Other Trial Designs

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Nothing to disclose

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Outline

- Cohort study designs
  - Cohort
  - Quasi-cohort
- Randomized controlled trial
- Cluster randomized trials
- Adaptive trials
- Pragmatic trials

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Study Design Question

Which of the following is true for cohort studies?

A. Better suited to rare diseases than case control studies

B. Confounding by indication not a concern

C. Outcomes may be binary or time-dependent

D. Cannot evaluate time-varying covariates

Study Design Question - Answer

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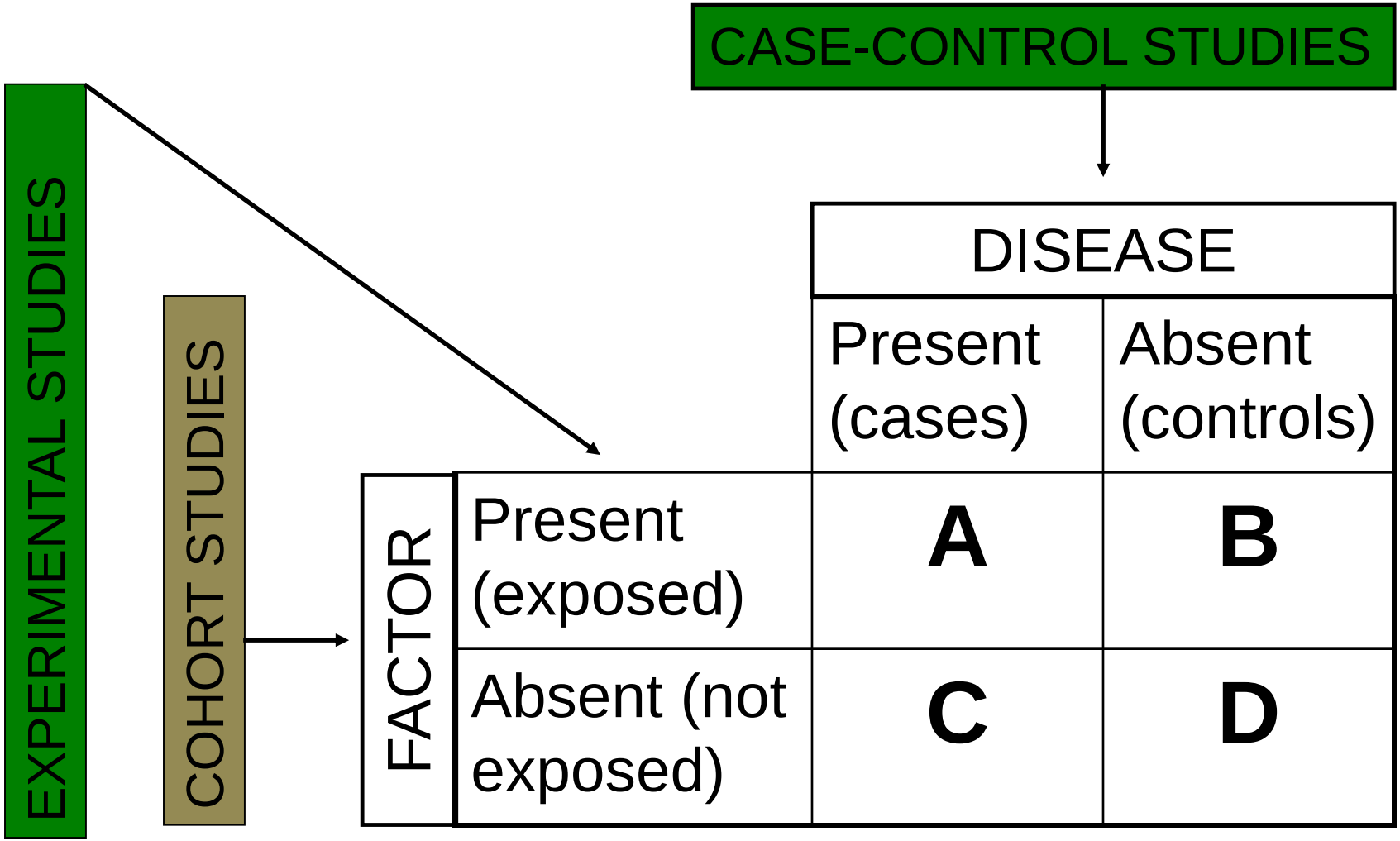
Study Design



