Research Methodology for Real-World Settings: Fundamentals of High-Quality CER

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Overview

- Improving value & reducing waste in research
- Framework for high-quality comparative effectiveness research (CER)
- PCORI Methodology Standards & common challenges in PCOR/CER
- Standards for studies of complex interventions

Improving Value & Reducing Waste in Research

Reducing Waste in Research

- **Avoidable waste in research is an extensive and pervasive problem.**
  - 85% of investment in biomedical research is wasted
  - Shared responsibility among stakeholders (researchers, funders, industry, regulators, & institutions)
  - Waste due to correctable problems

Where the Waste Occurs

- Research priorities & study questions
- Methods for design & analysis
- Research reports & publication practices

Increasing Value in Research

"We need less research, better research, and research done for the right reasons."*

- To increase the value of research (and ensure responsible use of scarce resources), researchers should:
  - Provide sufficient justification of proposed studies
  - Employ appropriate approaches for the design, conduct, and analysis of a study
  - Adhere to requirements and best practices for reporting results and ensuring accessibility to information needed to evaluate the quality and applicability of findings

*Altman DA. The scandal of poor medical research. BMJ 1994: 308: 283-84.

PCORI's Methodology Standards

- Required by PCORI's authorizing law
- Represent **minimal standards** for design, conduct, analysis, and reporting of comparative effectiveness research (CER) and patient-centered outcomes research (PCOR)
- Reflect generally accepted best practices
- Used to assess the scientific rigor of applications, monitor the conduct of research awards, and evaluate final research reports

2018 PCORI Methodology Standards (Updated 4/30/2018)

The 54 standards can be grouped into 2 broad categories and 13 topic areas.

Cross-Cutting Standards

- Formulating Research Questions
- Patient Centeredness
- Data Integrity & Rigorous Analyses
- Preventing/Handling Missing Data
- Heterogeneity of Treatment Effects

Design-Specific Standards

- Data Registries
- Data Networks
- Causal Inference Methods*
- Adaptive & Bayesian Trial Designs
- Studies of Medical Tests
- Systematic Reviews
- Research Designs Using Clusters
- Studies of Complex Interventions

**The first standard for Causal Inference Methods (CI-1) is considered cross-cutting and applicable to all PCOR/CER studies.*

Framework for High-Quality Comparative Effectiveness Research (CER)

Evidence-Based Information

- To be justified, a particular study must have the potential to generate the evidence needed to make an informed health decision
- **Clinical evidence is**: Valid, reliable, and relevant data about the outcomes experienced by patients who receive specific interventions
  - Clinical interventions are well-defined and reproducible
  - Outcomes include both benefits and harms associated with the specific interventions
  - Characteristics of the study population are sufficiently described to improve understanding about the extent to which the findings apply to patients not participating in the study

Comparative Effectiveness Research (CER)

- CER has been defined as follows:
  - Representative study populations
  - Address gaps in the evidence base
  - Head-to-head comparisons that can inform decision making
  - Outcomes that matter to patients (PCOR)

What is the Starting Point for CER?

- Examine the choices people make about the options for preventing, diagnosing, treating, and monitoring a disease
- Consider how compelling it is to make a choice among these options
- Consider how the need to compare these options could inform the focus of new research
  - Heterogeneity of the patient population
  - Understanding the important benefits and harms
  - Clarity about gaps in the current evidence base

PICOTS

- The **Population** that is studied
- The **Intervention** that is delivered to some patients
- The **Comparator** that other patients receive
- The important patient **Outcome**s that are assessed
- The **Timing** of when outcomes are assessed
- The study's clinical **Setting**

Features of Patient-Centered Outcomes Research (PCOR)

- P**ICO**TS: Project assesses whether two or more options differ in effectiveness (the benefits and harms experienced by patients)
- **P**ICOT**S**: Project is conducted in a clinical setting that is as close as possible to the real-world setting in which the intervention would be delivered
  - Not necessarily a single/unique real-world setting
- Study design, outcomes, and follow-up reflect real-word setting(s) as much as possible without sacrificing scientific rigor

PICOTS: Choosing Appropriate Outcomes & Outcome Measures

- Identify the most important benefits and harms
- Select appropriate outcome measures
- Determine time course of measurement
- Consider potential sources of bias
- Carefully select and measure “process variables”

Design & Analysis: Casual Inference in PCOR/CER

- **Causal Model**
  - Informed by the PICOTS framework
  - Represents the key variables, known or hypothesized relationships among them, and conditions under which the hypotheses are to be tested
- **Internal Validity**
  - Valid estimates of treatment effects in the study population
- **External Validity**
  - Generalizability of results to patients not included in the study population

Design & Analysis: Quality of Evidence

- **Data quality**
  - Primary data collection vs. secondary analysis of existing data
- **Study design**
  - Randomized vs. observational designs
- **Analytical methods**
  - Issues of confounding and bias

