

Pragmatic Clinical Studies

PCORI Experience

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NIH Collaboratory
Steering Committee Meeting
May 1, 2019

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

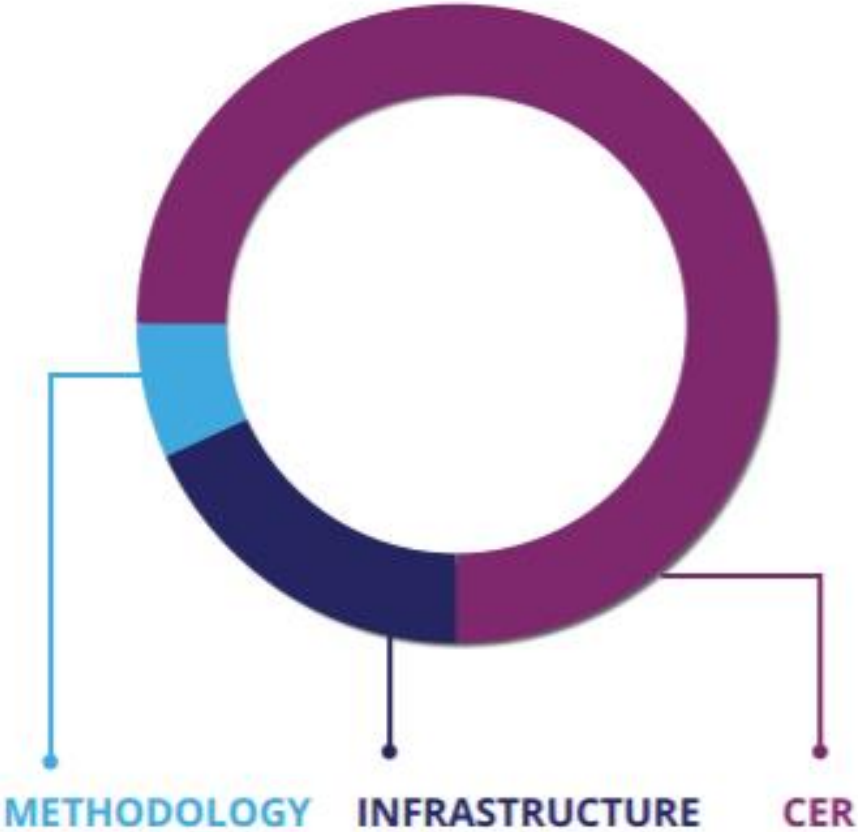
PCORI Investments in Real World Evidence



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 Pragmatic Studies > PCS Portfolio



