Pragmatic Clinical Studies
PCORI Experience

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NIH Collaboratory
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Patient Centered Outcomes Research Institute (PCORI)

• An independent, non-profit research institute authorized in 2010, mandated to support informed health decisions by a broad array stakeholders via research & dissemination activities

• Funds comparative clinical effectiveness research (CER) of >2 head-to-head options to care for a clinical condition or to improve health care delivery

• Strategic Research Priorities
  • Assessment, Prevention, Diagnosis, & Treatment Options
  • Improving Healthcare Systems
  • Disparities
  • Communication and Dissemination
  • Research Methods
PCORI Investments in Real World Evidence

MORE THAN $2.4B AWARDED
MORE THAN 600 RESEARCH-RELATED PROJECTS

Research Projects By Area

CER Portfolios
- Broad
- Targeted Topic Areas
- Pragmatic Clinical Studies

Infrastructure
- PCORnet development & pilot studies
• PCORI requires all its funded research have a pragmatic focus
  • Real-world populations and settings
  • Relevant patient-centered outcomes
  • Engage multiple stakeholders as well as patients

• CER requires head-to-head comparisons
  • Interventions are efficacious or in widespread use
  • “Usual care” comparators must be distinct & defined
PCORI’s Pragmatic Clinical Studies (PCS) Portfolio

Feb 2014: First Pragmatic Clinical Studies PFA announced

- First PCORI large studies research program (5 yr, <$10M direct costs)
- In addition to PCORI need for real-world populations & settings
  - Less complex protocols with minimal intrusion on routine practice
  - Large size to enable subgroups to be examined for heterogeneity
- PRECIS referenced, but no requirement to maximize pragmatic features, diagram, or explain
- Randomized designs encouraged, not required

11 funding cycles → 43 PCS awards totaling $494 million
Scale & Duration of PCS Portfolio Studies

Wide range of targeted sample sizes (median ~ 1700)
- Medications in Pediatric Crohn’s Disease  \( N=425 \)
- Annual vs. personalized breast cancer screening  \( N=100,000 \)

Prolonged exposures (median of active treatment ~ 12 mo)
- Medical management vs. surgery for recurrent diverticulitis  3+ years

Long-term primary outcome measures (median assessment ~ 18 mo)
- BMI changes in bipolar youth taking antipsychotics assessed at 6 and 24 mo
2 observational and 41 randomized

- 27 individually randomized
  - Annual vs. personalized breast cancer screening study N=100,000
- 14 cluster-randomized, including 2 stepped-wedge
  - Number of clusters ranges from 10 – 78 with median=33
  - Includes 1 cluster XO of surgical site antisepsis in open fracture repair

Primary non-inferiority comparisons used in 12 studies
Conditions Represented in PCS Portfolio

- Cancer
- Musculoskeletal Injury and Accident
- Infection
- Injury and Accident
- Mental Health
- Metabolic and Endocrine
- Musculoskeletal
- Neurological
- Non-Disease Specific
- Oral and Gastrointestinal
- Respiratory
- Skin
- Stroke
PCS Portfolio: Highlights of Research Questions

• PCS Portfolio reflects stakeholder interests + priorities/special emphasis areas
  • Mental health integration with physical health care (2)
  • Mental health counseling services via telemedicine or e-delivery (2)
  • Cancer treatment: proton radiotherapy (2) and DCIS (1)

• Surgical vs. medical treatments: 4 studies
  • Appendicitis, diverticulitis, bladder cancer, atraumatic rotator cuff tears
  • Risk of selection bias in recruited and enrolled patients offered & accepting randomization and enrollment
PCS Portfolio Challenges

- Usual trial challenges in start-up, recruitment/enrollment/retention, etc.
- Additional challenges of real-world research settings
  - Competition of research tasks with clinical and personal demands for time
  - Allowable fidelity/flexibility of interventions
  - Adherence by participants and providers
  - Unexpected events/sources of variation during study performance
- Misplaced assumptions about pragmatic design
  - Emphasis on maximal pragmatism vs. fit-for-purpose
  - Laissez-faire conduct vs. purposeful, optimized study design

