RAND HEALTH CARE

Spillover Due to Constraints on Care Delivery

A Potential Source of Bias in Pragmatic Trials

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NIH Pragmatic Trials Collaboratory Grand Rounds
Rethinking Clinical Trials
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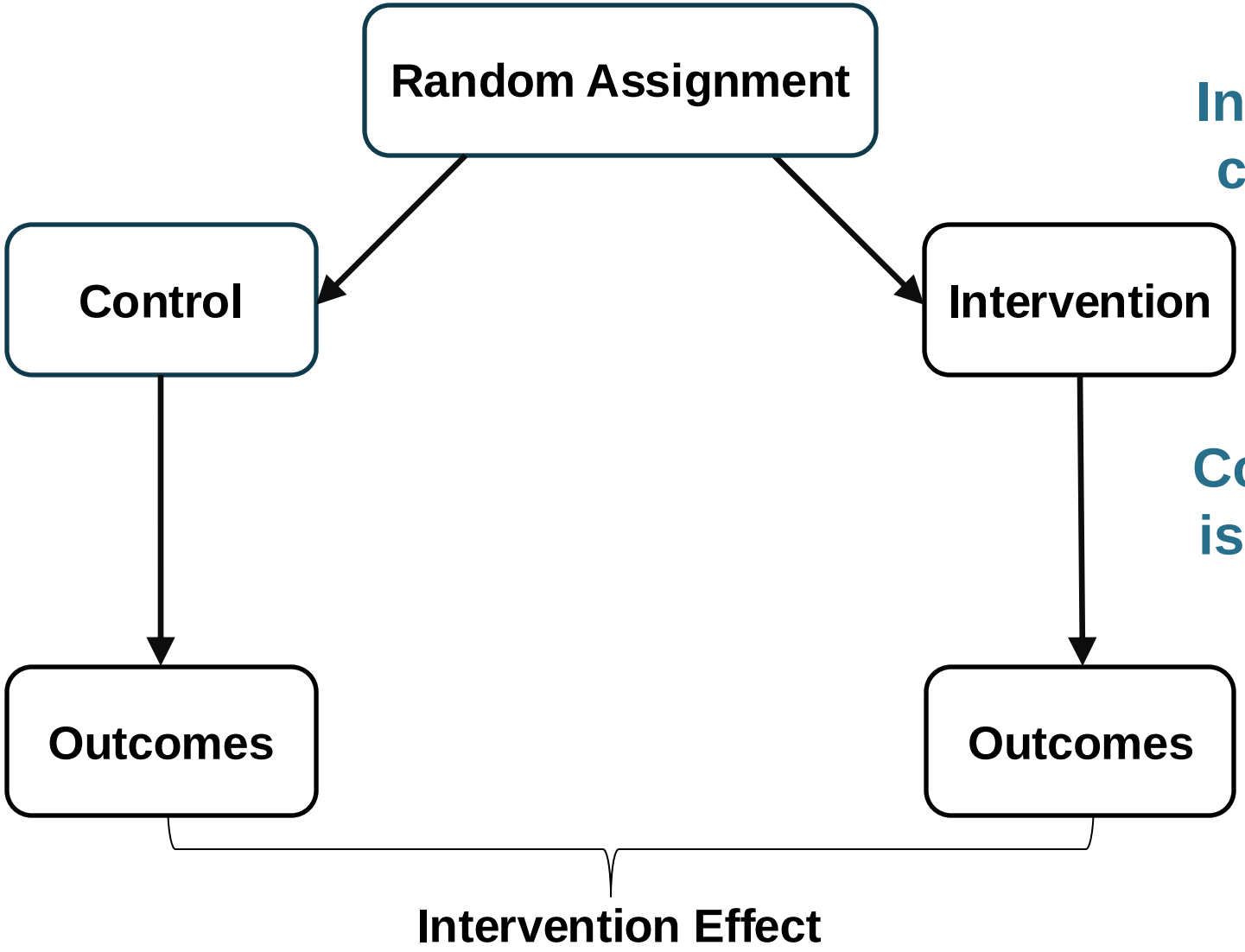
Pragmatic trials

