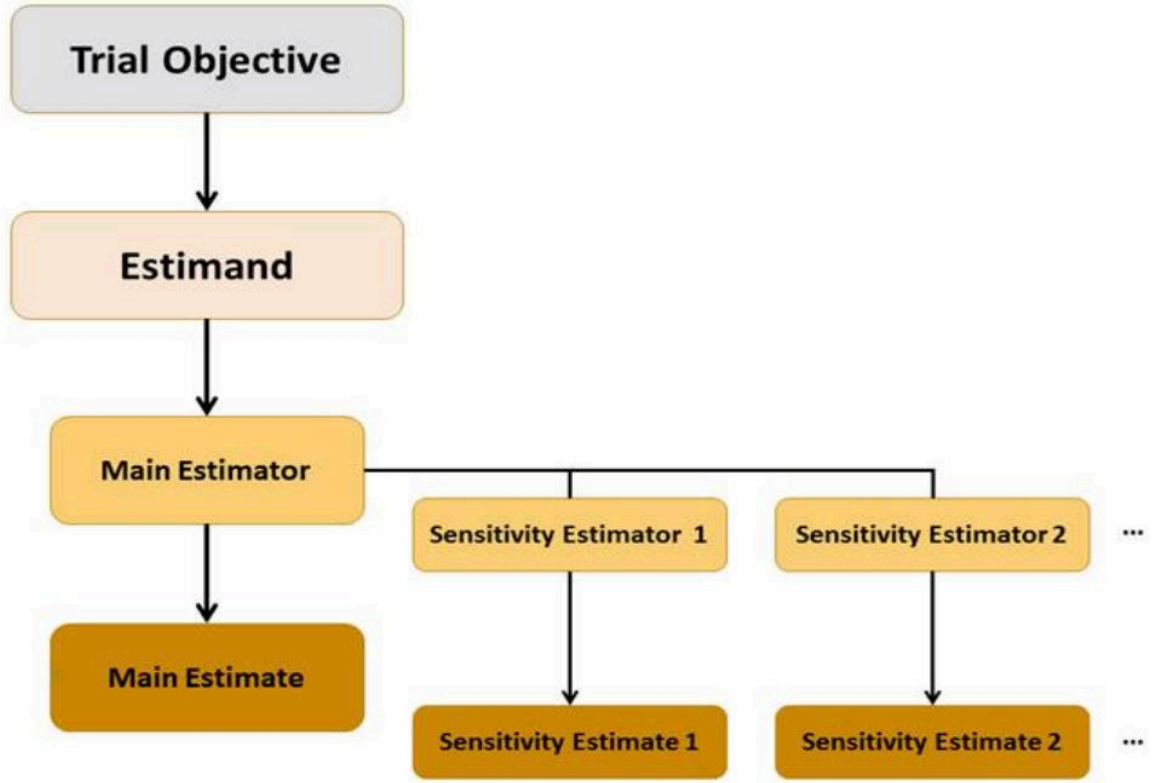
Methods for pragmatic trials

- As with traditional RCTs:
  - State a hypotheses
  - Prespecify the analyses
  - Calculate the sample size needed for desired power
  - Consider restricted randomization (such as stratified randomization)
  - Determine what data on participant characteristics will be collected
  - Anticipate sources of heterogeneity
- The trial design you choose will depend on the research question and how the intervention will be delivered

Start with a clear research question

Elements of a research question:

- **P**opulation
- **I**ntervention
- **C**omparisons
- **O**utcomes
- **T**iming



Source: European Medicines Agency, ICH E9 (R1): Aligning target of estimation, method of estimation, and sensitivity analysis, for a given trial objective

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Important things to know

Studies that randomize groups, or deliver interventions to groups, face special design and analytic challenges

Failure to address challenges of outcome clustering in design and analysis will result in an underpowered study and/or invalid inferences

Appropriate designs and analytic methods are the only way to advance the science

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OPTIMUM, an NIH Collaboratory Trial

Optimum
Optimizing Pain Treatment
in Medical Settings
Using Mindfulness

Optimizing Pain Treatment In Medical Settings Using Mindfulness (OPTIMUM)

- Intervention: Group-based, mindfulness-based stress reduction to reduce pain and opioid use
- Population: 450 adults with chronic low back pain
- Unit of randomization: individual
- Group-based online intervention; groups must be formed by study team; postrandomization interactions between participants
- **Individually randomized group treatment (IRGT) trial**, because postrandomization groupings induce correlated outcomes

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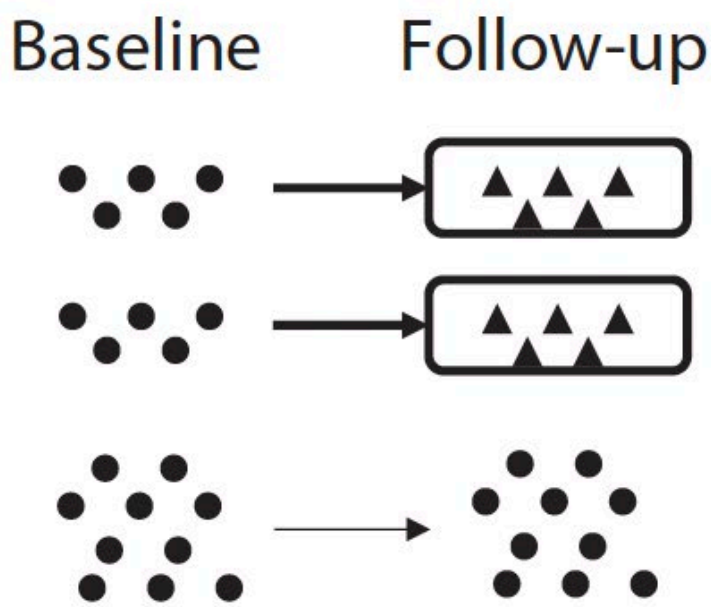
IRGT trial design in OPTIMUM



Individuals are randomized to intervention or control but treatments are delivered in small groups or through a common change agent.

▲ Individual measured under intervention
● Individual measured under no intervention

From Turner et al. *Am J Public Health*. 2017;107(6).

