Pragmatic Clinical Studies

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Welcome!

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In this Session

- PCORI's approach to evidence gaps and developing new clinical evidence
- Key features of the funding announcements for PCORI's Pragmatic Clinical Studies
- Methodological issues/standards
- Lessons we have learned
- PCORI priority topics

What is Evidence-based Information?

- Clinical evidence: Valid data about the outcomes experienced by patients who receive medical care.
  - The population is well defined.
  - The clinical interventions are well defined.
  - We have information about the most important outcomes (both benefits and harms).
- Comparative effectiveness
  - Starting point is the choices people make about the options for managing a disease.
  - These choices inform the focus of new research.
  - The research compares the benefits and harms associated with each option.

Perspectives on Comparative Effectiveness Research

- Comparative Effectiveness Research should be a public good that:
  - Gives health care decision makers – patients, clinicians, purchasers and policy makers – access to the latest open and unbiased evidence-based information about treatment options
  - Informs choices and is closely aligned with the sequence of decisions patients and clinicians face

First Steps in Developing New Comparative Effectiveness Research

- Understand the choices made by patients and clinicians
  - Which clinical options are realistically available to patients?
- Define the important patient sub-groups
  - Recognize disparities and their sources
- Define the outcomes (benefits and harms) that are important to patients
  - Benefits
  - Harms

New Comparative Effectiveness Research Must Address Important Evidence Gaps

- Assess the available evidence about important outcomes
  - Systematic reviews
  - Evidence gaps that are important to decision makers
- Design a study that can feasibly close the evidence gap
  - If the gap is not important, the research will not be useful

Timeline of PCORI Pragmatic Studies Initiative

- First funding announcement in February 2014
- First funded projects in mid-2015
- Competitive LOI's
- Deadline past for current (fourth) announcement
- Next LOI deadline fall 2015
- Emphasis on priority clinical topics
  - Investigator-initiated topics are also considered

Details About Funding

- Project durations of up to 5 years
- Up to $10M in total direct costs
- Expect to fund approximately 20 projects/year in 2015-16

What Are We Talking About?

- Pragmatic Clinical Studies are intended to provide information that can be directly adopted by healthcare providers.
- Mostly conducted in routine clinical settings
- Large, because the expected differences in effectiveness may be small, yet important or different in patient subgroups
- Less intrusive to routine clinical practice
- Sometimes called “Large Simple Trials”

Traditional Randomized Controlled Trials

- Study sample tends to be homogeneous, highly motivated (and therefore more adherent), relatively free of comorbid conditions
- Research tends to take place in specialized research settings
- Research protocols are often strict and do not represent typical clinical practice

What is a Pragmatic CER Study?

- Answers a practical, real world comparative effectiveness research question.
- Assesses whether two or more options differ in effectiveness when administered as they are in real life
- Project is conducted in a clinical setting that is as close as possible to a real world setting.
- The methodological approach (including study design, outcome measures, and follow-up) is as simple as possible without sacrificing scientific rigor.

Justification for the Design Elements of a Large Pragmatic Study

- Suggest reviewing pragmatic–explanatory continuum indicator summary (PRECIS) tool
- Consider tradeoffs
  - Eligibility criteria
  - Flexibility of intervention
  - Range and types of outcomes
  - Follow up intensity
  - Adherence
  - Etc.

Source: A pragmatic–explanatory continuum indicator summary (PRECIS): a tool to help trial designers. Thorpe, et al. CMAJ 2009; 180:E47-E57.

Research Activities Not Supported in this PFA

- Studies of decision aids
- Efficacy trials
- Evidence syntheses
- Cost-effectiveness analysis
- Research that aims to compare the overall costs of care between two or more alternatives and use the results to determine the preferred alternative

Study Design

- Compare the benefits and harms of at least two approaches known to be effective for a particular clinical condition
  - Drugs
  - Devices
  - Procedures
  - Behavior modification
  - Integrative services
  - Delivery-system interventions
- Projects can address comparisons of discrete clinical services or complex interventions
- RCTs or large prospective observational studies

Focus of Studies

- Outcomes meaningful to patients:
  - Morbidity
  - Mortality
  - Symptoms
  - Functional status
  - Quality of life
  - Absenteeism from work or school

Studies Must Have an Impact

- Focus on a CER question that is important to patients and decision makers
- Address an evidence gap that has been substantiated by existing rigorously conducted systematic reviews or specifically emphasized by a professional society's evidence-based clinical practice guideline
- Endorsement by relevant patient organizations, clinician organizations, payer/purchaser consortia, and/or life sciences industry representatives as being a critical question
  - one that, if adequately answered, would substantially improve decision making

Study Populations

- Examine diverse populations receiving care in real-world settings
- Have strong interest in and support for the study by host delivery systems and clinical care settings
- Specify broad and simple eligibility criteria that will allow wide generalization of results, while attending appropriately to any ethical concerns of excess risk in some patient subgroups