Real-world settings

Intervention and control groups



Randomized assignment

Control group is often usual care

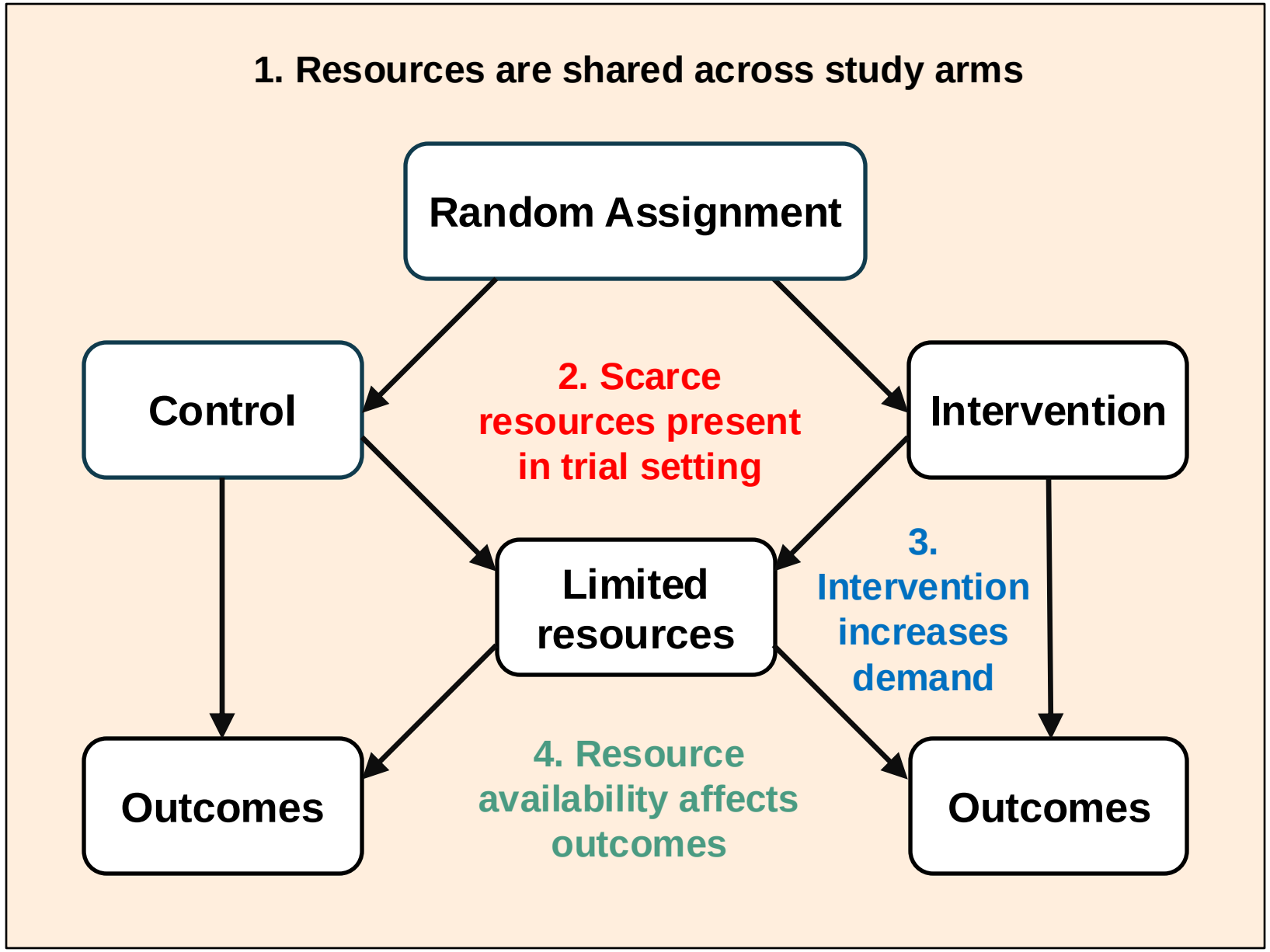
Spillover could occur due to constraints on care

- Resource scarcity
- Intervention affects utilization
- Known problem in economics
- Not addressed in clinical trial guidance

Example of patient navigation

- Navigator helps patients obtain diagnostic appointments
- Trial finds navigation leads to earlier diagnosis
- But appointment availability is limited
- Effect might be at expense of other patients