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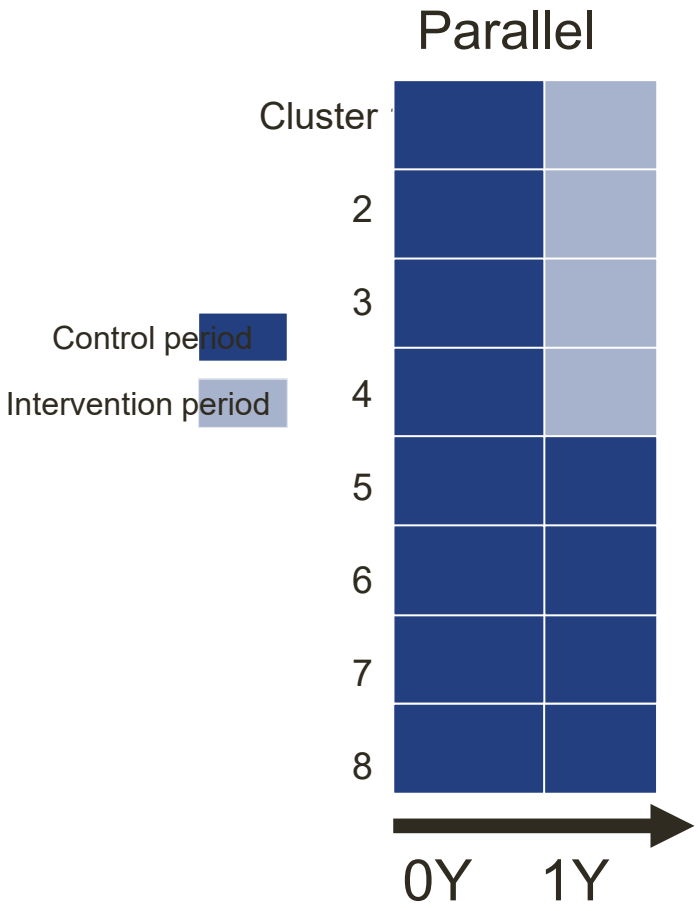
In this example:
- 8 clusters
- 1-year intervention



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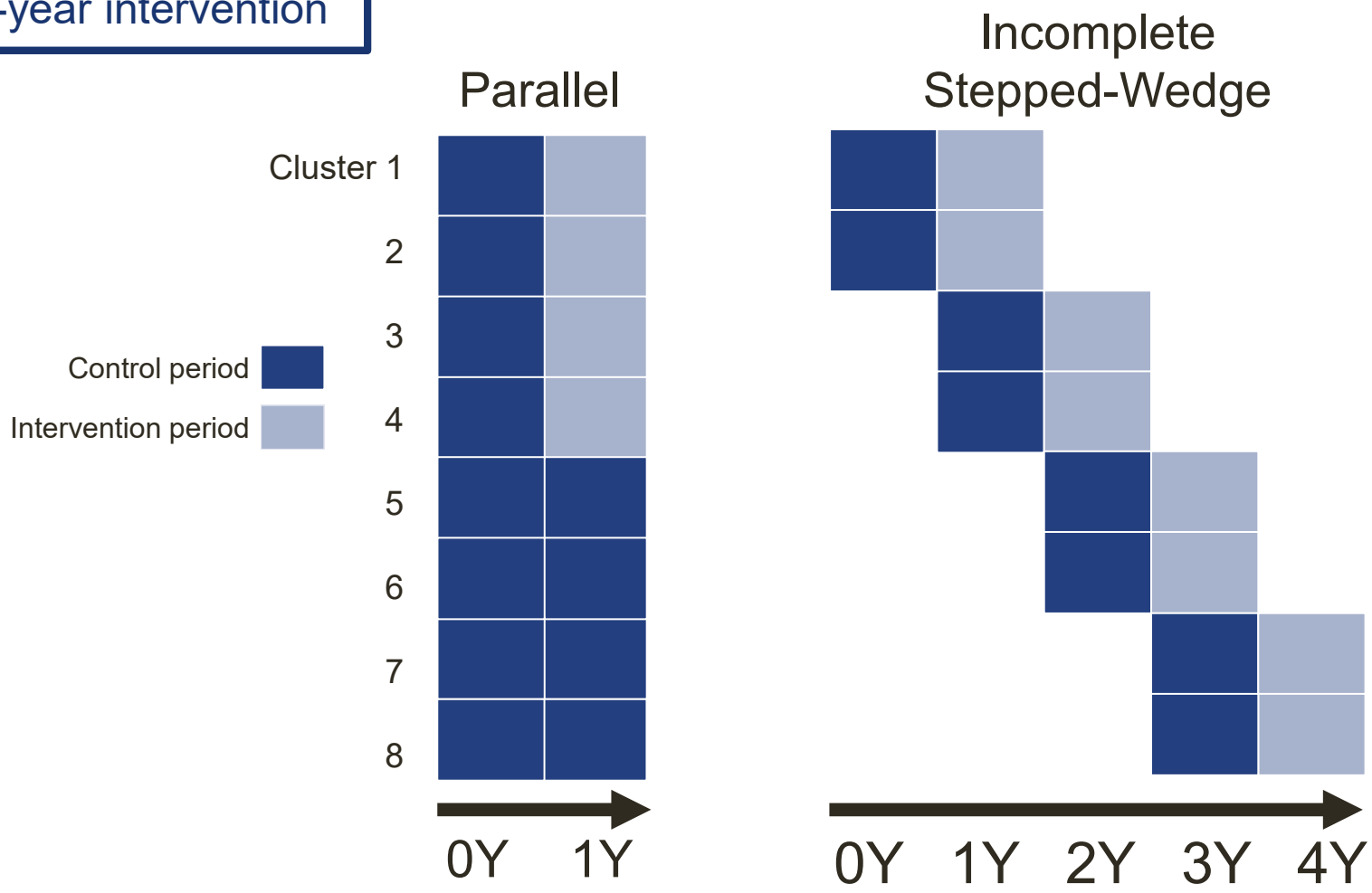

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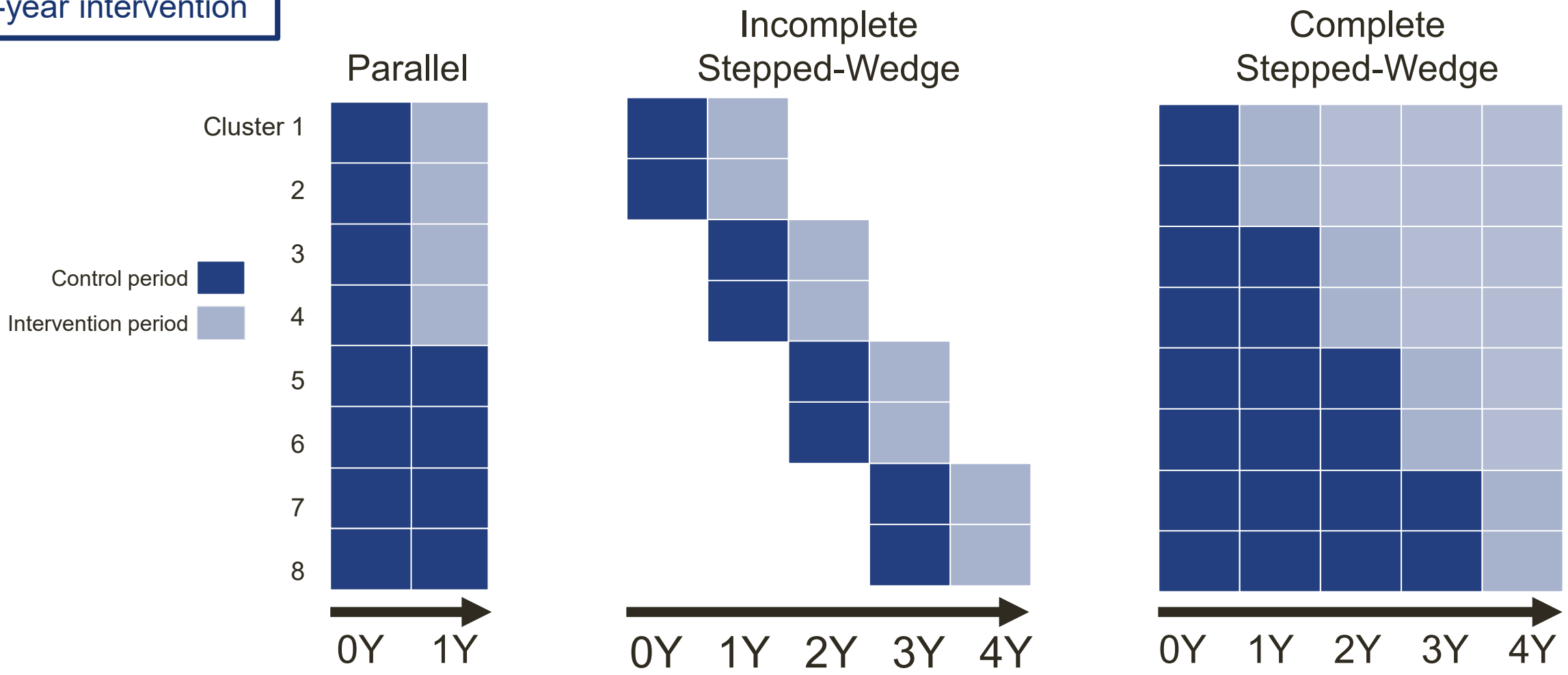