- **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

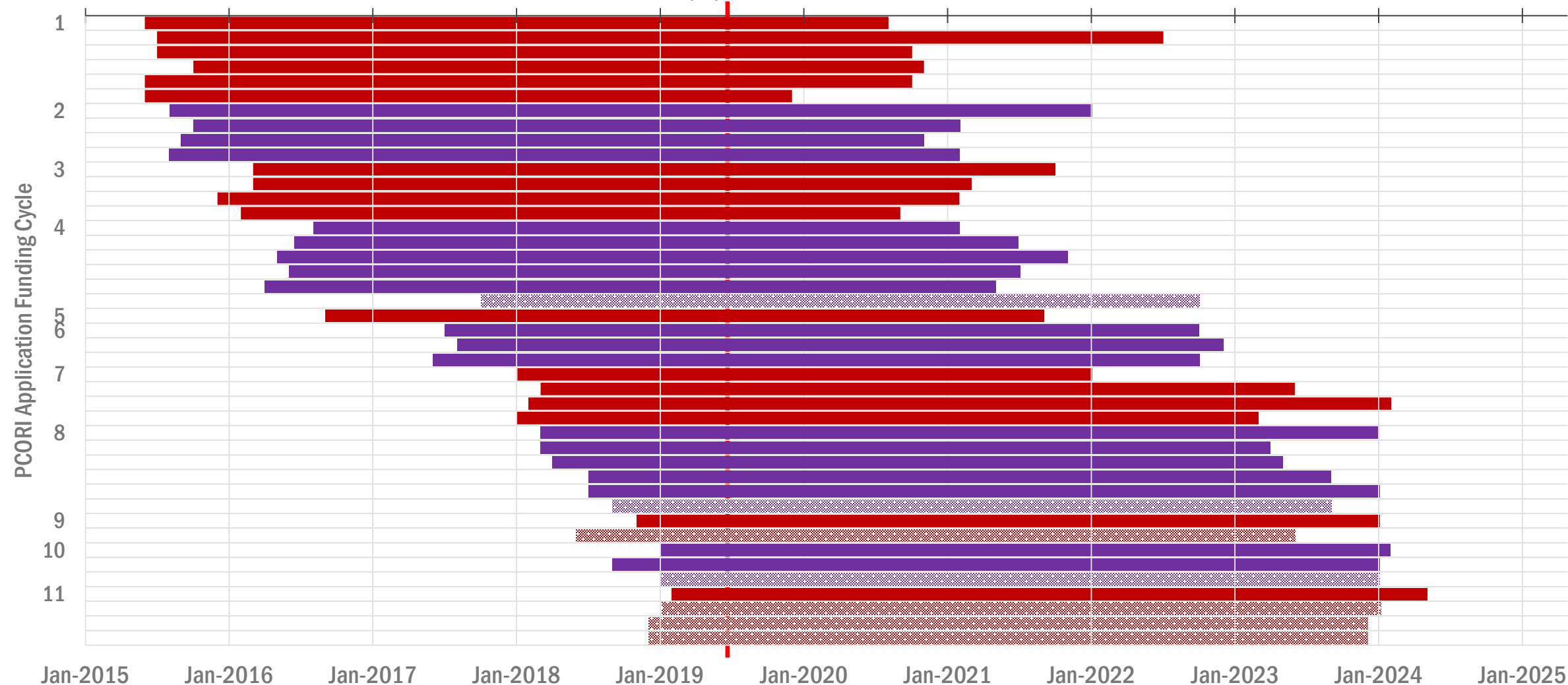
- First PCORI large studies research program (5 yr, \leq \$10M direct costs)
- In addition to PCORI need for real-world populations & settings
 - Less complex protocols with minimal intrusion on routine practice
 - Large size to enable subgroups to be examined for heterogeneity
- PRECIS referenced, but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

11 funding cycles → 43 PCS awards totaling \$494 million

PCS Portfolio: Study Timelines

Contract Start to End of Research Period

5/1/2019



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)

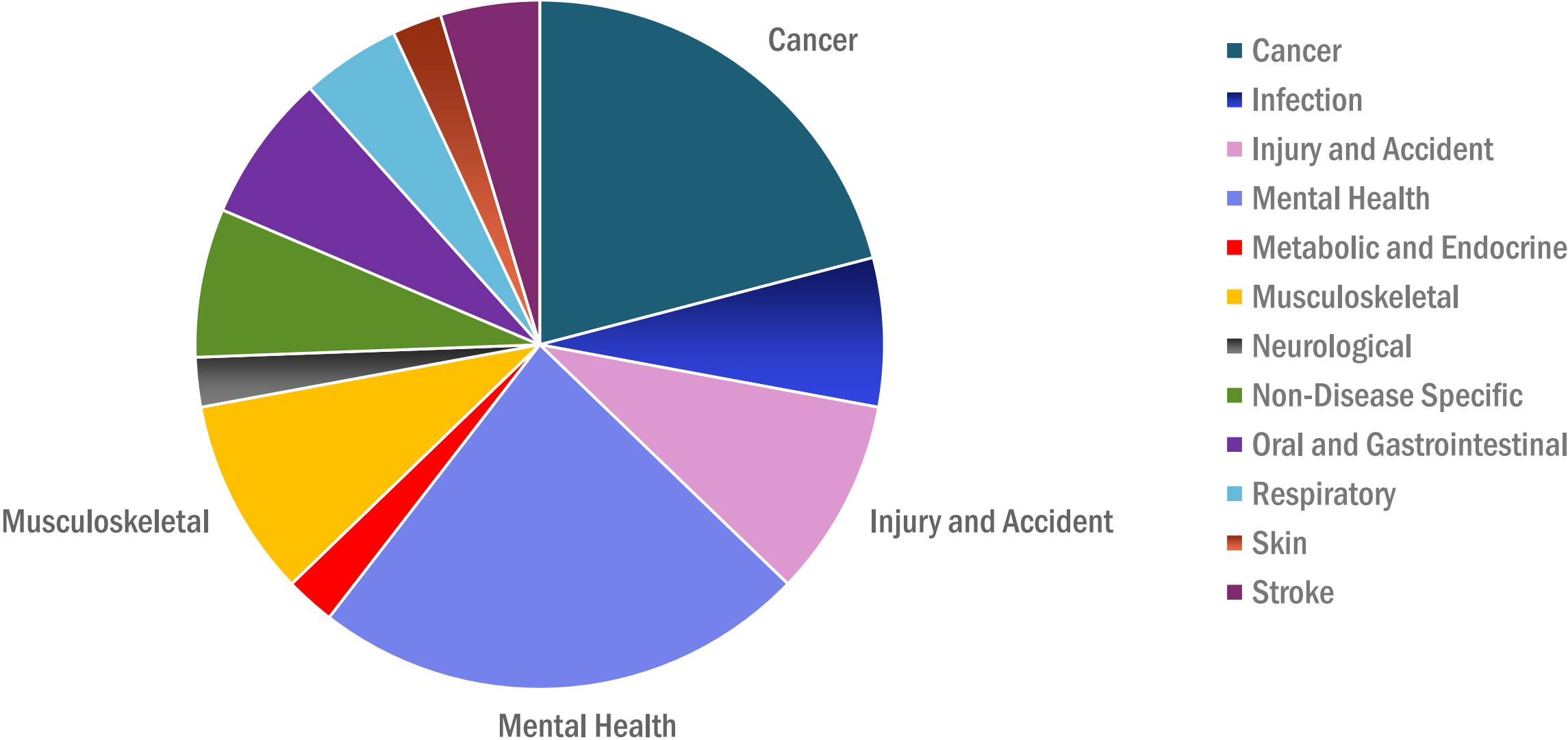
- BMI changes in bipolar youth taking antipsychotics assessed at 6 and 24 mo