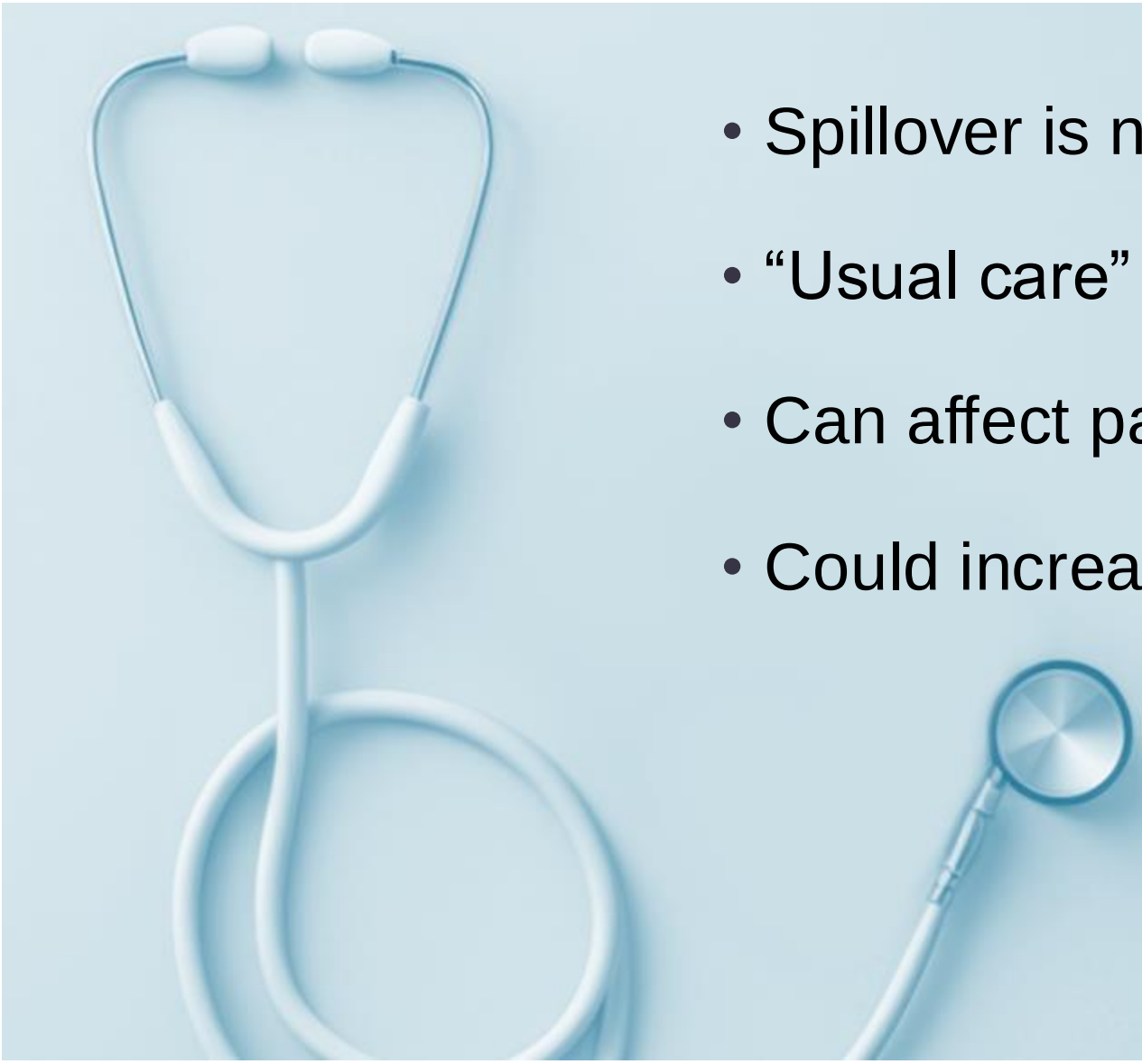
What causes spillover?



Spillover could affect a range of trials

- Cancer screening and diagnosis
- Elective induction of labor
- Physiological monitoring and alarms
- Nudges for vaccination

Patient safety



- Spillover is not just a source of bias
- “Usual care” may be of lower-than-usual quality
- Can affect patients not participating in trial
- Could increase burden on clinicians