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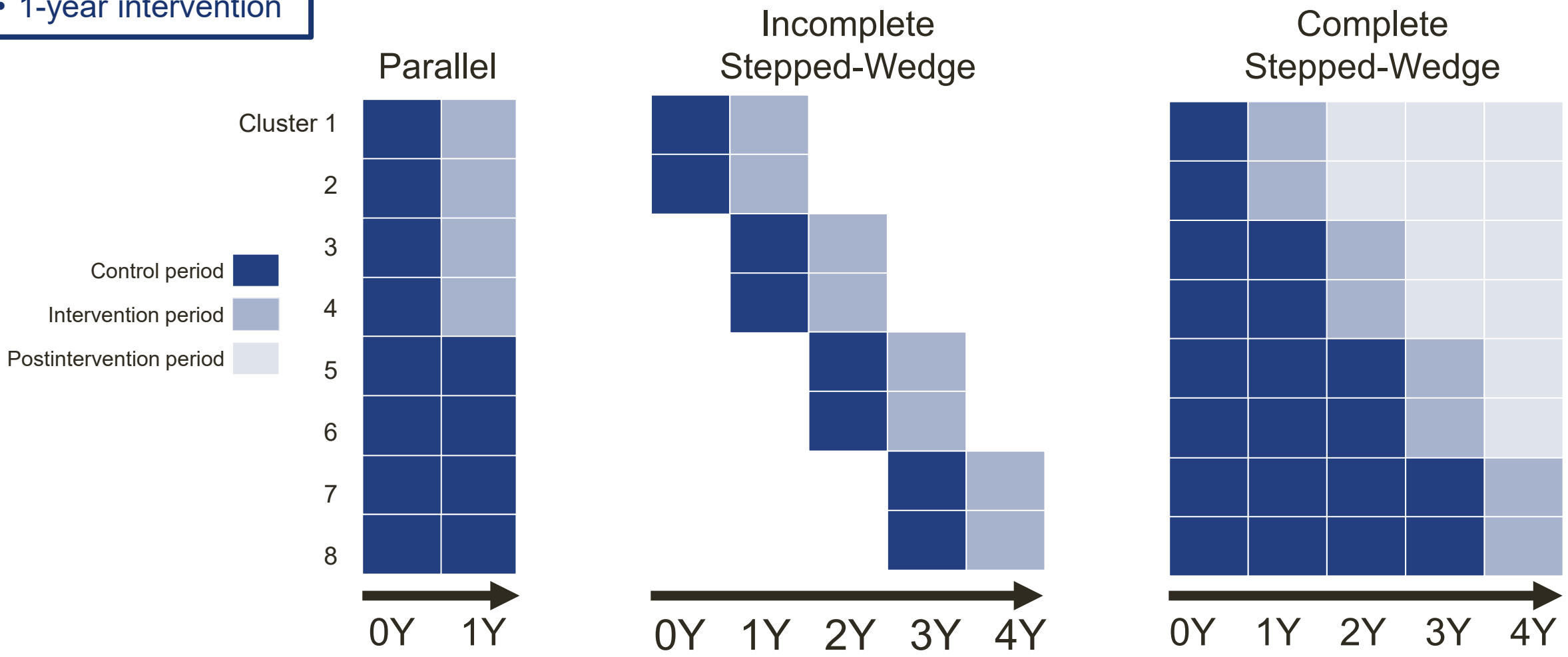

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STOP CRC, an NIH Collaboratory Trial

stop screen to prevent colon cancer

Strategies and Opportunities to Stop Colorectal Cancer in Priority Populations (STOP CRC)

- Population: More than 40,000 patients at 26 clinical sites
- Intervention: Healthcare system–based program to improve rates of colorectal cancer screening
- Unit of randomization: clinic
- Two-arm **cluster randomized trial (CRT)**

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Reasons to randomize clusters instead of individuals

- The intervention targets healthcare units rather than individuals

Healthcare Units

Individuals

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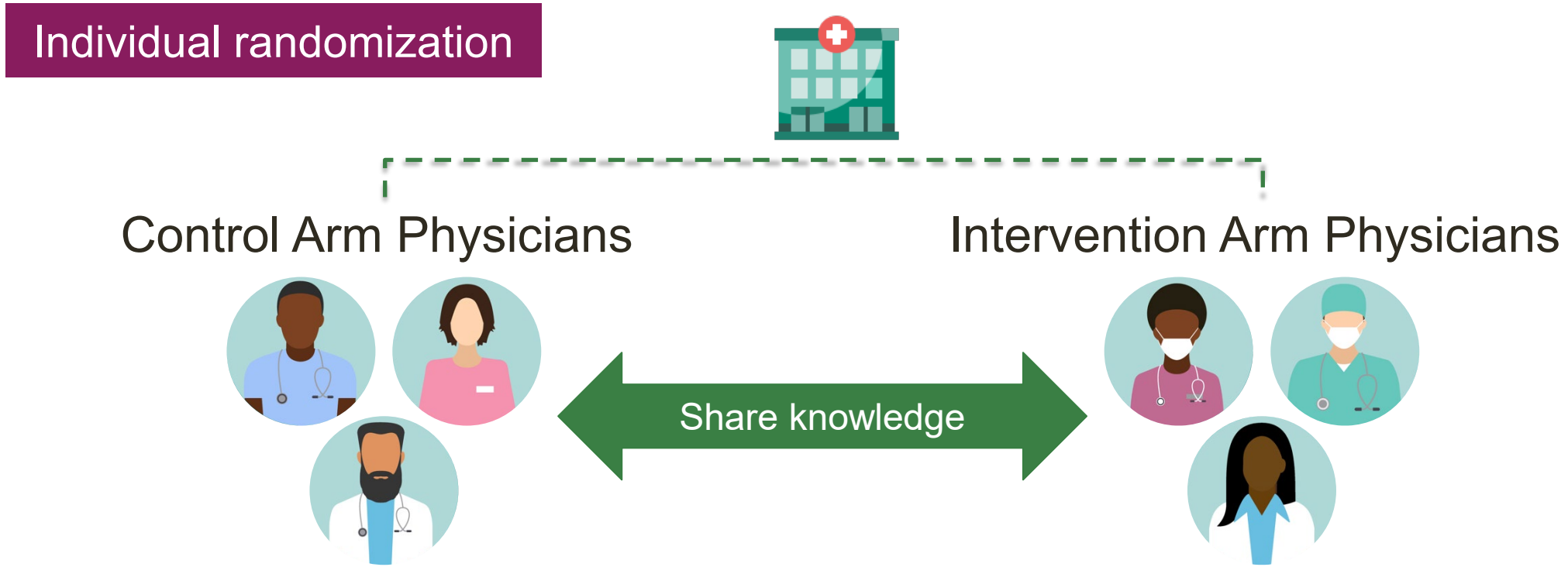
Reasons to randomize clusters instead of individuals