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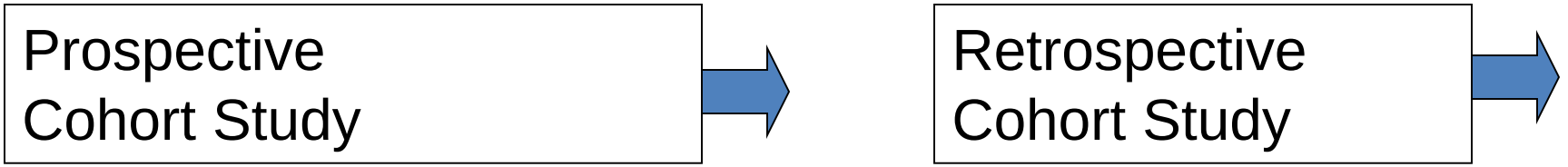
Cohort study

- A study comparing patients with an exposure to others without the exposure for differences in outcome
- Advantages
  - The study of any number of outcomes from a single risk factor/exposure
  - Incident rates available
    - Can calculate RR
  - Lack of bias in exposure data

Cohort study

- Disadvantages / Limitations
  - Potentially biased outcome data
  - Large sample size need for rare diseases
  - Long follow up needed
    - Subject to loss to follow up
    - Costly
    - Criteria and methods may change over time

Prospective vs Retrospective



Exposure ⟶ Disease

Time

Cohort study

- Example: Evaluation of a new procalcitonin-based guide for empiric antibiotic use in ICU sepsis

- Clinicians could choose to use the algorithm or not
  - Compare the results of patients for whom the algorithm is used to those for whom it is not used
  - Unadjusted analysis
  - Multivariable modeling to adjust for potential confounders

- Issues
  - Type of outcome (e.g., binary, time-dependent)
  - Clustering by clinician
  - Confounding by indication
    - Decision to use the algorithm is not random
    - Factors influencing use also associated with worse outcomes

Cohort study: Type of Outcome

- Example: Evaluation of a new procalcitonin-based guide for empiric antibiotic use in ICU sepsis
- Type of outcome:
  - Binary: “Were antibiotics discontinued after 72 hours more often in the PCT group vs the non-PCT group”
  - Time-dependent: “Were antibiotics discontinued earlier in the PCT group vs the non-PCT group”
- Binary outcome = Logistic regression analysis
  - Estimates the association between exposure status and binary outcome (yes or no)
  - Relative risk: incidence in exposed vs unexposed
  - Control for multiple confounders
- Time-dependent outcome – Cox proportional hazards
  - Estimates association between exposure and time to event
  - Hazard ratio: survival in exposed vs unexposed at a given point in time
  - Accounts for censoring of subjects (loss to follow up)
  - Allows for time-varying covariates

Confounding by Indication

- Major concern in non-randomized stewardship studies
  - Why do patients receive different treatments/strategies?
    - Measured and unmeasured factors
  - Approaches
    - Multivariable modeling
    - Propensity score analysis
    - Instrumental variables

Multivariable Modeling

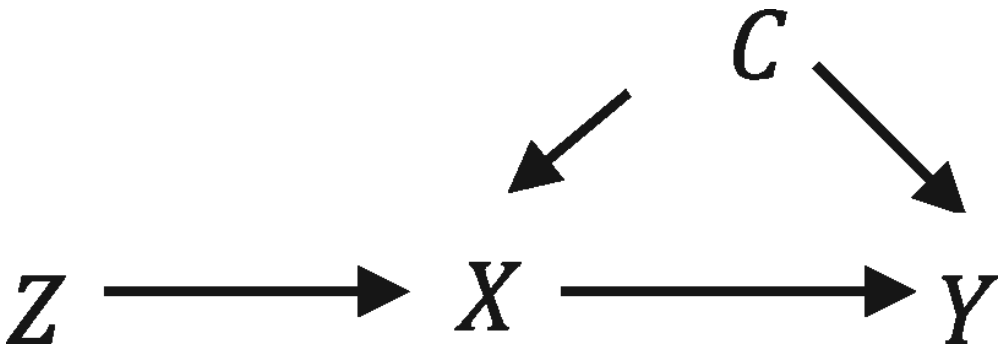
- Ascertainment of known potential confounders
- Inclusion of confounders in multivariable model
- Independent effect of the exposure/treatment
- Good when you have a large number of outcomes