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



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

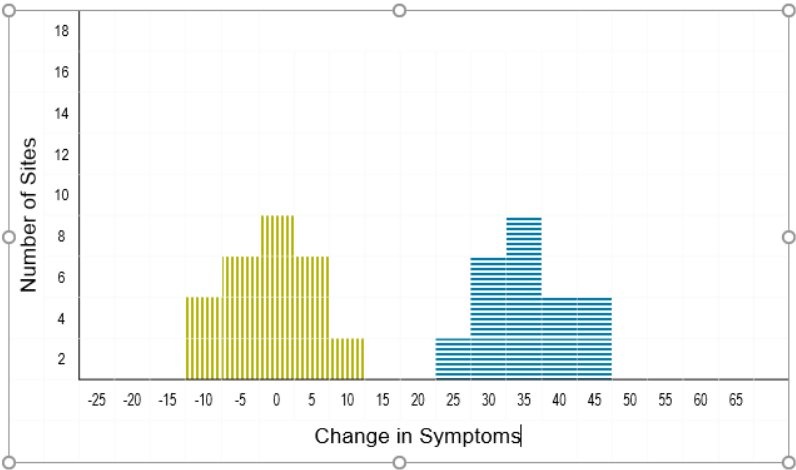
Design and Conduct of Trials in Real-World Settings: Factors to Consider in Pragmatic Patient-Centered Research