Randomized Controlled Trials (RCTs)

- **Pros:**
  - Best way to control for confounding
    - Randomization (ideally) distributes all factors that might influence the outcome (both known and unknown) between the intervention groups
  - Systematic data collection (reduces missing data)
  - Outcome assessments are tailored
- **Cons:**
  - Sample sizes must be large to assess heterogeneity of treatment effects (HTE)
  - Expensive & may take a long time to complete

Example 1: PCORI-funded study that uses a randomized design

- Compares immediate surgery (appendectomy) to antibiotics for the treatment of acute appendicitis
- Evidence Gap
  - Existing evidence is from non-US sites and with varying antibiotic regimens
  - Surgical techniques also have evolved
- Outcomes are relatively short-term (12 months)
- Project has partnerships with multiple hospitals in a single geographic region
- Randomized trial is feasible

Observational Studies

- **Pros:**
  - Large, representative populations from “real world” practice
  - Completed more quickly at a lower cost
- **Cons:**
  - Imperfect methods to control for confounding
    - Confounding by indication: Did the intervention cause the difference in outcomes? Or did the characteristics of the patient that influenced choice of treatment directly influence the outcomes?
  - Missing data
  - Outcomes may not be well-defined or hard to assess

Data Sources for Observational Studies (1/2)

- Prospective Registries (prospective cohorts)
  - Designed prior to data collection and often before research question defined
  - Control methods for selection of participants and collection of data
  - Require a long time to complete patient follow-up
- Retrospective Cohorts
  - Research question is identified prior to selection of data source
  - Built upon existing data sources
  - Quicker and much less expensive

Data Sources for Observational Studies (2/2)

- Administrative Databases
  - Data inherently collected for non-research purposes
  - Often require merging of datasets
  - Potential for very large datasets

Quantity and availability of data cannot compensate for poor quality or lack of appropriate fit with the specific research question!

Example 2: PCORI-funded study that uses an observational design

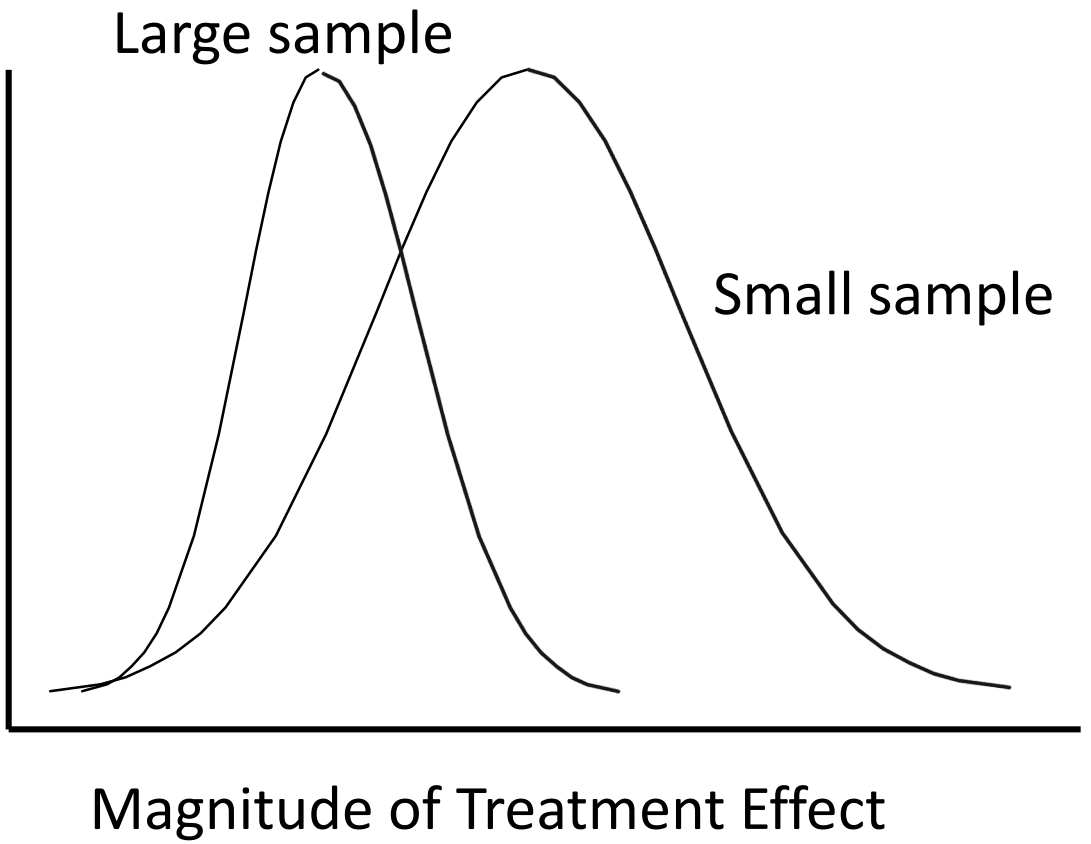
- Compares 2 different regimens of antipsychotic medications for people with schizophrenia
- Evidence gap
  - Existing evidence focused on a relatively narrow range of medications
  - Many remaining questions about drug classes and dosage regimens
- Outcomes are long-term (years)
- Randomized trial is likely not feasible
- Available and appropriate data source
  - Nationwide Medicaid database linked to a pharmacy database that captures medication changes