- The intervention targets individuals, but there is risk of contamination



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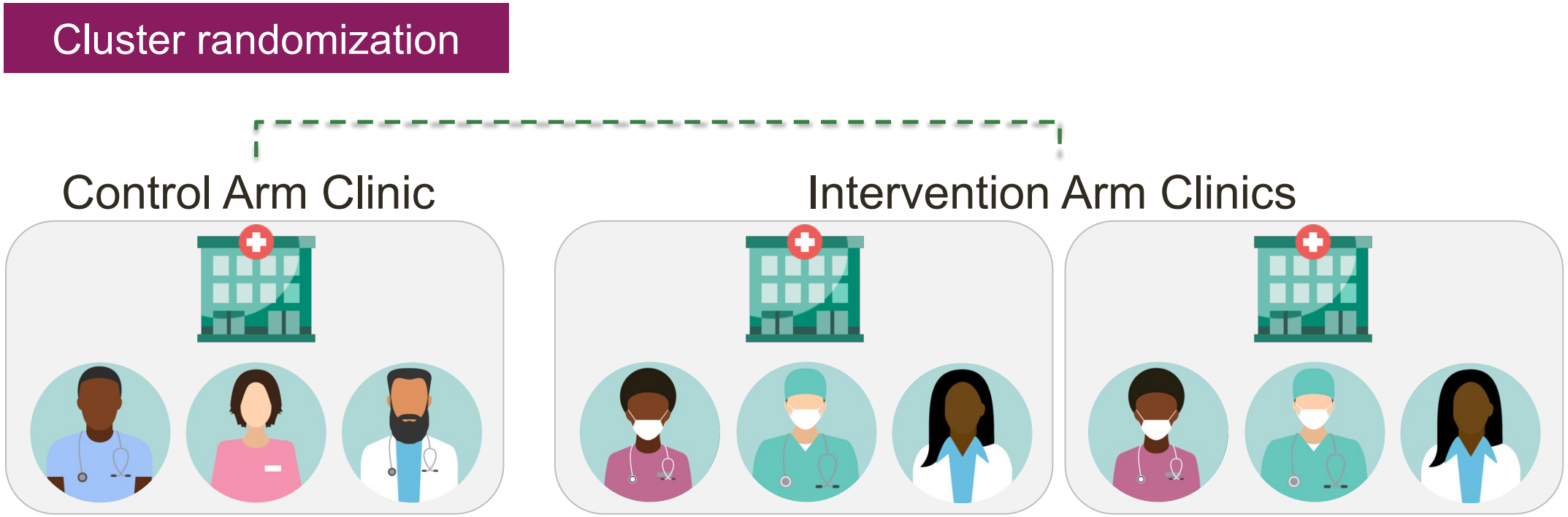

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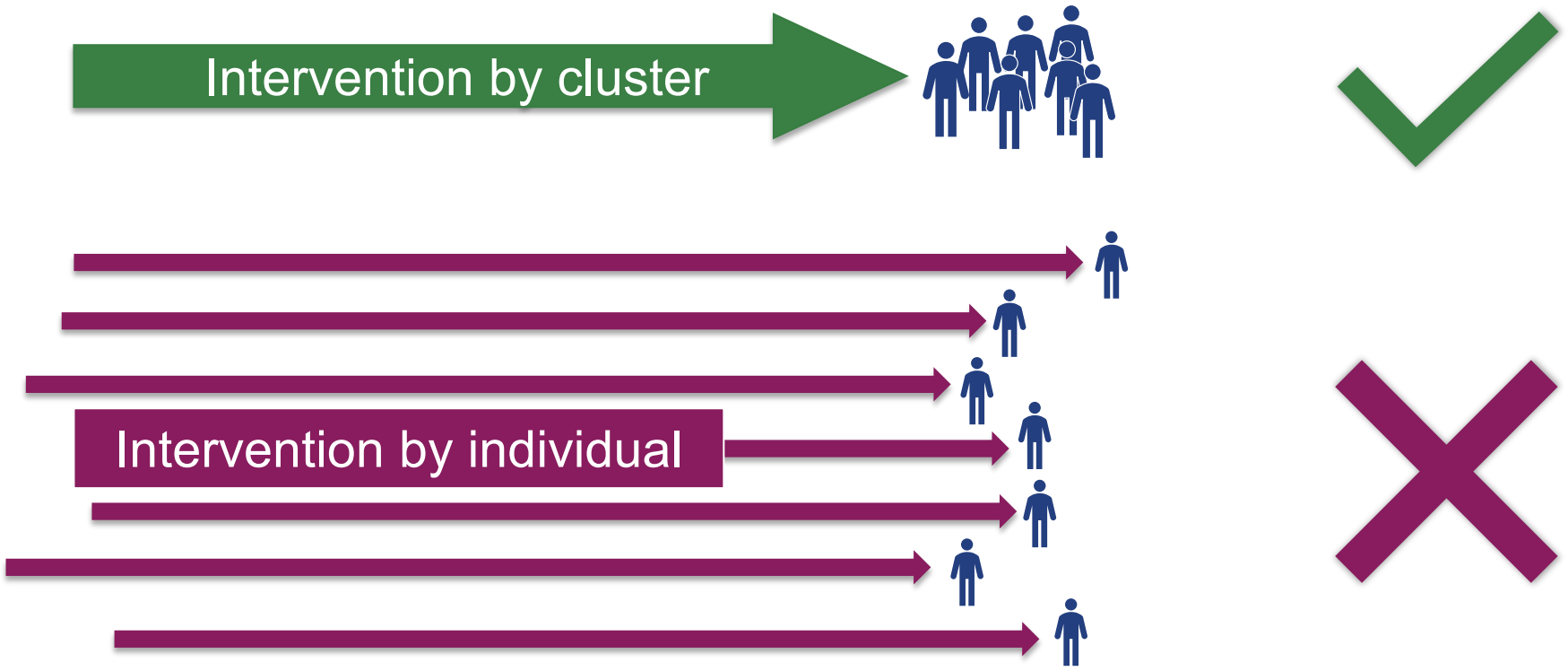
Reasons to randomize clusters instead of individuals