Propensity Score Analysis

- Develop statistical model to predict receipt of treatment
  - Propensity score
- Two general analysis approaches
  - Stratification or Matching
- Stratification
  - Exposed and unexposed subjects stratified by propensity score (e.g., deciles)
  - Analyses conducted within strata
- Matching
  - Exposed and unexposed subjects matched based on propensity score
  - Determine association after accounting for matching
- Can see how propensity score distributed across groups
  - Often limited data at extremes
- Good when small number of outcomes

Instrumental Variables

- Another approach to addressing confounding by indication
- Instrumental variable
  - Correlated with the exposure
  - Not associated with the outcome
  - Not associated with any confounder in the exposure-outcome relationship
  - External to the exposure-outcome association
- External cause of the intervention but is by itself unrelated to the outcome
  - "Natural randomization"
  - Policy change, geographic differences
- Not always available
- Weak or strong
  - Depending on how much of the variance in the exposure it explains



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Quasi-Experimental Study

- (a.k.a.- non-randomized pre-post intervention design
- Evaluate intervention without using RCT
- The most basic type:
  - Collect baseline data
  - Implementation intervention
  - Collect same data as during baseline period
- Many different variations of quasi-experimental
  - 1) institution of multiple pretests
    - (i.e., collection of baseline data on more than one occasion)
  - 2) repeated interventions
    - (i.e., instituting and removing the intervention on sequentially);
  - 3) inclusion of a control group
    - (i.e., a group on which baseline and subsequent data is collected but on which no intervention is implemented).

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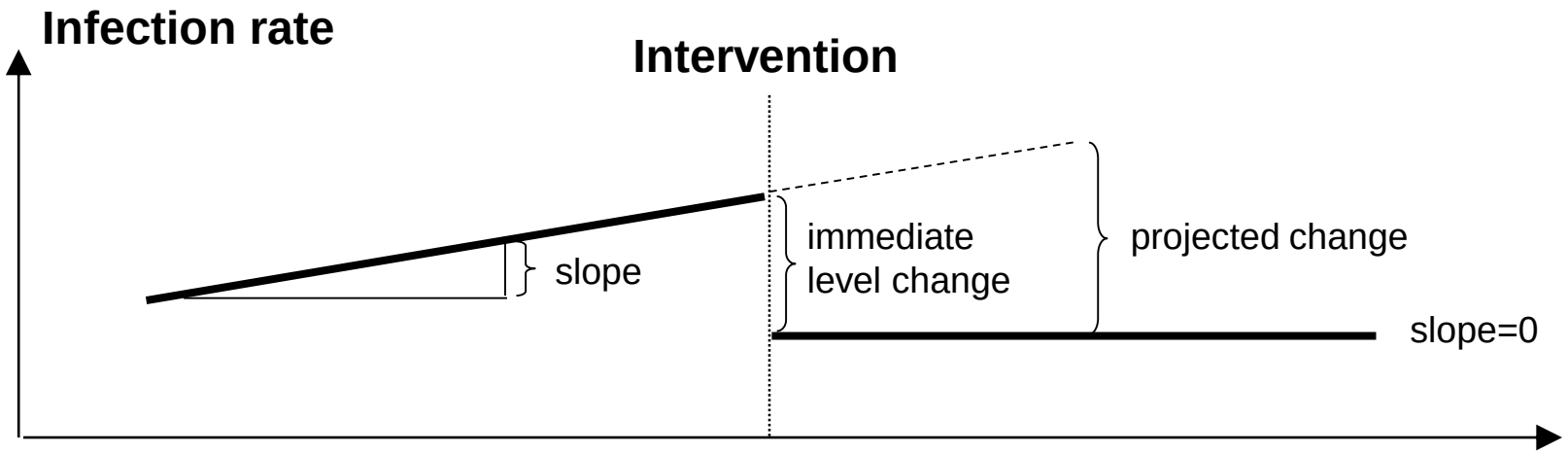
Harris AD, *Clin Infect Dis*, 2004;38:1586

Analysis of Quasi-Experimental Studies: Interrupted Time Series

- **Segments**
  - Specific event causes a change in the series, dividing it into distinct segments
  - Estimating the change in the series allows you to assess the impact of the event
- **Validity**
  - Strongest non-experimental research design
  - Pre-event level and trend serves as a built-in “control”

Hypothetical Changes in Level and Slope of a Time-Series

Analysis of an intervention effect using segmented linear regression



Assumption:
Extrapolating the pre-intervention level and trend reflects the (counterfactual) outcome that would have occurred had the intervention not happened.