Studies Need to Launch Quickly

- Compare interventions that are either known to be efficacious, or are commonly in use, and can be implemented in real-world settings
- Capacity to collect efficiently patient-centered outcomes periodically during follow-up
- Provide preliminary evidence of the potential for efficient recruitment, high participation rates, and appropriate oversight by local or centralized Institutional Review Boards (IRBs), including plans for streamlining or waiving individual informed consent in cases of low-risk interventions
- Plan for sharing de-identified data

Strategies for Engagement with Clinical Partners

- Identify and engage with major patient and stakeholder organizations that would implement study findings—as well as with existing local communities of patients and care providers—to formulate the research questions, design the study, help monitor progress, and disseminate the findings
- Minimize disruption to participants' daily routines (e.g. minimize participant visits intended solely for study-assessment purposes; capture PROs during office visits, electronically, or via phone)

More Strategies

- Design the study so that the conduct can be, as seamlessly as possible, integrated with routine clinic/office operations
- Use efficient methods to obtain participant consent while still meeting ethical and legal requirements
- Capitalize on the existing electronic health records and other computerized information to identify and recruit eligible patients, monitor study conduct and patient safety, and collect study outcomes information
- If data standardization and interoperability across study sites has not already been accomplished, develop methods that will enhance the standardization of data that are accessed from different electronic health record systems.

How Large?

- Sample size large enough to enable precise estimates of the rates of benefits and harms of the clinical services being compared
  - Support testing of hypotheses related to potential differences in effectiveness in relevant patient subgroups (heterogeneity of treatment effects)
- Studies should be large enough and long enough to
  - Capture the relevant outcomes
  - Allow examination of possible differences in effectiveness in key patient subgroups
- At least 2,000 patients
- More than 45,000 in several trials
- Must include a broad and diverse population

Human Studies Requirements

- Applicants should provide preliminary evidence of the potential for:
  - efficient recruitment
  - high participation rates
  - appropriate oversight by local or centralized Institutional Review Boards (IRBs)
- Intensity of oversight and complexity of informed consent procedures should be closely related to the degree of risk from study participation.

Engagement in PCS

- Applicants must partner with relevant patient, clinician, and other stakeholder organizations
- Partners must strongly endorse the proposed study and be involved with research teams throughout the conduct of the study
  - Research is more relevant
  - Findings are more likely to be disseminated and implemented

Partnerships

- Expectation that applicant researcher have partnered with relevant patient organizations, specialty professional organizations, healthcare systems, insurers, and/or employer purchasers in preparing applications
- Partner finalization and endorsement is essential for labeling high priority
- **When partnerships should be established**

Methodological Issues

- In the case of randomized trials, adherence to current best practices for conducting pragmatic trials:
  - Standardized inclusion/exclusion criteria
  - Proper randomization
  - Techniques to minimize potential for missing data
  - Appropriate safety monitoring (including establishment of a data-safety monitoring board, or discussion of why such a board is unnecessary)

The Application Process

First Steps

- Register and create an account in PCORI Online
- Submit Letter of Intent (LOI)
- Full Applications by Invitation Only

LOI Evaluation Criteria

- Importance and relevance of the topics to PCORI priorities
  - Other topics are considered but preference will be given to the PCORI Priority Topics
- The likelihood of meaningful change in patience outcomes and/or healthcare practices
- The clarity and credibility of applicants' responses to the LOI questions, as well as justification of the need for a large pragmatic study
- Prior relevant research experience and programmatic fit and balance, taking into consideration whether the particular proposal fills a gap in the portfolio of proposals with certain characteristics including disease category, topics, priority population, methodologies, and other variables

Budget

- Will vary widely among studies based on
  - Study topic and design
  - Needs for recruitment and/or primary data collection
  - Required length of follow-up
  - Analytic complexity

Lessons We Have Learned

- New options are less desirable than an option that is commonly available
- PCORI is not looking to fund new or untested interventions

Pitfalls

- Comparative Efficacy
- Usual Care
- Placebo as comparison
- Tests efficacy (or comparative efficacy) within a tightly protocol-controlled research setting (as opposed to more real-world, pragmatic CER)
- Formal cost-effectiveness analysis in the form of dollar-cost per quality-adjusted life-year to compare two or more alternatives
- Direct cost analysis
- Natural history of disease
- Instrument development

PCORI Funded Studies

Cancer Care	Stroke	Back Pain
3	1	1

Improving Healthcare Systems	PCORI Priority Topics
2	2

PCORI Priority Topics

- Medical versus invasive procedures for asymptomatic carotid artery disease
- Surgical options for hip fracture in the elderly
- Pelvic floor mesh implants

Questions?

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Thank You!

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