PFAs updated over time
Design and Conduct of Trials in Real-World Settings: Factors to Consider in Pragmatic Patient-Centered Research

- Applies to all PCORI-funded studies not just PCS
- Design should be fit for purpose of answering stakeholder questions
- Re-emphasize usual care comparators be distinctive, detailed, & measurable (e.g. clinical practice guideline-concordant care)
- Fidelity and adherence to treatments require judicious, unobtrusive attention and should reflect the conditions of anticipated future treatment use(s)
- Manage variability with consideration of PCORI Methodology Standards for Complex Interventions
CER and Variance Risks

Large effect size & moderate variance

Large effect size & high variance

Low effect size & high variance
PCORI Methodology Standards: Complex Interventions (CI)

- CI: multiple components that interact such as behaviors, activities, personnel, and contexts
- A causal model must be specified
- Function(s) and form(s) of an intervention should be specified
  - Core functions = intended purpose that is derived from the causal model (e.g. surgical removal of the appendix)
  - Forms = activities/format to achieve the core function (e.g. mode of delivery or providers = e.g. open, laparoscopic, or robotic appendectomy)
- Specify permissible or planned adaptations to the intervention forms
- Do an integrated process evaluation with measurements
Goal of Complex Interventions Standards: Fit-for-Purpose Research

- For dichotomous decisions of which intervention is more effective
- To inform the manner in which an intervention is delivered
  - Under what circumstances does it work? For whom? What settings?
  - What modifies or improves effectiveness?
- To assist dissemination and implementation by identifying important contextual, mediating, and moderating factors
Pragmatic trials in CER face distinct challenges

- Distinguishing known efficacious/effective interventions
- Managing & measuring variability judiciously
  - Intervention
  - Participant adherence

Rich opportunity to use PCORI study experiences to refine best approaches to RWE generation and implementation
Contributors

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Guidance on the Design and Conduct of Trials in Real-World Settings: Factors to Consider in Pragmatic Patient-Centered Outcomes Research


PCORI Methodology Standards (with Standards for Studies of Complex Interventions)
https://www.pcori.org/research-results/about-our-research/research-methodology/pcori-methodology-standards

PCORI Funding Opportunities https://www.pcori.org/funding-opportunities
Thank you

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PCORI Investments in Real World Evidence

BY THE NUMBERS

Research Projects By Area

Most Studied Conditions*
- Mental/Behavioral Health: 121
- Cancer: 86
- Neurological Disorders: 74
- Cardiovascular Diseases: 69
- Multiple/Comorbid Chronic Conditions: 58

Most Studied Priority Populations*
- Racial/Ethnic Minorities: 301
- Low Socioeconomic Status: 200
- Women: 154
- Older Adults: 137
- Individuals with Multiple Chronic Conditions: 112

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PCS Portfolio: Topic Areas & Intervention Settings

• Comparison of health delivery/point of care options: 21/22

• Settings of care
  • 22 have >1 setting of care
  • 34 outpatient
  • 12 home care
  • 5 FQHCs
  • 4 inpatient
PCS Portfolio: Study Size Distribution

Median: 1716

Range: 425 – 100,000
PCS Portfolio: Long-term Treatments and Follow-up

Active intervention
- Median: 3 mo
- Mean: 12 mo

Primary outcome timepoint
- Median: 14 mo
- Mean: 18 mo

All endpoints can extend to 4+ years
PCS Portfolio: Study Designs

2 observational, 41 randomized
27 individually-randomized
  • Breast cancer screening of 100,000
14 cluster-randomized
  • Clusters ranges from 10 – 78
  • Cluster XO of surgical site preps in open fracture repair
Non-inferiority designs 12 studies

Cluster number: 10 – 78 (median=33)
Cluster size (avg): 20 – 1600 (median=132)