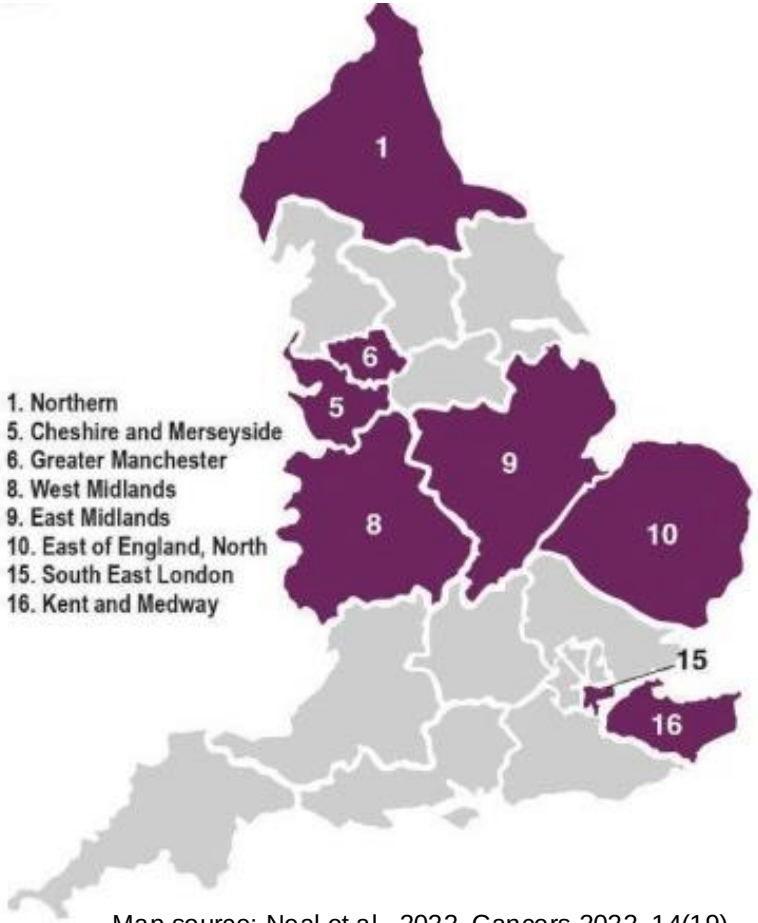
Additional considerations

- Spillover remains hypothetical
- Positive spillover also possible
- Study results affected by spillover can still be valid indication of an effect on utilization
- Implications for health equity

