

# Pragmatic Clinical Studies

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# Welcome!

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# In This Session

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- 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 and standards
- Lessons learned
- PCORI priority topics



# What Is Evidence-Based Information?

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- Clinical evidence: Valid data about the outcomes experienced by patients who receive specific medical interventions
  - The population is well defined.
  - The clinical interventions are well defined.
  - We have information about the most important outcomes (both benefits and harms) associated with specific clinical interventions.



# What is the Starting Point of Comparative Effectiveness?

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- 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.
- The research should compare the benefits and harms associated with each option.



# Perspectives on Comparative Effectiveness Research

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- Comparative Effectiveness Research (CER) 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



# New Comparative Effectiveness Research Must Address Important Evidence Gaps

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- Assess the evidence about available options and their 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

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- First funding announcement in February 2014
- First funded projects in mid-2015
- Competitive letters of intent (LOIs)
- 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

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



# What Are We Talking About?

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- 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, 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), and 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?

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- 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

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- Suggest reviewing pragmatic–explanatory continuum indicator summary (PRECIS) tool
- Consider trade-offs
  - Eligibility criteria
  - Flexibility of intervention/adherence
  - Range and types of outcomes
  - Follow-up intensity

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

*Update: The Precis-2 tool: designing trials that are fit for purpose. Loudon, et al. Research Methods & Reporting 2015; 350:h2147*



# Research Activities Not Supported in This PCORI Funding Announcement (PFA)

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



# Study Populations

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- 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

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- Compare interventions that are either known to be efficacious, or are commonly in use, and can be implemented in real-world settings
- Capacity to efficiently collect 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





# How Large?

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- 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
- Typically at least 2,000 patients in a two-arm trial
- More than 45,000 in several trials
- Must include a broad and diverse population



# Strategies for Engagement with Clinical Partners

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- Identify and engage with major patient and stakeholder organizations that would implement study findings to
  - Formulate the research questions
  - Design the study
  - Help monitor progress
  - Disseminate the findings
- Minimize disruption to participants' daily routines (e.g., minimize participant visits intended solely for study-assessment purposes; capture patient-reported outcomes (PROs) during office visits, electronically, or via phone)



# Human Studies Requirements

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- Applicants should provide preliminary evidence of the potential for:
  - Efficient recruitment
  - High participation rates
  - Appropriate oversight by local or centralized IRBs
- Intensity of oversight and complexity of informed consent procedures should be closely related to the degree of risk from study participation.



# Engagement in Patient Centered Studies (PCS)

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- 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.



# Methodological Issues

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- In the case of randomized trials, adherence to current best practices for conducting pragmatic trials **involves:**
  - Standardized inclusion and 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

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- Register and create an account in PCORI Online
- Submit LOI
- Full applications by invitation only



# LOI Evaluation Criteria

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- 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 patient 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 Learned

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



# PCORI Funded Studies

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- Targeted interventions to Prevent Chronic Low Back Pain in High Risk Patients: A Multi-Site Pragmatic RCT
- Enabling a Paradigm Shift: A Preference-Tolerant RCT of Personalized vs. Annual Screening for Breast Cancer
- Pragmatic Trial of More versus Less Intensive Strategies for Active Surveillance of Patients with Small Pulmonary Nodules
- Early Supported Discharge for Improving Functional Outcomes After Stroke
- A Pragmatic Trial to Improve Colony Stimulating Factor Use in Cancer



# PCORI Funded Studies

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- Anti-TNF Monotherapy versus Combination Therapy with Low Dose Methotrexate in Pediatric Crohn's Disease
- MOBILITY: Improving Patient-Centered Outcomes Among Overweight and Obese Youth with Bipolar Spectrum Disorders Treated with Second-Generation Antipsychotics
- Pragmatic Randomized Trial of Proton vs. Photon Therapy for Patients with Stage II or III Breast Cancer
- A Practical Intervention to Improve Patient-Centered Outcomes after Hip Fractures Among Older Adults (Regain Trial)
- Integrating Patient-Centered Exercise Coaching into Primary Care to Reduce Fragility Fracture



# PCORI Funded Studies

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- The safety and effectiveness of antibiotics versus surgery in treating patients with uncomplicated appendicitis
- Comparative Effectiveness of Pulmonary Embolism Prevention after Hip and Knee Replacement (PEPPER): Balancing Safety and Effectiveness
- Integrating Behavioral Health and Primary Care
- Integrated Versus Referral Care for Complex Psychiatric Disorders in Rural FQHCs



# Questions?



# Thank You!

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