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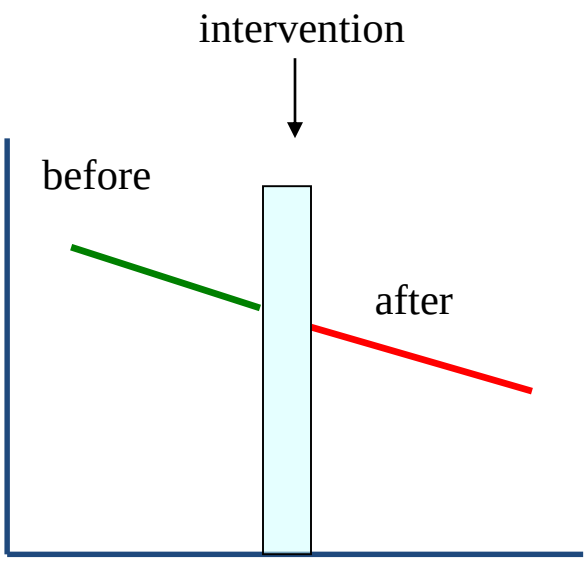
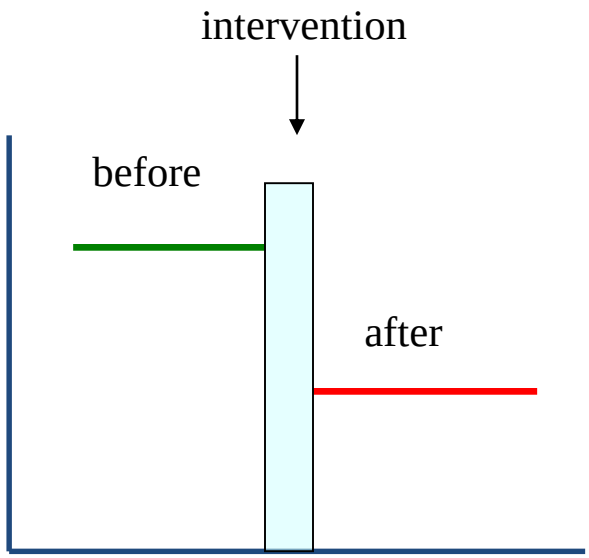
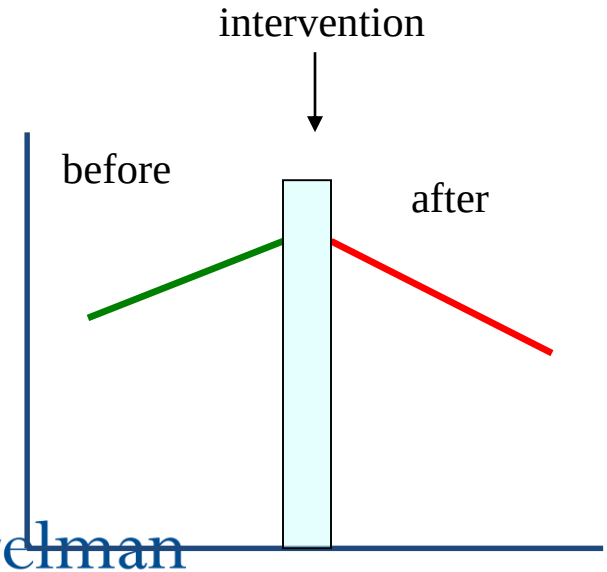
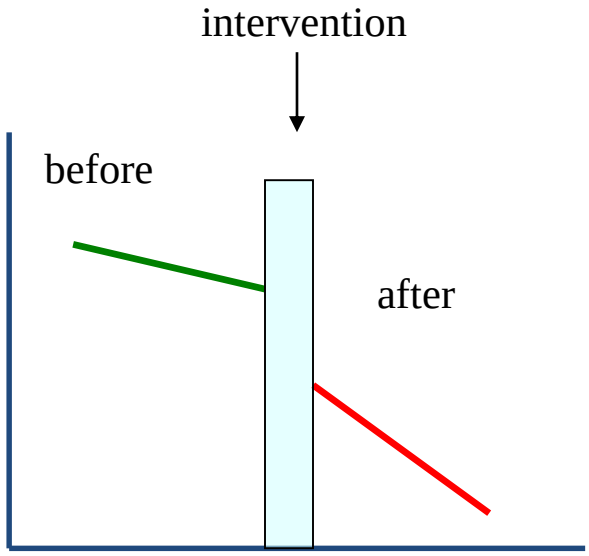
Adapted from Schneeweiss et al, Health Policy 2001