- Logistically easier to implement the intervention by cluster



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Cluster randomization in the STOP CRC trial

stop screen to prevent colon cancer

Target population	40,000 patients across 26 clinical sites
Intervention	Health system–based program to improve colorectal cancer screening rates

Cluster

Cluster

Cluster

Level 2

Randomize at the level of the clinic

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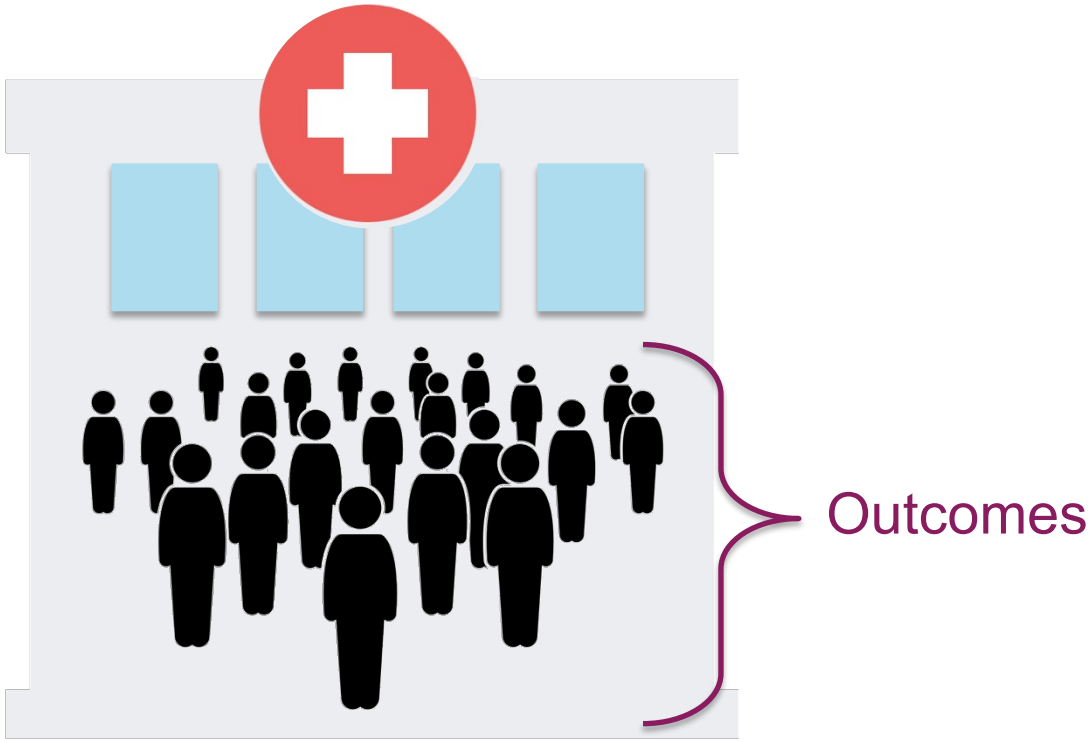

Level 1

Patient-level outcomes are nested within the clinic

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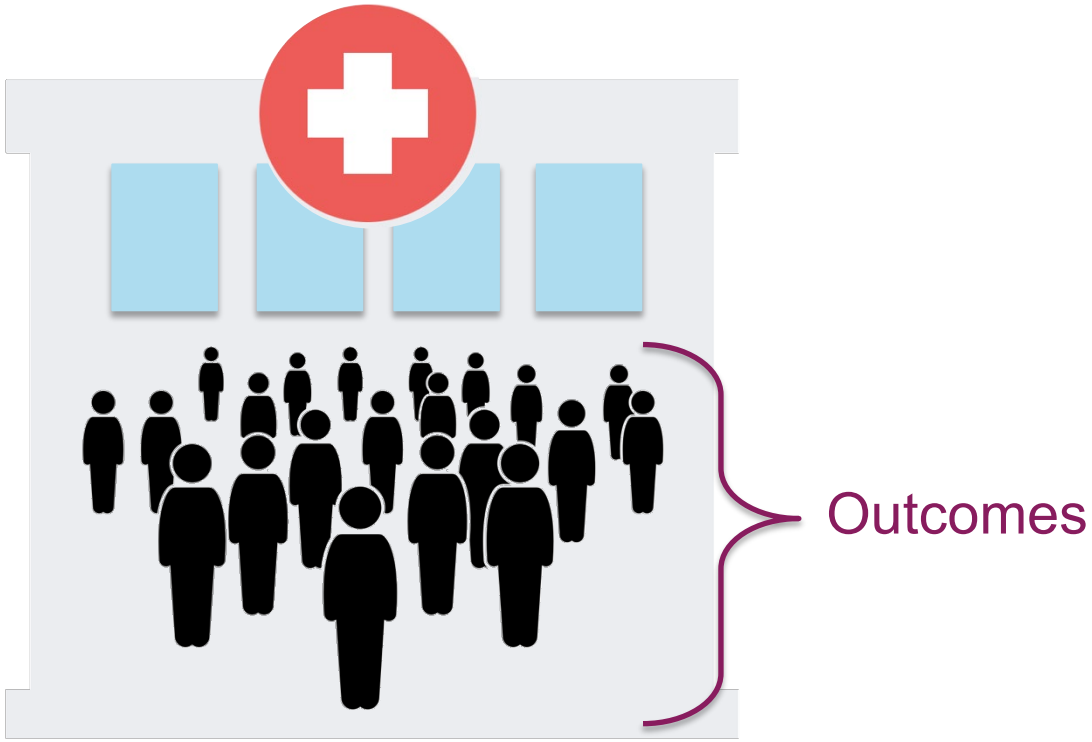

STOP CRC outcomes

Did the patients agree to be screened for colorectal cancer?

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stop
screen to prevent
colon cancer

Individual outcomes within the same clinic are expected to be correlated

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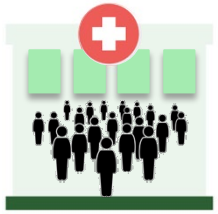
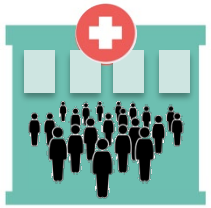
Clustering = Outcome Clustering



Outcomes

Outcomes



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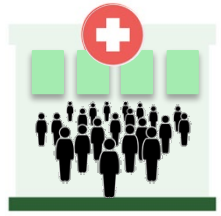
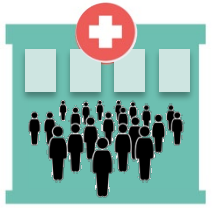


Outcomes



Outcomes

stop
screen to prevent
colon cancer

STOP CRC outcomes

Did the patient agree to be screened for colorectal cancer?

