Advisory Panel on Clinical Trials Spring 2016 Meeting

Arlington, VA

April 14, 2016

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Welcome and Plans for the Day

Evelyn P. Whitlock, MD, MPH

Chief Science Officer, PCORI

Elizabeth A. Stuart, PhD, AM (Chair)

Professor of Mental Health and Biostatistics, The Johns Hopkins Bloomberg School of Public Health

John D. Lantos, MD (Co-Chair)

Professor of Pediatrics, Children's Mercy Hospital

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Housekeeping

- Today's webinar is open to the public and is being recorded.
- Members of the public are invited to listen to this teleconference and view the webinar.
- Anyone may submit a comment through the webinar chat function or by emailing advisorypanels@pcori.org.
- Visit www.pcori.org/events for more information.
- Chair Statement on COI and Confidentiality

Today's Agenda

Start Time	Item	Speaker
9:00 a.m.	Welcome and Plans for the Day	E. Whitlock E. Stuart J. Lantos
9:15 a.m.	CTAP R & R: Recap and Reexamination of Opportunities for Impact	E. Whitlock
9:40 a.m.	CTAP Activities and Work Products – Past, Present, & Future	A. Trontell
10:10 a.m.	PCORI's Clinical Trials Portfolio	D. Hickam
10:40 a.m.	Break	
11:00 a.m.	Application Enhancement	E. Whitlock
11:30 a.m.	Open Science Update	J. Gerson
12:00 p.m.	Lunch & Recognition of Panelists	

Today's Agenda (cont.)

Start Time	Item	Speaker
1:00 p.m.	Methodology Standards for Clinical Trials	D. Hickam
1:45 p.m.	n-of-1 Designs	E. Whitlock
2:15 p.m.	Break	
2:30 p.m.	Advisory Panel on Clinical Trials Charter Update	D. Hickam
2:45 p.m.	Panel Discussion	E. Stuart J. Lantos
3:15 p.m.	Recap and Next Steps	E. Stuart J. Lantos A. Trontell J. Gerson
3:30 p.m.	Adjourn	E. Whitlock

CTAP R&R: Recap and Reexamination of Opportunities for Impact

Evelyn P. Whitlock, MD, MPH

Chief Science Officer

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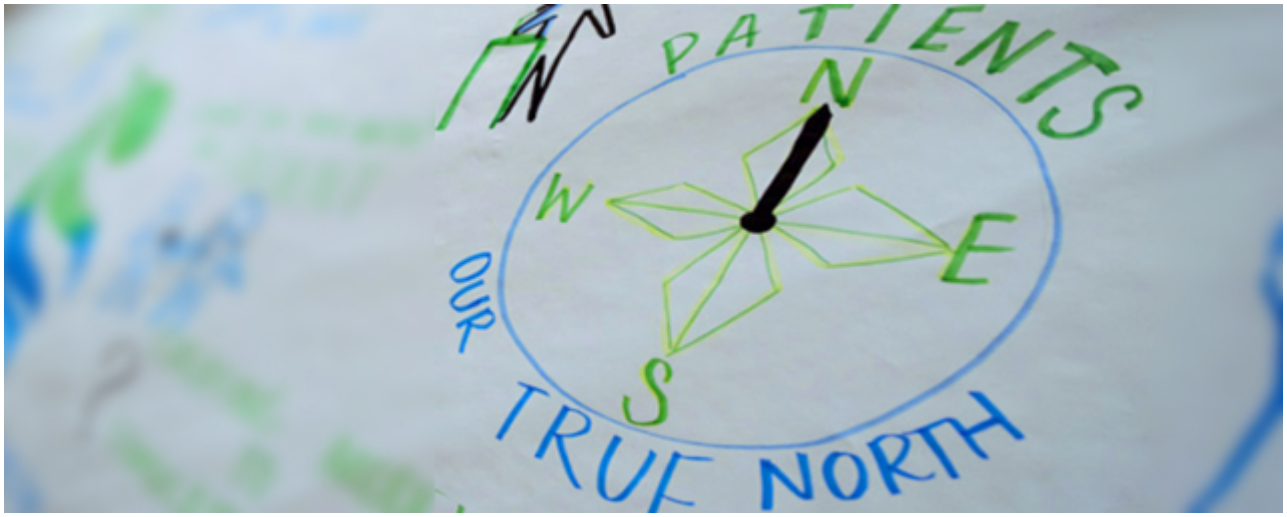
Gearing up for the next three “certain” years