- 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

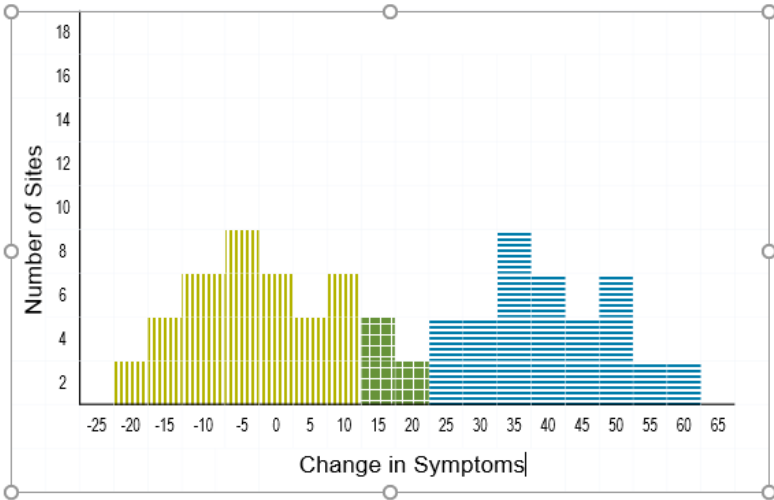
CER and Variance Risks



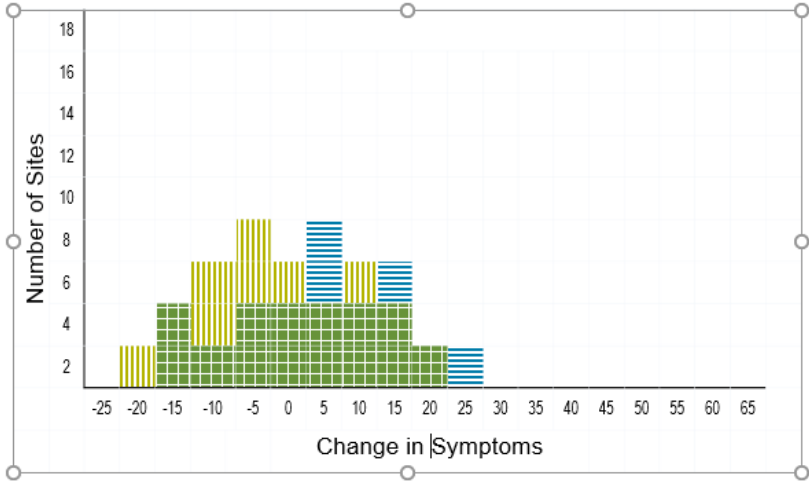
Large effect size & moderate variance



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

Allie Rabinowitz, MPH

Laura Esmail, PhD, MSc

Nick Wilson, MPH

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

<https://www.pcori.org/sites/default/files/PCORI-Guidance-Design-and-Conduct-of-Trials-Real-World-Settings-Factors-to-Consider-Pragmatic-PCOR.pdf>

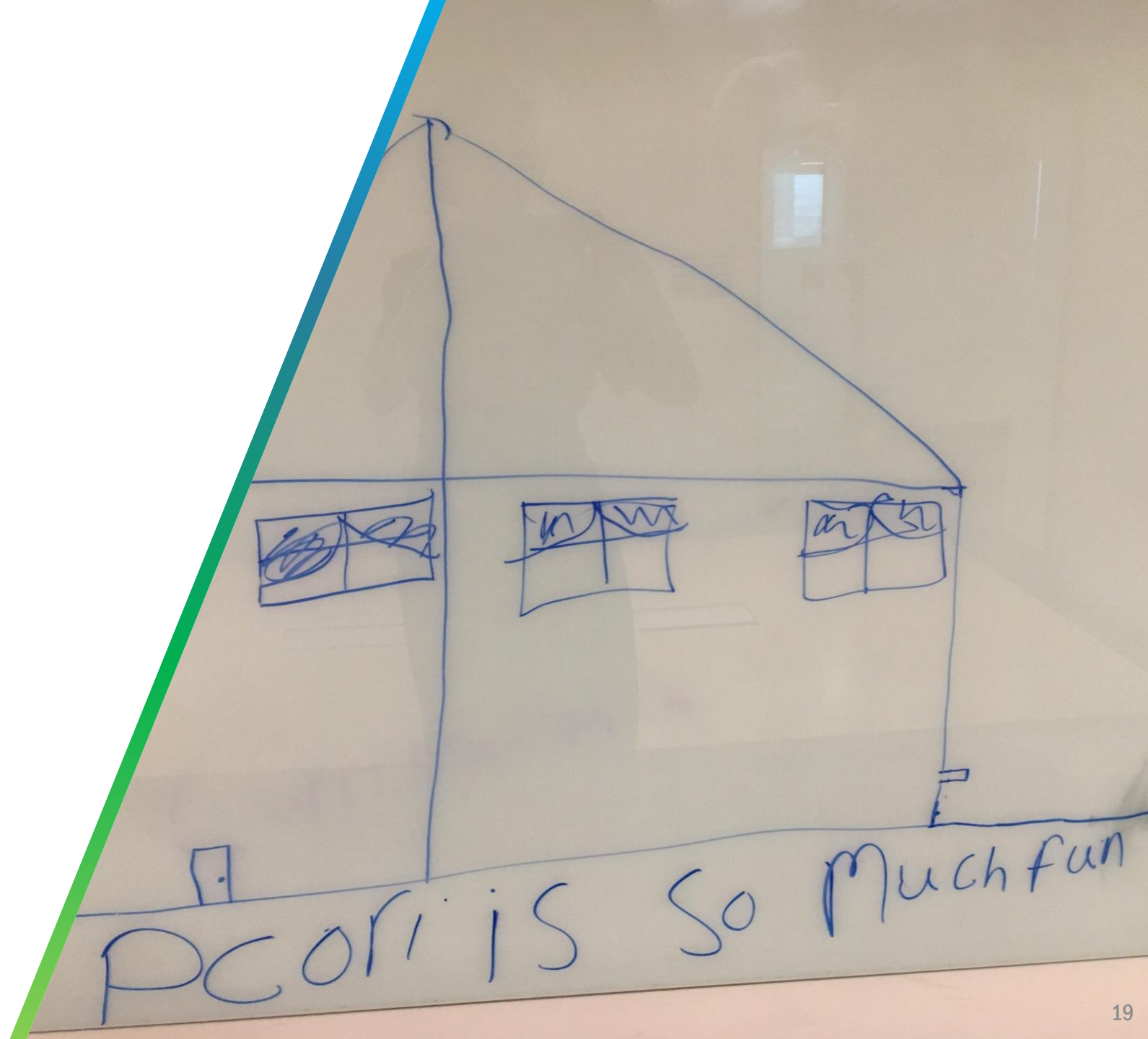
PCORI Methodology Standards (with Standards for Studies of Complex Interventions)