Binary outcome

Yes

No

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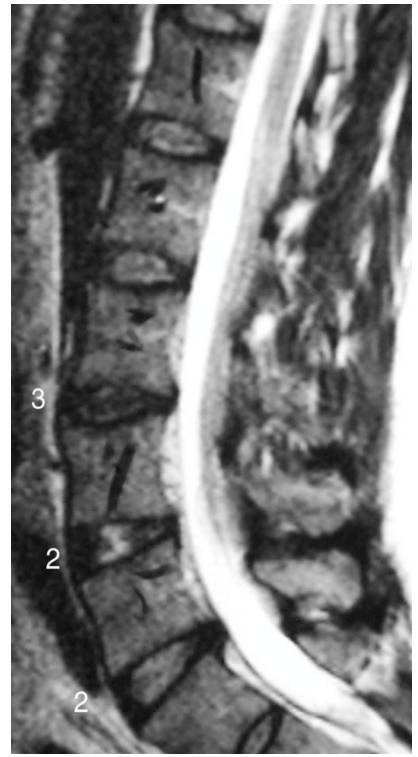
  - **Stepped-wedge CRTs**

LIRE, an NIH Collaboratory Trial

Lumbar Imaging With Reporting of Epidemiology (LIRE)

- Population: 250,401 patients in 98 primary care clinics in 4 large healthcare systems
- Intervention: Insert benchmark information about common imaging findings in lumbar spine imaging reports to reduce spine-related healthcare utilization
- Unit of randomization: clinic
- All clinics will eventually receive intervention
- **Stepped-wedge CRT**



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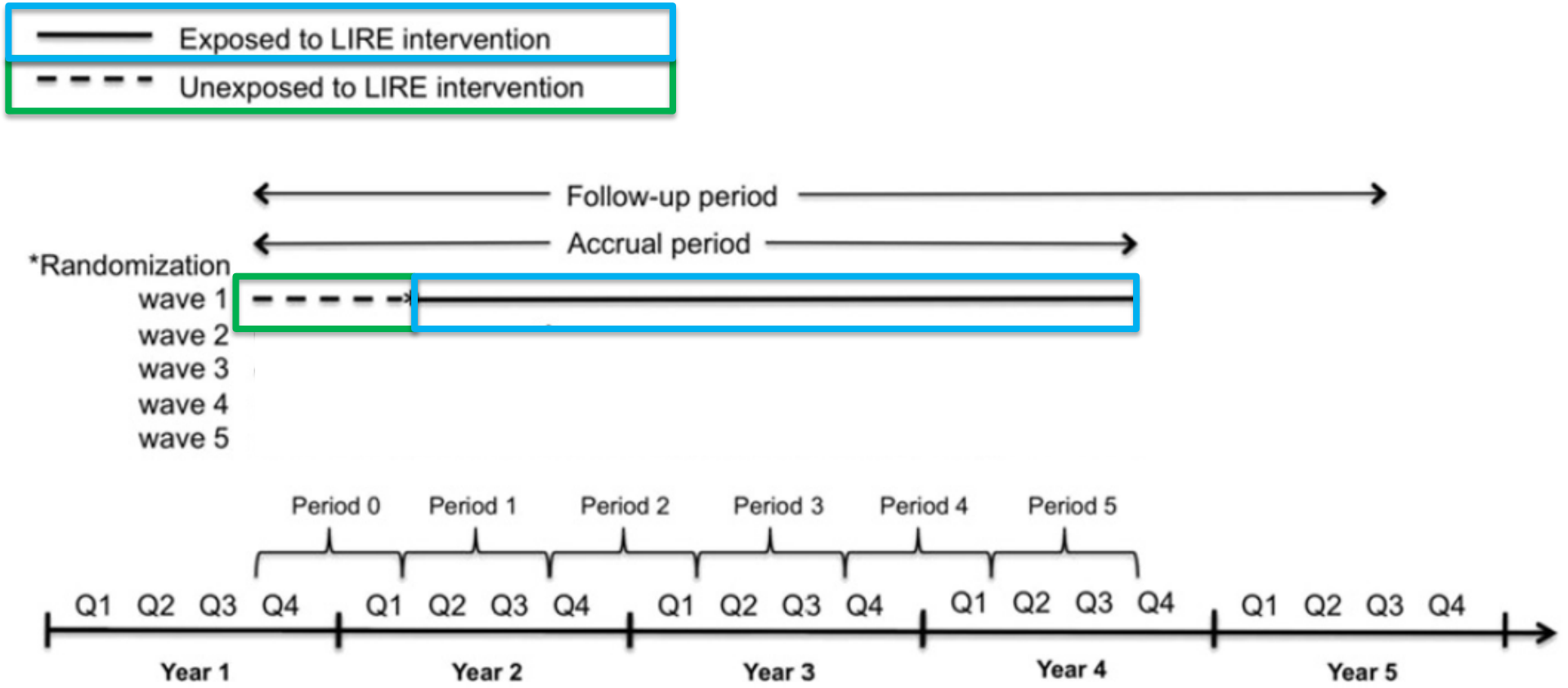
Design of LIRE trial



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

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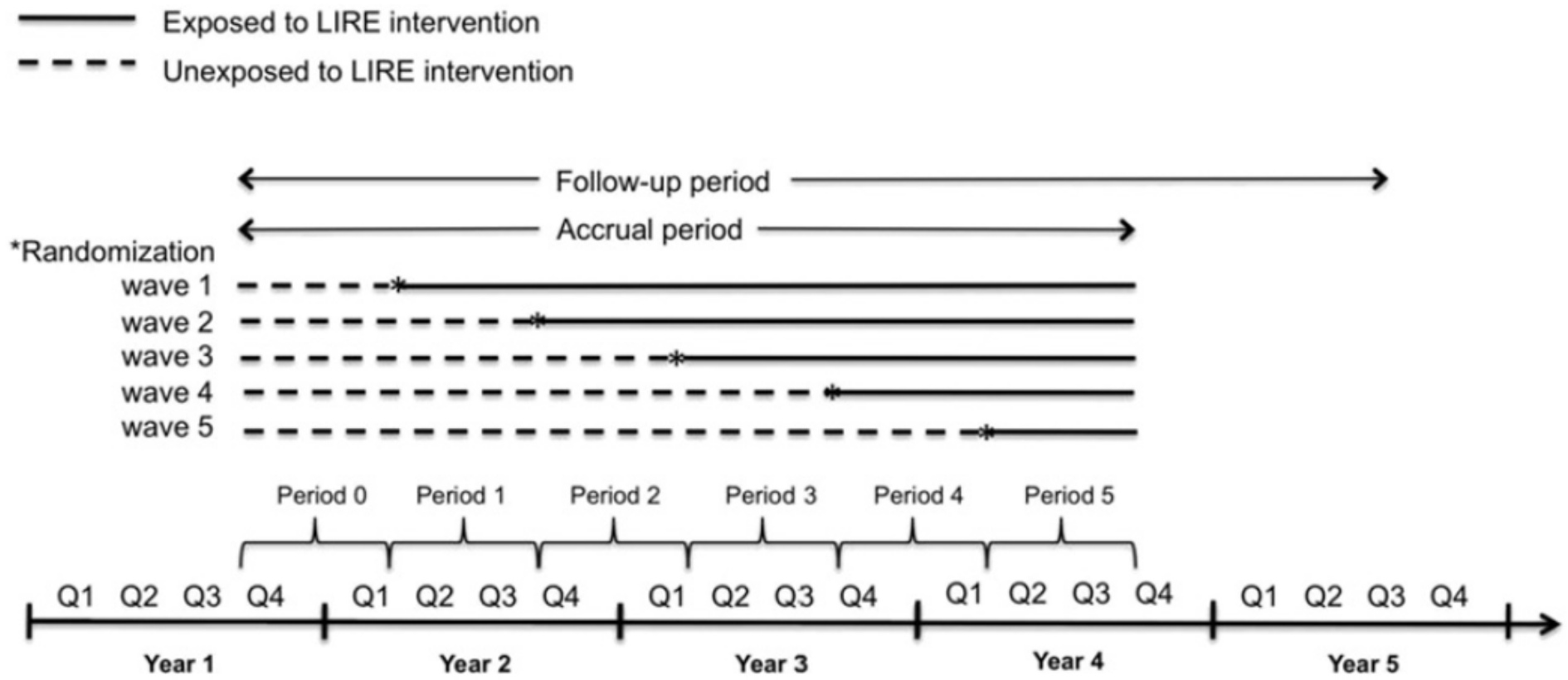
Design of LIRE trial