- Move towards accelerated funding strategies, particularly in pragmatic clinical trials (most awards in 2016-2018)
- Emphasize larger targeted studies in high priority topic areas, including sequential announcements
- Include special emphasis areas in the pragmatic trial announcements to boost outreach to key applicant communities



Focus on portfolio oversight, execution and dissemination

- Aligned with the authorizing legislation, ensure that the research portfolio has adequate oversight for active portfolio management.
- Create systems and guidance to guide execution of our funded CER projects
- Disseminate the work through multiple mechanisms in ways that patients and clinicians can understand and use

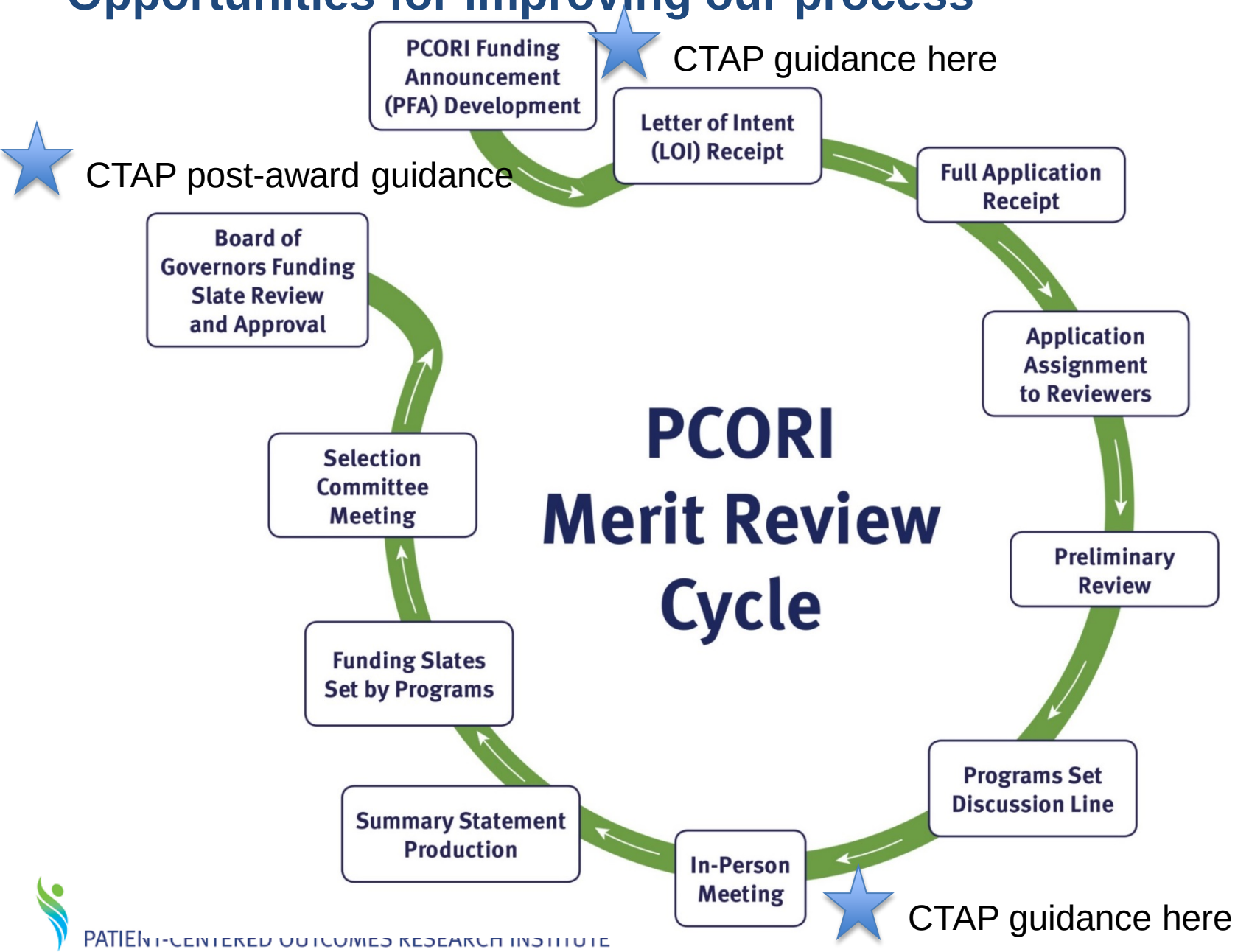
"The purpose of the Institute is to **assist patients, clinicians, purchasers, and policy-makers in making informed health decisions** by advancing the quality and relevance of evidence concerning the manner in which diseases, disorders, and other health conditions can effectively and appropriately be prevented, diagnosed, treated, monitored, and managed **through research and evidence synthesis...**
... and the dissemination of research findings with respect to the relative health outcomes, clinical effectiveness, and appropriateness of the medical treatments, services..."