Possible Intervention Effects









Quasi-Experimental Study

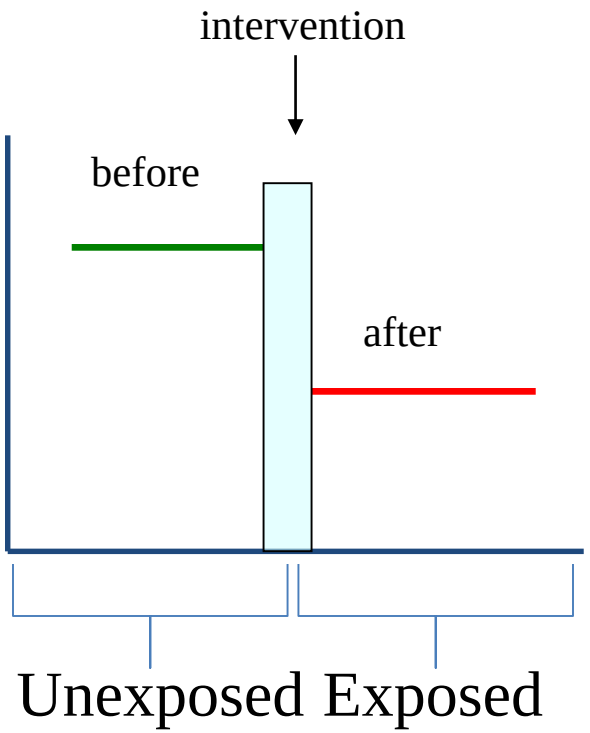
- Advantages
  - Use when RCT not ethical
  - Use when intervention must be instituted rapidly (e.g., outbreak)
  - Use when RCT not logistically feasible
    - Broad interventions difficult to randomize to individual patients or hospital floors/units.
- Disadvantages
  - Difficult to control for potential confounding variables
    - e.g., patient severity of illness, quality of medical and nursing care, comorbidities, demographics, etc
    - Control for summary measures of potential confounders in a segment
    - Inability to control for individual level confounders

Harris AD, *Clin Infect Dis*, 2004;38:1586

Cohort Study Design

- A study comparing patients with the exposure of interest to those without the exposure of interest
  - Exposure in this case is the intervention period

- Rather than the segment being the unit of analysis, it is the individual subject
- Works better if the intervention targeted at the individual



Comparison of Analyses (Cohort v Quasi)

- Example: Evaluation of a new procalcitonin-based guide for empiric antibiotic use in ICU sepsis

- Interrupted time series
- Time segments pre and post intervention
- Analysis: Segmented regression
- Outcomes
  - Monthly antibiotic use, death rates, length of stay
- Confounders
  - Census ; Case-mix
- Limitations
  - No ability to adjust for individual level confounders

- Cohort Study
- Individual subjects
  - Pre period = unexposed
  - Post period - exposed
- Analysis: Logistic regression or cox proportional hazards model
- Outcomes
  - Duration of antibiotic use; antibiotic days; death
  - Monthly death rates
- Confounders
  - Demographics, comorbidities; time varying covariates?
- Limitations
  - Temporal trends, other interventions; clustering

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RCT

- Unit of analysis typically the individual
- If prescriber is the target of the intervention, analysis at patient level difficult
- Given prescriber will have both intervention and control subjects
  - Contamination of the intervention
- Randomization at level of prescriber is common in stewardship studies
  - Case mix of patients will differ across prescribers and will be based on characteristics of the prescriber
  - Weighted randomization by prescriber characteristics
    - Requires having a sufficient variability in characteristics across prescribers

Efficacy v Effectiveness

RCT

- Efficacy trial
- Ideal setting
- Restrict inclusion criteria
- Drug v placebo
- Single endpoint
- Internal validity
- Less clinical relevance
- “Can it work?”