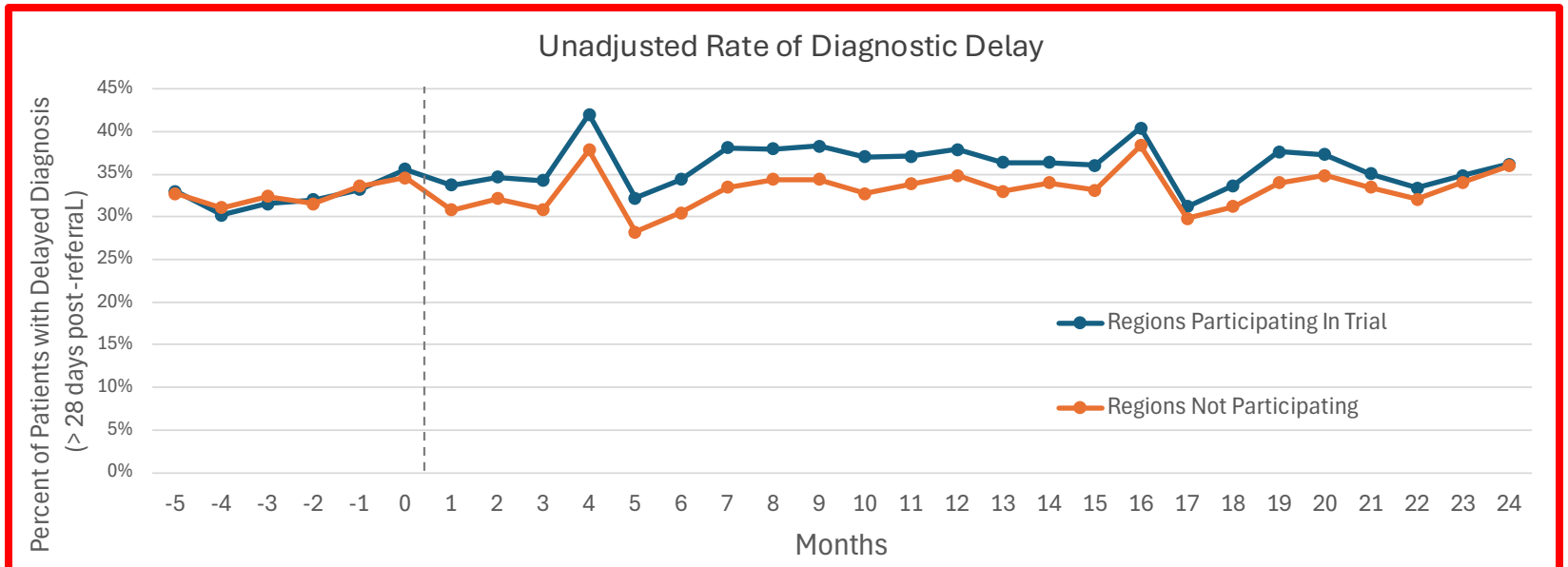
Detecting spillover

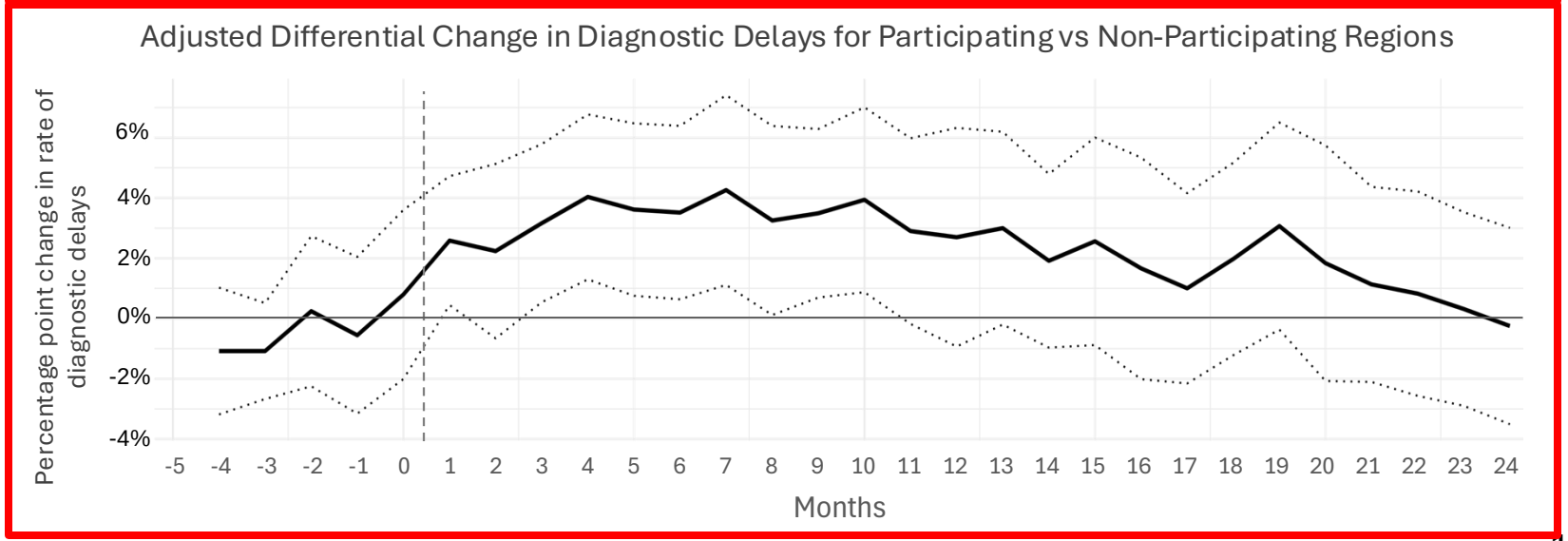
- Reanalyze data
  - Compare to pre-trial baseline
  - Exploit site-level variation
- Include data from all patients sharing care resources
- Use non-participating health systems as external controls
- Collect data on site capacity, resource availability, and utilization

Example: A multi-cancer early detection (MCED) trial



Map source: Neal et al., 2022, Cancers 2022, 14(19), 4818; https://doi.org/10.3390/cancers14194818