Importance of Sample Size

- Larger sample sizes are important for reducing statistical uncertainty
  - Small sample sizes:
    - Cannot reflect heterogeneity of the patient population
    - Decrease the precision of the findings
    - May generate results that are not representative of a larger patient population
- Size of the treatment effect impacts ability to draw valid conclusions

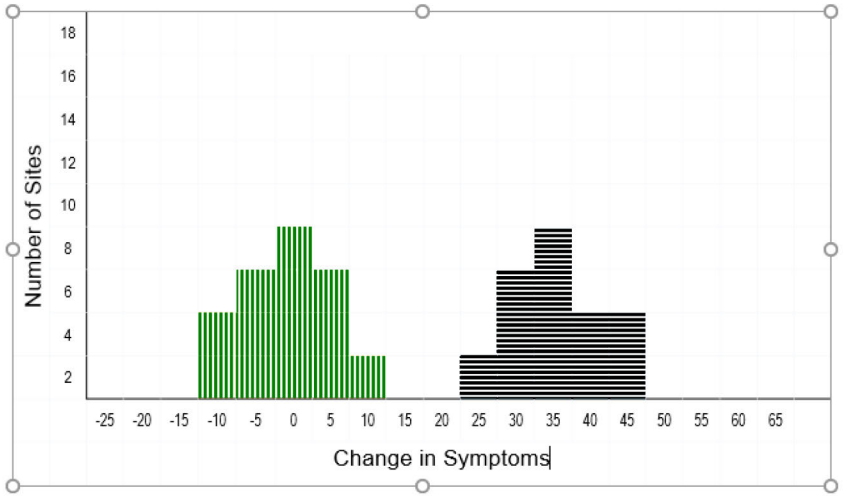
Sample Size & Precision

Probability of experiencing treatment effect

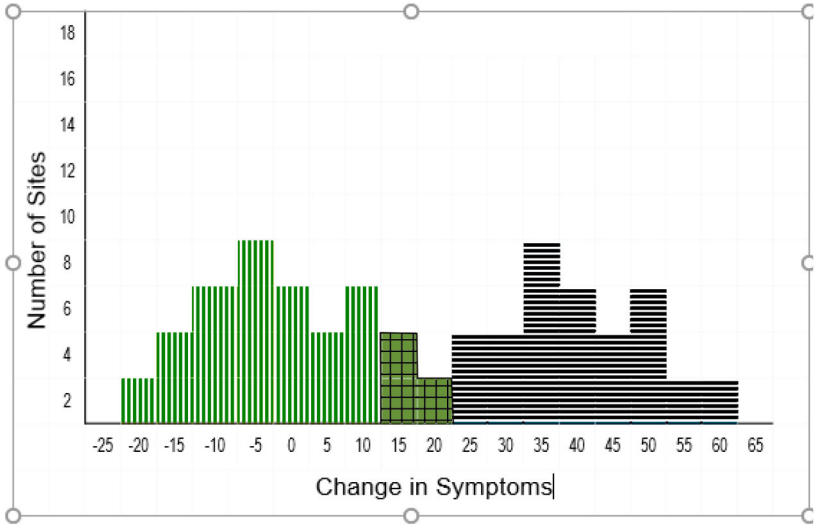


Sample Size & Variance

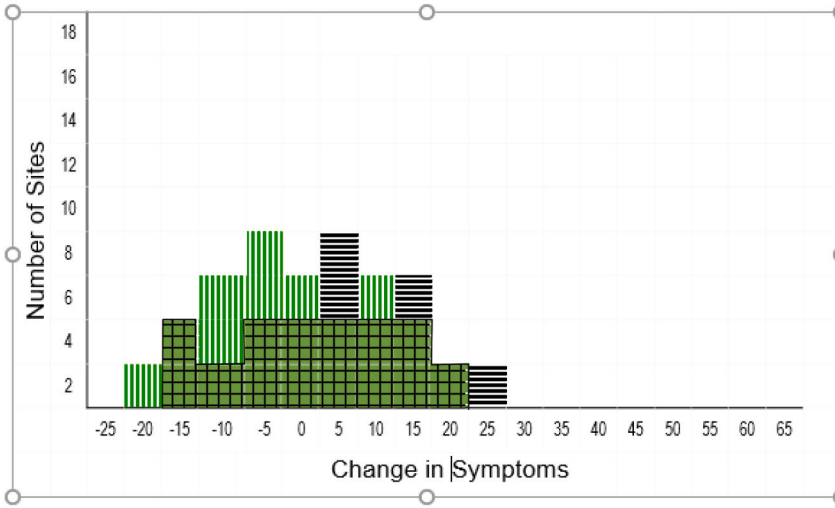
Large effect size & moderate variance



Large effect size & high variance



Low effect size & high variance



Sample Size & Significance

- Statistical significance ≠ clinical significance
- Increasing sample size does not address sources of confounding and bias

PCORI Methodology Standards & Common Challenges in PCOR/CER

PCORI Methodology Standards: General Themes (1/2)

- **Getting the question right (PICOTS model)**
  - RQ-1: Identify gaps in evidence.
  - RQ-3: Identify specific populations and health decision(s) affected by the research.
  - RQ-5: Select appropriate interventions and comparators.
  - RQ-6: Measure outcomes that people representing the population of interest notice and care about.

- **Basing the research on a rigorous causal model**
  - CI-I: Specify the causal model underlying the research question (cross-cutting standard, applies to all PCOR/CER studies).
  - CI-2: Define and appropriately characterize the analysis population used to generate effect estimates
  - CI-3: Define with the appropriate precision the timing of the outcome assessment relative to the initiation and duration of exposure.

PCORI Methodology Standards: General Themes (2/2)

- **Ensuring high-quality data**
  - IR-1: A priori, specify plans for quantitative data analysis that correspond to major aims.
  - IR-2: Assess data source adequacy.
  - IR-7: In the study protocol, specify a data management plan that addresses, at a minimum, the following elements: collecting data, organizing data, handling data, describing data, preserving data, and sharing data.
- **Specific design & analysis issues**
  - MD-2: Use valid statistical methods to deal with missing data that properly account for statistical uncertainty due to missingness.
  - MD-4: Examine sensitivity of inferences to missing data methods and assumptions, and incorporate into interpretation.
  - CI-4: Measure potential confounders before start of exposure and report data on potential confounders with study results.

Challenges in PCOR/CER (1/2)

- **Study Designs**
  - Choosing “trendy” study design (cluster and SMART designs) vs. most appropriate design
  - Simplified consent processes
- **Data Quality**
