Research in Real-World Settings: PCORI's Model for Comparative Clinical Effectiveness Research

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Welcome!

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Overview

- Framework for understanding the purpose and approaches used in comparative effectiveness research (CER)
- Issues in designing and conducting a study to answer a CER question

What is evidence-based information?

- Clinical Evidence
  - Valid data about the outcomes experienced by patients who receive specific medical interventions
  - Assurance that the most important outcomes are captured and recorded
  - Characteristics of the patients are sufficiently well-described to improve understanding about variation in outcomes across important subgroups
- Key Features
  - Clinical characteristics of the study population are comparable to those of the patients to whom the evidence will be applied
  - Clinical interventions are well-defined and reproducible
  - Outcomes include both benefits and harms associated with the specific clinical interventions

What is PICOTS?

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

What is the starting point of comparative effectiveness?

- Examine the choices people make about the options for managing 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

Features of Patient-Centered Outcomes (PCOR) projects

- Project assesses whether two or more options differ in effectiveness (the benefits and harms experienced by patients)
- Project is conducted in a clinical setting that is as close as possible to a real-world setting
- Methodological approach (including study design, outcome measures, and follow-up) reflects the real-word setting(s) as much as possible without sacrificing scientific rigor

What are the qualities of a good PCOR project?

- PCOR studies should be designed to generate scientifically valid evidence
  - Relevant, testable scientific hypotheses
  - Internal validity required for external validity
  - Adherence to appropriate standards and best practices
    - PCORI Methodology Standards provide guidance for thinking about how to design and conduct a study to answer a CER question

Design & Analysis Issues in PCOR

Choosing a study design: the problem of comparability of groups

- Confounding: systematic differences between patients receiving alternative interventions
  - Differences in outcomes between the groups of patients may be due to factors other than the treatment received.
- Example: Studies comparing immediate and delayed use of invasive management in acute cardiac ischemia

Randomized Controlled Trials (RCTs)

- **Pros:**
  - Best way to control for confounding
  - Outcome assessments are tailored
- **Cons:**
  - Sample sizes must be large to assess heterogeneity of treatment effects (HTE)
  - Take a long time to complete

Observational Studies

- **Pros:**
  - Large sample sizes
  - Real-world populations
  - Can be completed quickly
- **Cons:**
  - Imperfect methods to control for confounding
  - Outcomes may not be well-defined or hard to assess

Sources of data in clinical research projects: observational studies

- **Prospective Registries (prospective cohort)**
  - The registry is designed prior to data collection and often before defining the research question
  - Records data on both receipt of services and outcomes
  - Controls methods for selection of participants and collection of data
  - May not be perfectly aligned with goals of a specific research question
  - Require a long time to complete patient follow-up
- **Retrospective Cohorts**
  - The research question is identified prior to constructing the registry
  - Built upon existing data sources
  - Includes people who were identified and treated in the past
  - Imperfect identification of participants
  - Timing of data collection is problematic
  - Quicker and much less expensive

Other sources of data for clinical research projects

- **Administrative Databases**
  - Data inherently collected for non-research purposes
  - Often require merging of datasets
    - Patient matching
    - Different clinical systems
  - Potential for very large datasets
    - Does size outweigh the limitations?

Choosing the right outcomes

- Identify the most important benefits and harms
  - Value of engagement with clinical and patient partners
- Patient-reported outcomes (PROs)
  - Can be tailored to those outcomes that are important to patients
  - May require significant infrastructure to obtain these measures
  - Issues of validity of measurement instruments
- Time course of measurement
  - Is the follow-up sufficiently long?

Other considerations for choosing outcomes

- Potential sources of bias
  - Testing effects
    - Frequent measurement of patient-reported outcomes
  - Respondent fatigue
    - Measuring too many outcomes
- Careful selection and measurement of "process variables" for estimating treatment effects
  - Outcomes that may not be considered "patient-centered" may still be important for ensuring validity and reliability of results

Causal inference in PCOR

- **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

Choosing appropriate statistical methods

- **Missing data**
  - Particular challenge in PCOR
  - Understanding the missing data mechanisms
  - Sensitivity analyses
- **Confounding**
  - Not necessarily eliminated by randomization
  - Measured vs. unmeasured confounding
  - Statistical approaches rely on assumptions, not all of which are testable
- **Heterogeneity of Treatment Effects (HTE)**
  - Justification and pre-specification of HTE analyses
  - Hypothesis-driven (confirmatory) vs. hypothesis-generating (exploratory)

PCORI Works to Improve Research Methodology

In any study, methods matter. That's why we've developed methodology standards that all research should follow, at a minimum.

Methodology Standards: 11 Broad Categories

- Formulating Research Questions
- Patient-Centeredness
- Data Integrity and Rigorous Analyses
- Preventing/Handling Missing Data
- Heterogeneity of Treatment Effects
- Data Networks
- Data Registries
- Adaptive and Bayesian Trial Designs
- Causal Inference
- Studies of Diagnostic Tests
- Systematic Reviews

Conclusions

- The starting point of all PCOR is to define important healthcare decisions that need better evidence.
- The ending point of all PCOR is the generation of results that are useful to decision makers.
- The choice of study design, data source(s), and analytical methods affects the quality and strength of evidence generated by a study.

Questions?

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Thank You

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