Comparative effectiveness

- Effectiveness trial
- Real world
- Wide spectrum of patients
- Active comparator
- Multiple endpoints
- External validity
- More clinical relevance
- “Does it work?”

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Cluster Randomized Trials

- Intervention randomized to different clusters
- Outcomes compared between intervention and control cluster
- Unit of randomization is a naturally occurring group
  - Hospital unit, practice site, hospital
  - No individual level randomization
  - No assumption that individuals within a group are independent
- Often used when intervention will benefit more than just a given subject
  - Infection prevention; transmission
- Unit of analysis is the group
  - Hospital, practice site, unit

Cluster Randomized Trials: Advantages

- More “real world”
  - Built into workflow of clinical care
  - One intervention implemented per site
- Greater external validity
  - Broader patient/clinician eligibility
- Implementation easier
  - Clinicians/administrators
  - Fewer IRB issues (e.g., waiver of consent)
- Avoids issues of contamination
  - Particularly relevant for infectious diseases
- Randomization controls for known and unknown confounders at the cluster level

Cluster Randomized Trials: Challenges

- Requires larger number of patients than an RCT
- Difficult to standardize intervention across sites
- Important to measure adherence
  - Intention to treat analysis
  - Per-protocol analysis
- Sample size calculations can be complex
- Assessing effects on patient-level outcomes
  - Assess how data are correlated within a cluster
    - Account for this in analysis
  - Account for differences in cluster sizes (weighting)
  - Adjustment for confounding variables

Cluster Randomized Crossover Trials

- Similar to cluster-randomized trials except more interventions
- Sites randomized to sequence of 2 or more interventions
- Need for washout periods?
  - Duration depends on intervention
  - Sensitivity analyses if unclear
- Analyses similar to cluster randomized trails

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Adaptive Trials: Pros and Cons of Traditional RCTs

- Traditional Clinical Trials
- Provide the highest quality evidence for/against a hypothesis
- Can be complex, lengthy, costly
- Results can be inconclusive
- Trial protocol fixed once started
  - Unable to adjust to:
    - Emerging data
    - New literature

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Huskins WC et al, *Clin Infect Dis* 2017

Study Design Question

Which of the following can't be modified over the course of an adaptive trial?

A. Sample size
B. Intervention
C. Number of trial arms
D. Eligible population
E. None (i.e., all can be modified)

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Adaptive Trials: Definition and Goals

- Clinical Trials with Adaptive Design
- Definition: Design that uses data that accumulates during study to modify study elements
- Nature of the change driven by accumulating data
- Plan for change is pre-specified in advance
- Elements that can be modified
  - Sample size
  - Endpoints
  - Eligible population
  - Randomization ratio
  - Number of arms
  - Intervention

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Huskins WC et al, *Clin Infect Dis* 2017

Adaptive Trials: Goals

- Goals
  - Provide more flexibility to study can serve as definitive test of the primary hypothesis
  - Ideally shorten study period
  - Fewer human subjects
  - Lower cost
  - Modifications need to be pre-specified
  - Design that changes in response to accumulating evidence
    - New treatments; early signals
  - Goal: increase relevance of final results

Huskins WC et al, *Clin Infect Dis* 2017

Adaptive Trials: Study Issues and Adaptive Design

Study design issue identified in trial planning	Adaptive design to potentially address the issue
Imprecise estimate of control group response rate or variation in responses	Sample size adjustment
Imprecise magnitude and/or precision of effect size	Sample size adjustment Predicted intervals
Uncertainty regarding subjects most likely to experience a benefit or a toxicity	Population enrichment
Uncertainty regarding the optimal dose of a new drug to assess its efficacy	Seamless Phase II/III trial Multi-arm, multi-stage trial
Multiple drugs, drug combinations, or treatment or testing strategies need to be evaluated in a consistent and efficient manner	Multi-arm, multi-stage trial Platform trial
Uncommon or rare condition makes it difficult to recruit sufficient subjects	Umbrella or basket trial
Uncertainty or evolution in optimal endpoint(s) to evaluate efficacy or safety	Changing endpoints

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Evans SR, Publishing Trial Results. Fundamental Concepts for New Clinical Trialists. Boca Raton, FL Chapman & Hall/CRC; 2015