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Analysis Considerations

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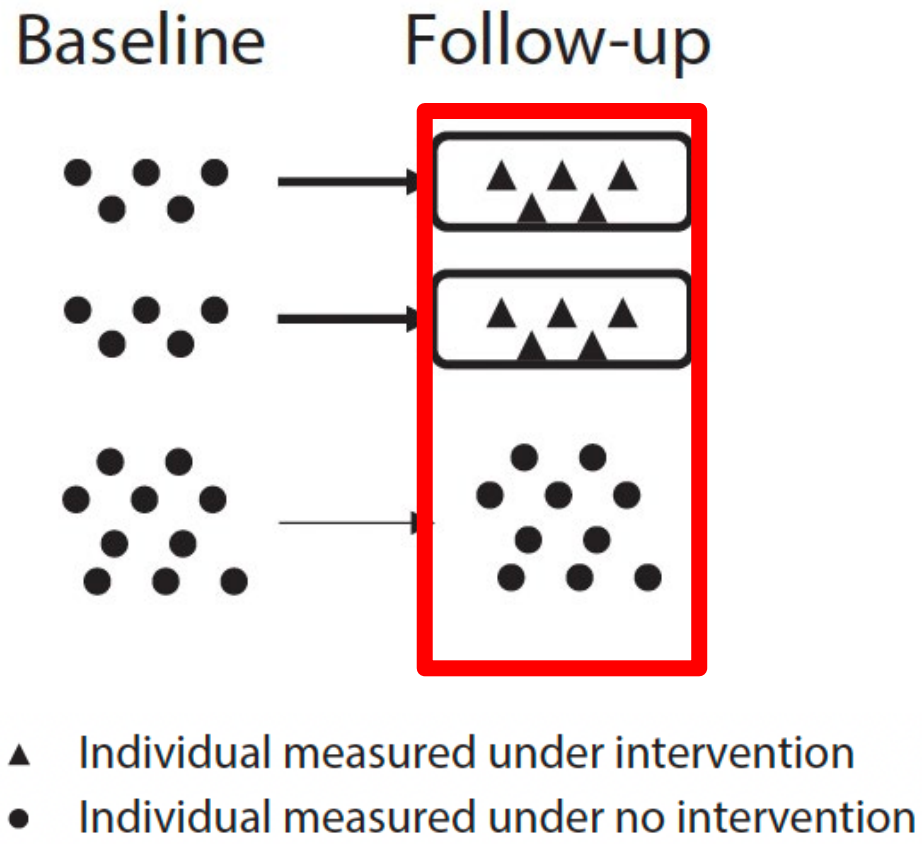
Analysis of IRGT trials



Parallel design

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

Turner et al. *Am J Public Health*. 2017;107(6).

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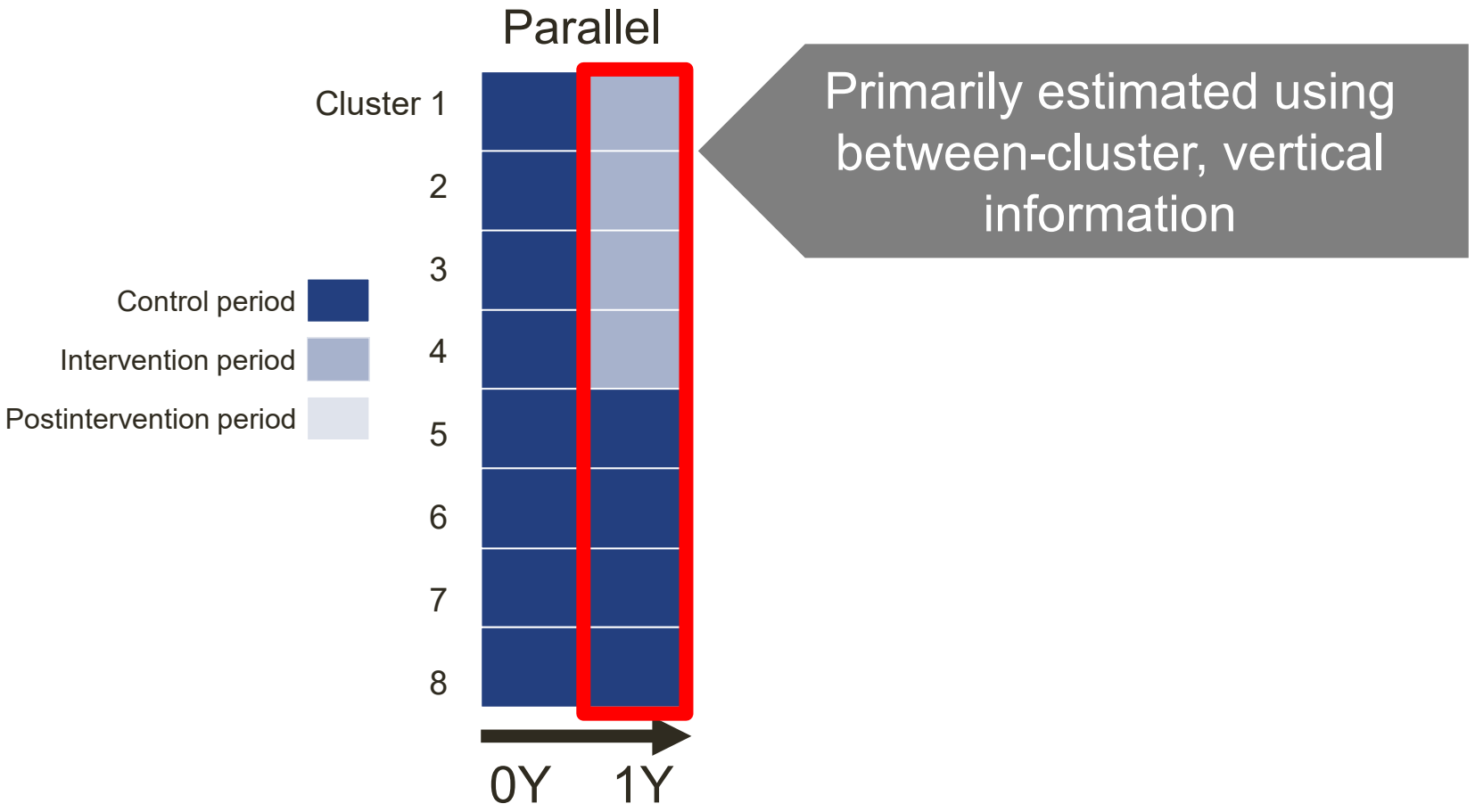
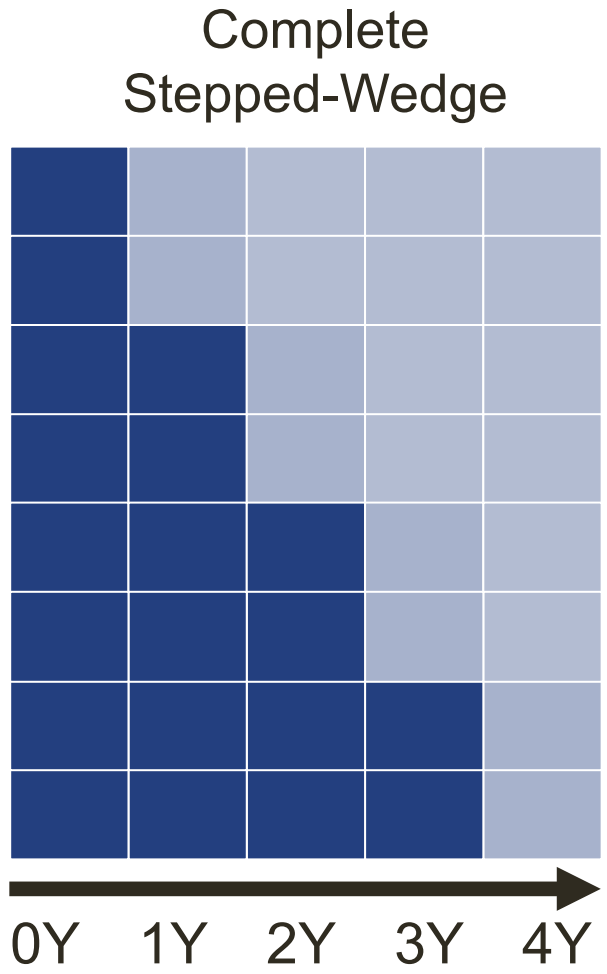
Analysis of IRGT trials