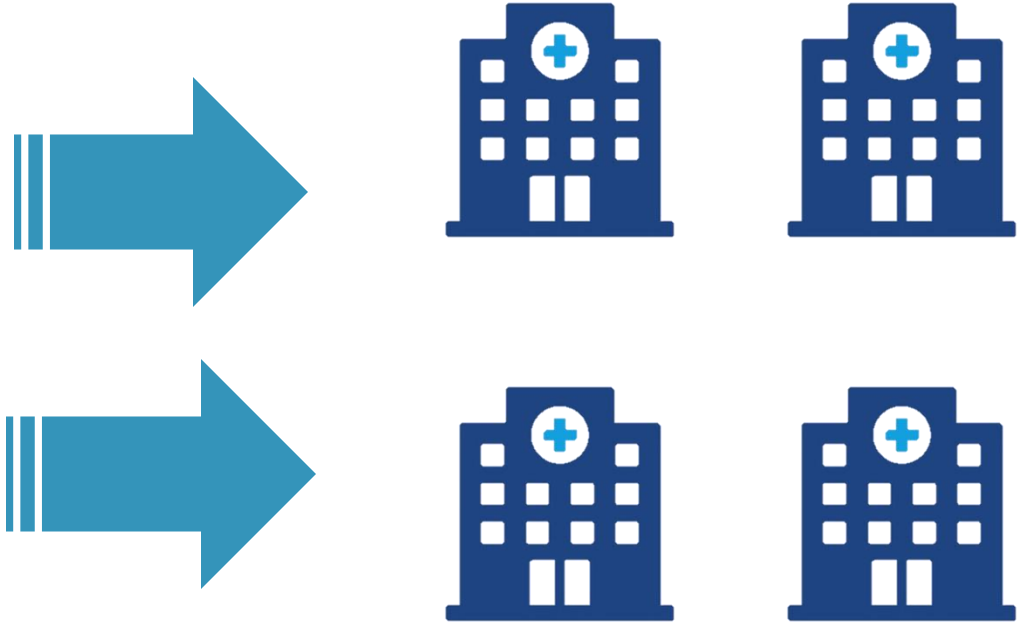




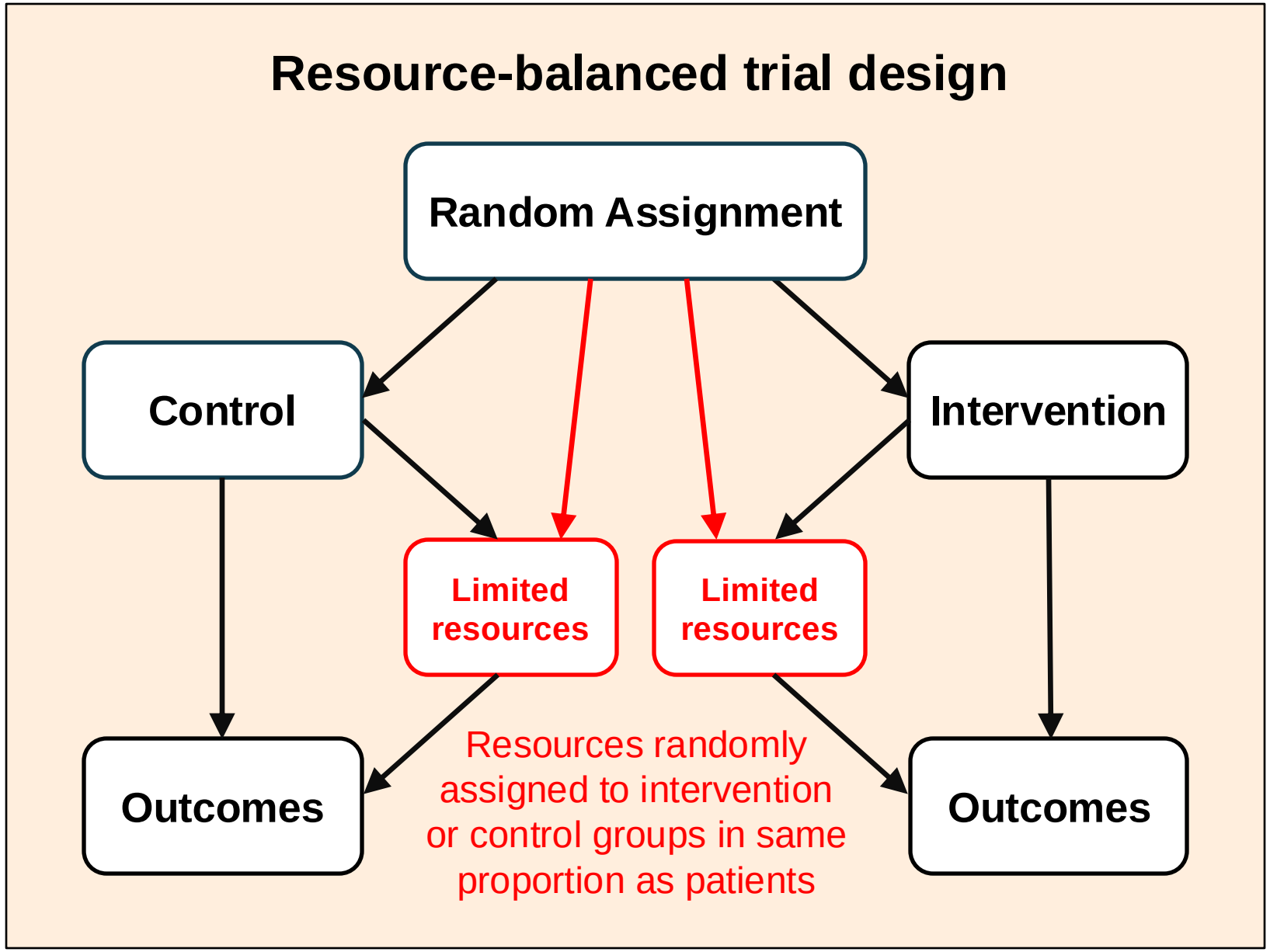
Avoiding spillover

Individually randomized design

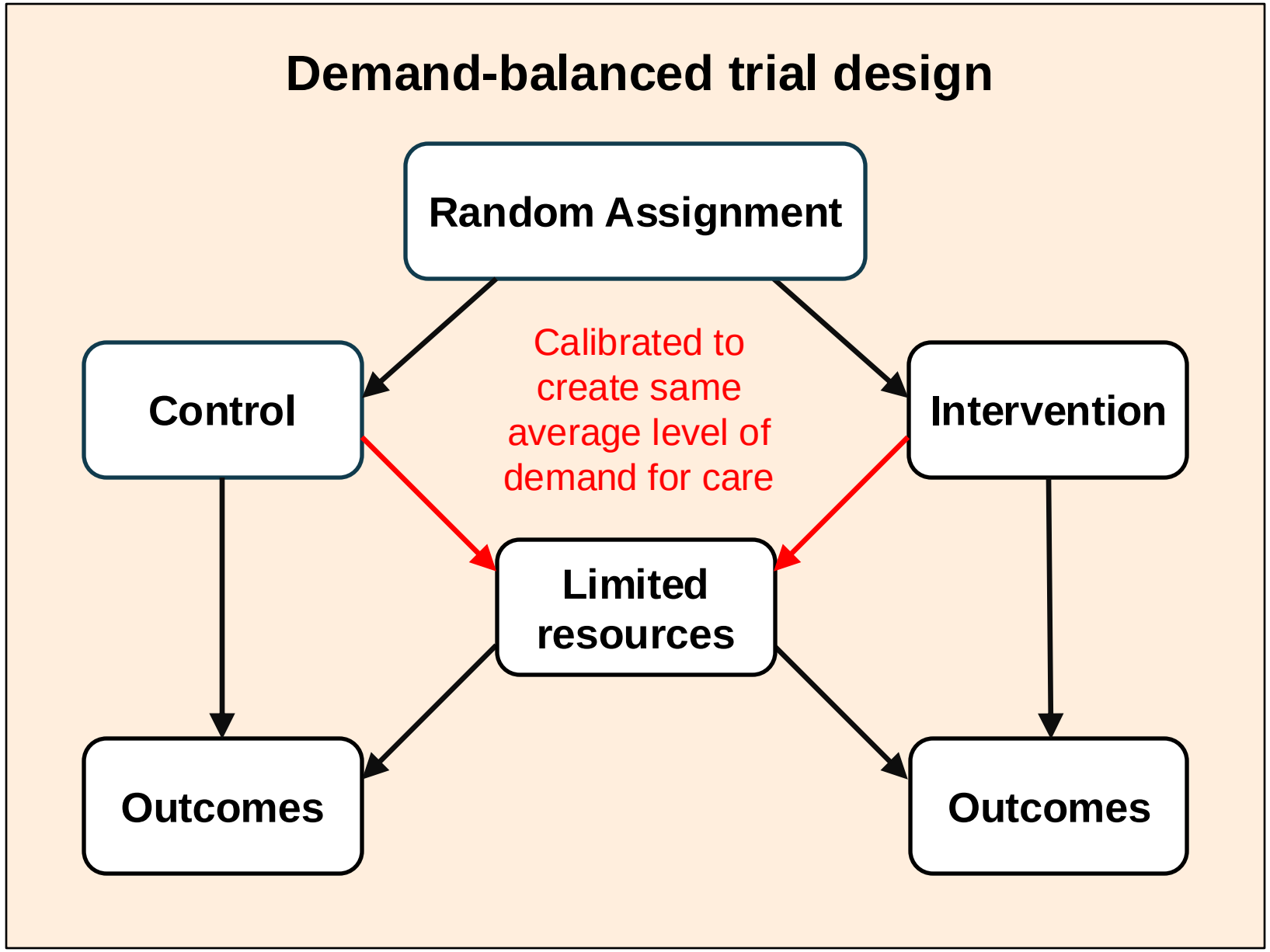
Cluster randomized design



Avoiding spillover



Avoiding spillover



Bundling resources with intervention

- Roll out intervention together with expanded supply of care
- Health system may also adjust supply to reach equilibrium

Characteristics of potentially affected trials

- Real-world setting
- Individually randomized
- Intervention affects resource use
- Outcomes affected by availability of care

Related sources of bias

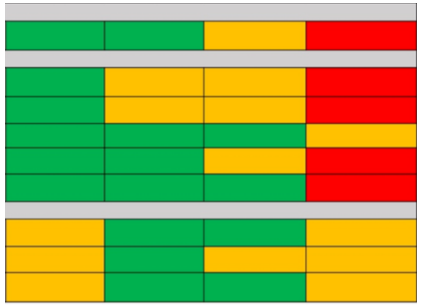
- Interference / other spillovers
  - Contamination
  - Disease transmission
- Lack of blinding
- Intercurrent events

Where do we go from here?

Guidance on trial design

Reporting guidelines

Risk of bias assessment



Risk to human subjects

How much precaution should be taken due to hypothetical concerns about spillover?

Next steps

Mann *Trials* (2024)25:833
https://doi.org/10.1186/s13063-024-08675-9

Trials

COMMENTARY Open Access

Negative spillover due to constraints on care delivery: a potential source of bias in pragmatic clinical trials

Sean Mann[1*]

Abstract

Background Pragmatic clinical trials evaluate the effectiveness of health interventions in real-world settings. Negative spillover can arise in a pragmatic trial if the study intervention affects how scarce resources are allocated across patients in the intervention and comparison groups.