<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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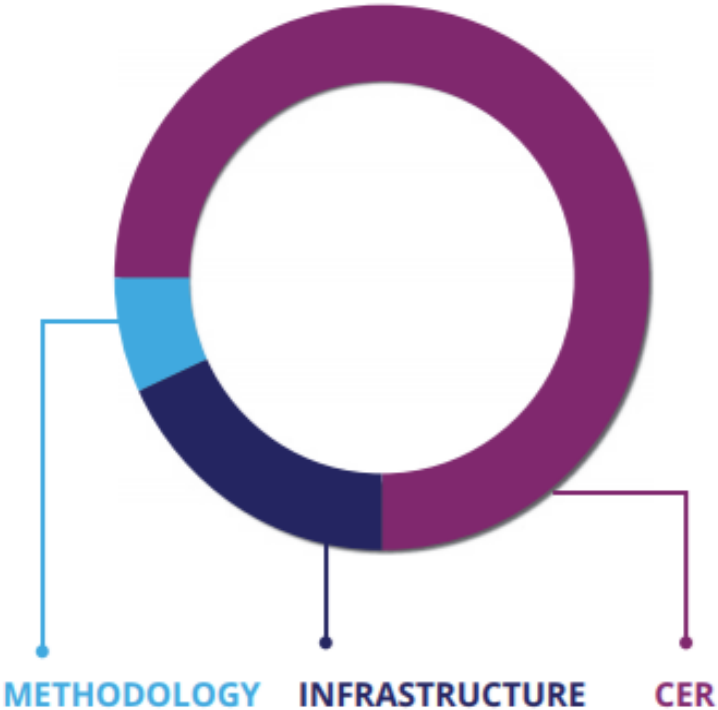
Additional Slides