Adaptive Trials: Challenges (I)

- Complex to implement
- Prolonged planning process
  - How will study elements be modified in the response to accumulating data?
- Unmasking for interim results may introduce operational bias resulting in:
  - Changes in recruitment/retention of subjects
  - Adherence to the intervention
  - Objectivity of the outcome assessment
- Role of DSMB in mitigating bias
  - DSMB shouldn't be responsible for redesigning study after reviewing unmasked data

Huskins WC et al, *Clin Infect Dis* 2017

Adaptive Trials: Challenges (II)

- Design changes may be based on observed effects ultimately determined to be irrelevant clinically.
- Statistical methods for adaptive designs complex
  - Must account for inflation of the type 1- (alpha) error (false positive interpretation of trial results) associated with interim analyses
- Modifying a study element during course of trial may raise ethical concerns
  - Can complicate informed consent
- May be difficult to estimate the cost for the trial

Huskins WC et al, *Clin Infect Dis* 2017

Adaptive Trials: Reporting Suggestions

Guidelines for the Reporting of Adaptive Trials	
Describe	The adaptation Whether the adaptation was planned or unplanned The rationale for the adaptation When the adaptation was made Data upon which adaptation is based Whether the data were unblinded The planned process for the adaptation Who made the decision regarding adaptation Deviations from the planned process Consistency of results before vs. after the adaptation
Discuss	Potential biases induced by the adaptation Adequacy of firewalls to protect against operational bias The effects on error control and multiplicity context

- Extension of the CONSORT statement for adaptive trials is under development

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Pragmatic Trial (I)

- Concept arose from concerns that results from traditional trials didn't adequately inform clinical practice due to optimization of efficacy
- Pragmatic trials emphasize real-world effectiveness and thus generalizability
- Types of Intervention trials: explanatory v pragmatic
- Explanatory trials
  - Seek to confirm physiological or clinical hypothesis
  - Measure efficacy under ideal conditions
  - Carefully defined subjects
  - Further scientific knowledge
- Pragmatic trials
  - Seek to inform a clinical or policy decision
  - Measure effectiveness under more usual conditions
  - Conducted in routine clinical practice
  - Aims to inform choices about treatments

Pragmatic Trials (II)

- Treatment strategies reflect variations that occur in real clinical practice
  - Should be clearly defined
  - Not always possible to blind
  - Same treatment doesn't have to be offered to each subject
  - Allow prescriber to target different treatments to different subjects
    - The target for study is management protocol, not specific treatments
- Study population should represent patients to whom the treatments/interventions would be applied
    - Often sicker, more comorbidities
    - Excluded only if contraindicated
    - Typical Practice settings
- Outcome measures
  - Explanatory trials
    - Intermediate outcomes; understand biologic basis for response
  - Pragmatic trials
    - Represent full range of health gains
    - Whether it worked, not why it worked

Assessing Trial Pragmatism

Table 1. Nine Dimensions for Assessing the Level of Pragmatism in a Trial, as Proposed in the Pragmatic–Explanatory Continuum Indicator Summary 2 (PRECIS-2) Tool.*

Dimension	Assessment of Pragmatism
Recruitment of investigators and participants	
Eligibility	To what extent are the participants in the trial similar to patients who would receive this intervention if it was part of usual care?
Recruitment	How much extra effort is made to recruit participants over and above what would be used in the usual care setting to engage with patients?
Setting	How different are the settings of the trial from the usual care setting?
The intervention and its delivery within the trial	
Organization	How different are the resources, provider expertise, and organization of care delivery in the intervention group of the trial from those available in usual care?
Flexibility in delivery	How different is the flexibility in how the intervention is delivered from the flexibility anticipated in usual care?
Flexibility in adherence	How different is the flexibility in how participants are monitored and encouraged to adhere to the intervention from the flexibility anticipated in usual care?
The nature of follow-up	
Follow-up	How different is the intensity of measurement and the follow-up of participants in the trial from the typical follow-up in usual care?
The nature, determination, and analysis of outcomes	
Primary outcome	To what extent is the primary outcome of the trial directly relevant to participants?
Primary analysis	To what extent are all data included in the analysis of the primary outcome?

* Information in the table is adapted from Loudon et al.[22]

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Drazen JM, NEJM 2016;375:454

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