  - Use of electronic health record (EHR) data in CER for cohort identification and outcome assessment
  - Completeness, accuracy, and consistency
- **Analysis Plans**
  - Unrealistic (and unsupported) estimates of effect size
  - Focus on confounding as the only potential source of bias
  - No systematic approach to addressing potential confounding
  - Inappropriate use of heterogeneity of treatment effect (HTE) analyses

Challenges in PCOR/CER (1/2)

- **Emphasis on Patient-Reported Outcomes (PROs)**
  - Requirements for contact with study participants for data collection
  - Approaches to data collection (phone banks, web-based portals)
  - Problems with missing data
  - PROs are not always the most relevant patient-centered outcomes
- **Delivery of interventions**
  - Compliance with treatment assignment (cross-over)
  - Fidelity to intervention
  - Expensive interventions

Standards for Studies of Complex Interventions

Evaluating Complex Interventions in PCOR/CER

- Delivery of clinical services can be uneven
  - Dependence on skills and behaviors of health providers
  - Multiple components
    - Surveillance over time and dose adjustment
    - Variations in procedures
    - Communication among members of the clinical team
- Interactions among patient characteristics and the components of the clinical service can make it difficult to interpret findings
  - A causal model is essential to understanding potential interactions and differential effects
  - Patient populations should be carefully characterized

What Counts as a Complex Intervention?

"Simple" Intervention

- fixed
- robust
- simple causal path
- average effect size is predictive

Complex Intervention

- adaptable
- context sensitive
- complex causal path
- average effect size estimate is not predictive

PCORI Methodology Standards: Complex Interventions

- **Studies need to be based on a specified causal model**
- **Specification of both functions and forms of the intervention**
  - Core functions are derived from the causal model.
  - Forms are how the functions are achieved.
- **Forms can be adapted to meet the clinical situation (while still meeting the core functions)**
  - Specify permissible adaptations
  - How does this relate to “manualized interventions”?
- **Studies of complex interventions need to include an integrated process evaluation**
- **Measure both clinical outcomes and “process” outcomes**

Studying & Using Complex Interventions

- **Function**
  - Purpose, intended effect(s); linked to needs
- **Form**
  - Activity, format, operationalization
- **Complex interventions usually can be, will be – and should be – adapted**
  - *Adaptation should be embraced, studied, and guided rather than ignored or suppressed!*

Questions?

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Thank You!

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