PCORI Investments in Real World Evidence

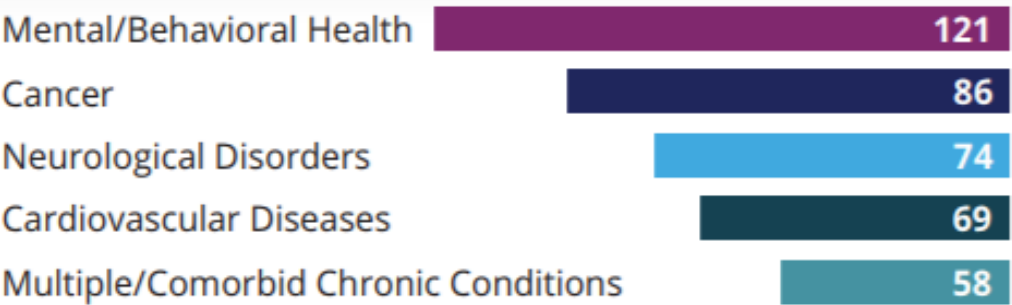


BY THE NUMBERS

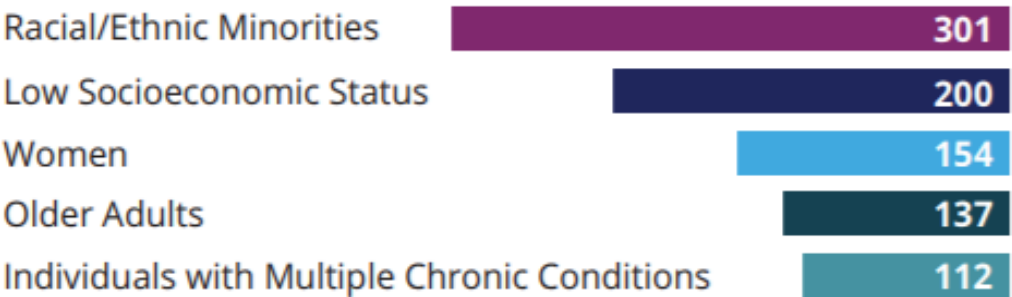
Research Projects By Area



Most Studied Conditions*



Most Studied Priority Populations*



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PCS Portfolio: Topic Areas & Intervention Settings



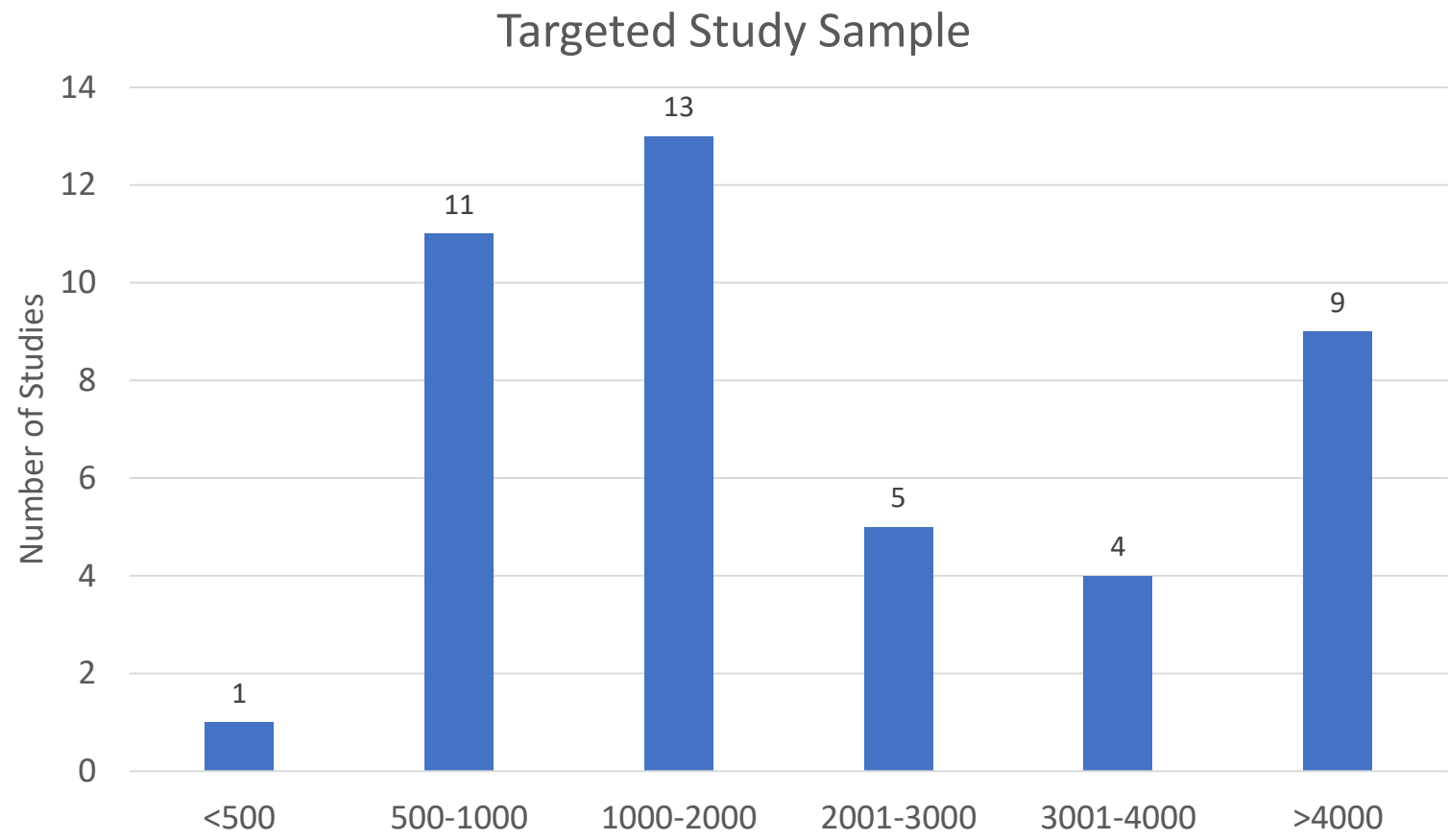
- Comparison of health delivery/point of care options: 21/22
- Settings of care
 - 22 have >1 setting of care
 - 34 outpatient
 - 12 home care
 - 5 FQHCs
 - 4 inpatient