- Analyze individual-level data accounting for clustering
  - Random effects or mixed effects models
  - Generalized estimating equations (GEE)
- Considerations on clustering
  - Clustering in both arms: if both conditions group-based and may need different degree of clustering in 2 arms
  - Clustering in intervention arm only: if intervention group-based but control condition not
  - Clustering due to shared agents or group-based intervention delivery often overlooked

Analysis of parallel CRTs



Primarily estimated using between-cluster, vertical information



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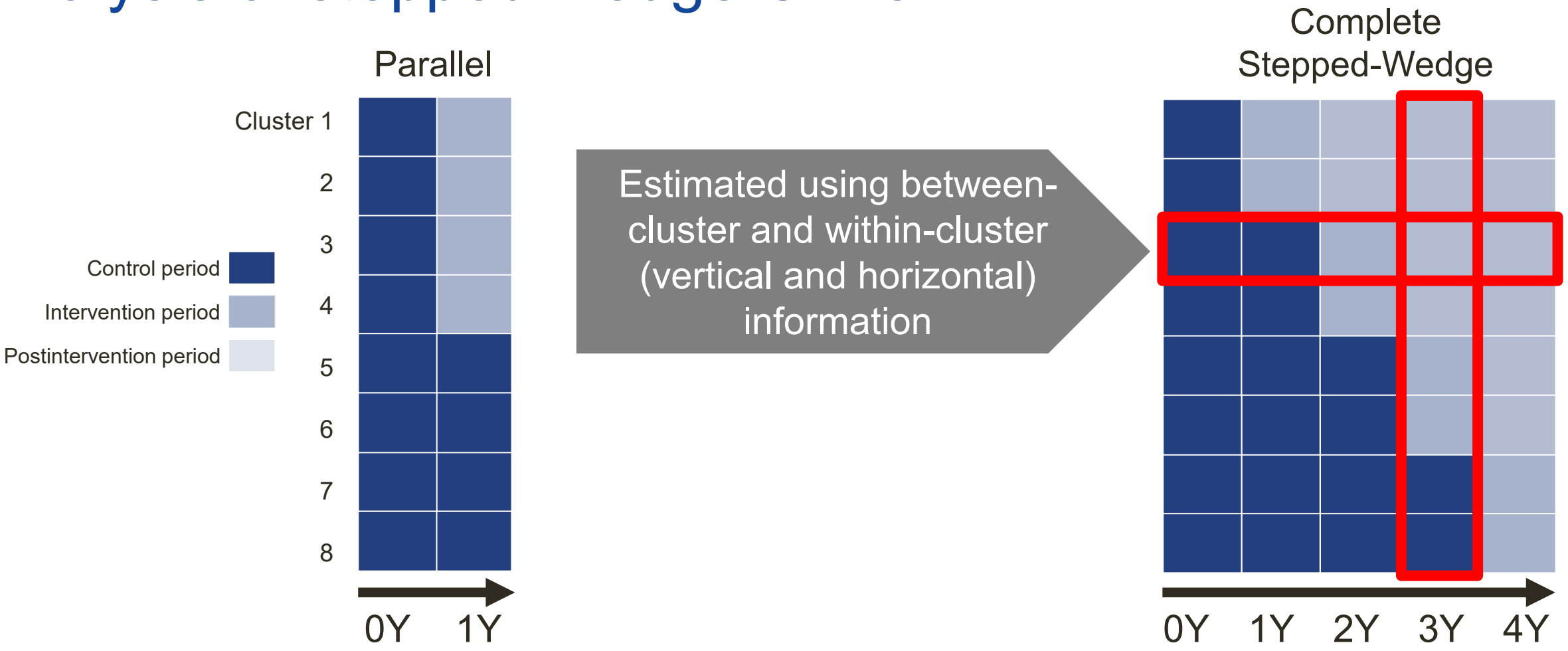
Analysis of stepped-wedge CRTs



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Analysis of IRGT trials and CRTs

- Clustering must be accounted for in analysis
  - Ignoring can lead to inflated Type I error, even with low outcome clustering
    - Type I error rate may be 30%-50% in a CRT
    - Type I error rate may be 15%-25% in an IRGT
- Challenges in “small” trials (fewer than 50 clusters)
  - Intervention effect SE may be underestimated
    - Mixed models: degree of freedom & use of t-test for inference
    - GEE: small sample corrections of SE & use of t-test for inference

Analytic challenges and trade-offs

- Stepped-wedge designs “roll out” over time and are more susceptible to disruption, and confounding of time and intervention must be accounted for in analysis
- Parallel CRTs are simple and powerful, but still need to address clustering for design and analysis
- IRGT trials designs have benefits of individual-level randomization but still need to address clustering due to shared agents or group-based interventions in design and analysis

Important things to know about many pragmatic and implementation trials

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Q&A

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