Main body Negative spillover can lead to overestimation of treatment effect and harm to patients assigned to usual care in trials of diverse health interventions. While this type of spillover has been addressed in trials of social welfare and public health interventions, there is little recognition of this source of bias in the medical literature. In this commentary, I examine what causes negative spillover and how it may have led clinical trial investigators to overestimate the effect of patient navigation, AI-based physiological alarms, and elective induction of labor. Trials discussed here are a convenience sample and not the result of a systematic review. I also suggest ways to detect negative spillover and design trials that avoid this potential source of bias.

Conclusion As new clinical practices and technologies that affect care delivery are considered for widespread adoption, well-designed trials are needed to provide valid evidence on their risks and benefits. Understanding all sources of bias that could affect these trials, including negative spillover, is a critical part of this effort. Future guidance on clinical trial design should consider addressing this form of spillover, just as current guidance often discusses bias due to lack of blinding, differential attrition, or contamination.

Keywords Clinical trial, Study design, Bias, Health system capacity, Resource utilization, Patient safety

Background

Pragmatic clinical trials are used to evaluate the effectiveness of health interventions in real-world settings. In these trials, patients, providers, facilities, or other groups are randomly assigned to receive either usual care or an intervention [1]. Randomization serves to produce balanced groups of patients, so that differences in study outcomes can be attributed solely to the effect of the intervention [2]. Randomized trials are considered the "gold standard" of evidence and their results can lead to changes in clinical practice [3]. Yet, one aspect of these trials' real-world settings is often overlooked and could lead to biased results.

Clinical resources in real-world settings are sometimes scarce, meaning that their supply is insufficient to meet the needs of all patients [4–6]. During a trial, if an intervention increases patients' utilization of scarce medical resources (such as specialist appointments or hospital beds), this can negatively affect availability of care for patients in the control group. This problem is referred to by economists as "negative spillover" or "crowding out" and is sometimes addressed in trials of social welfare and

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For more information, see Mann, S. Negative spillover due to constraints on care delivery: a potential source of bias in pragmatic clinical trials. *Trials* 25, 833 (2024).

Looking to collaborate

- Analysis of data from past trials
- Design of future trials
- Adapting guidance
- Systematic review, simulation studies, etc.
- My email is smann@rand.org

Discussion