PCS Portfolio: Study Size Distribution



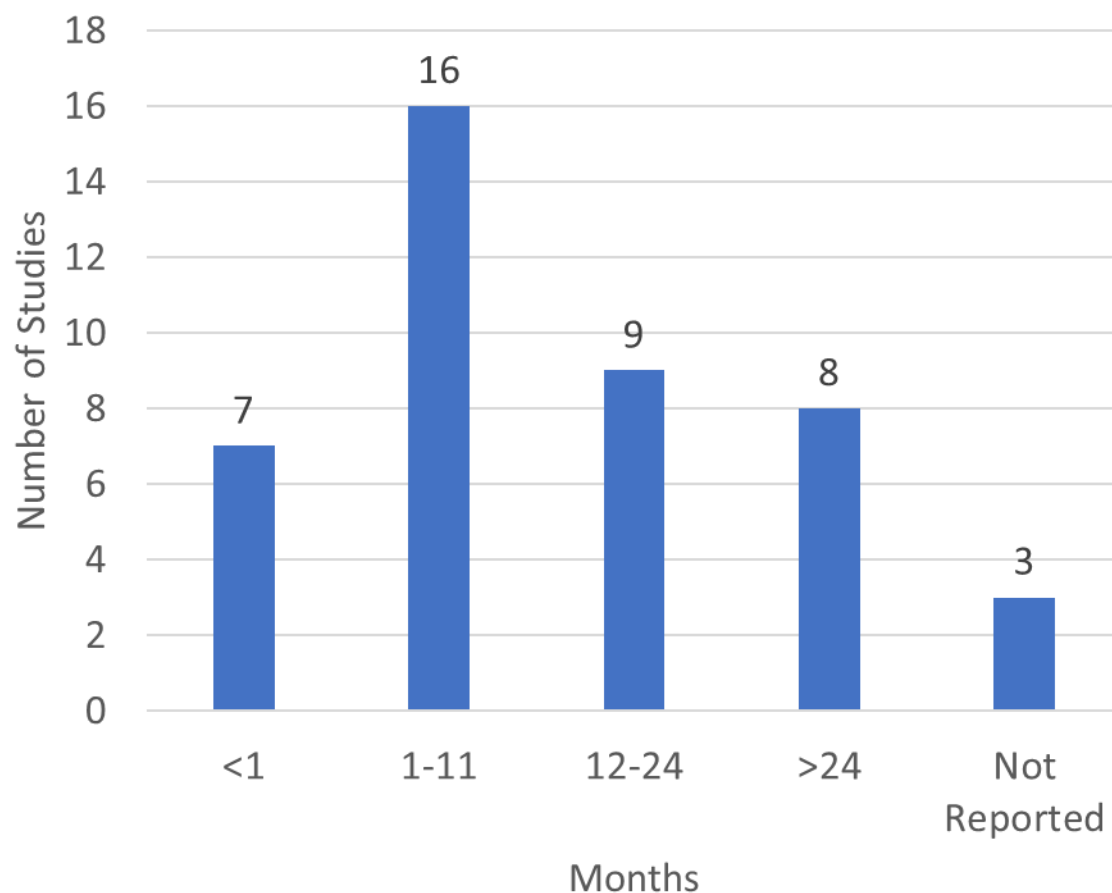
Median: 1716

Range: 425 – 100,000



PCS Portfolio: Long-term Treatments and Follow-up

Duration of Active Intervention



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)