--from PCORI's authorizing legislation

Improving the process for researchers (PCORI 2.0)

- Improve:
  - Application quality
  - Applicant experience
  - Change management for funding announcements and application process
- Reduce frequency of changes to minimize negative impact on internal/external
- Recognize researchers as key stakeholders

Opportunities for improving our process

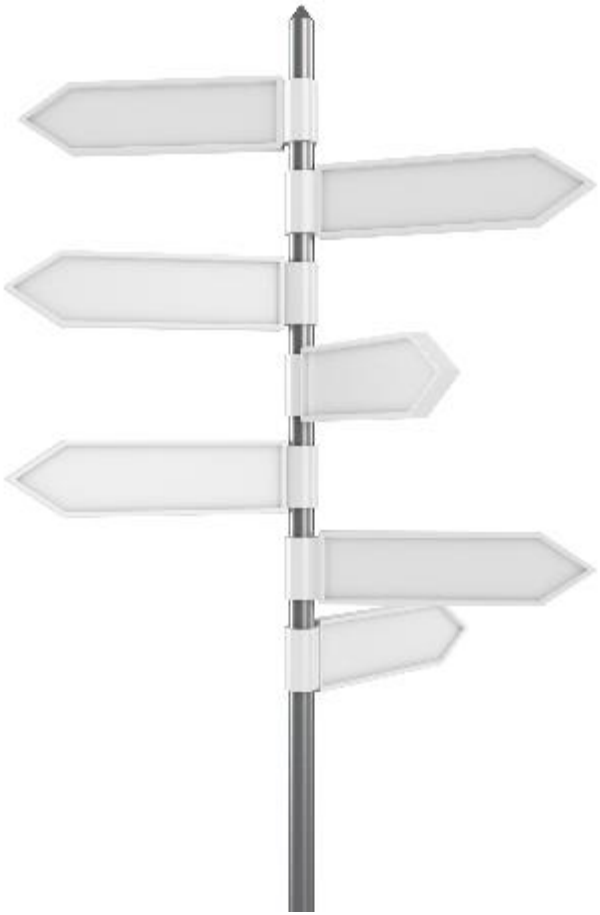


Determine areas for greatest CTAP Impact

- Complement Methodology Committee's work on methods standards
- Provide key input into critical areas of trials portfolio:
  - Better trial proposals selected
  - Better clinical trial management
  - Issues in trial close-out/dissemination
- Demonstrate PCORI's unique contribution to research
  - Evaluating the impact of our trials

Next steps for CTAP activity

- Work with key staff members to move the work forward:
  - Anne Trontell, CTAP activities
  - David Hickam, Methodology Committee activities
  - Jessie McCreary, point-of-contact for CTAP



Thank You

Evelyn P. Whitlock, MD, MPH
Chief Science Officer

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CTAP Activities and Work Products – Past, Present, & Future

Anne Trontell, MD, MPH

Senior Program Officer, Clinical Effectiveness Research, PCORI

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CTAP Activities to Date

- Committee advisory input on PCORI policies under development (e.g. DSMPs)
- Input to Methodology Committee re standards of particular relevance to clinical trials
- Pre-award methodology reviews of candidate pragmatic studies for award (Subcommittee members + pool of experts)
- Post-award advice on specific trials (Subcommittee members + pool of experts)
- Subcommittees/workgroups charged to synthesize and document expert knowledge and advice

CTAP Activities to Date

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- **Subcommittees/workgroups charged to synthesize and document expert knowledge and advice**

Subcommittee/Workgroup Efforts

- Two CTAP subcommittees/workgroups established to date
  - Both initiated as PCORI was launching its pragmatic clinical studies initiative
  - Complex Concepts Subcommittee to define/characterize pragmatic trials, led by Merrick Zwarenstein
  - Recruitment, Accrual, and Retention Subcommittee to address study enrollment, led by Margo Michaels

- PCORI, Subcommitee members, and others involved in development, writing, and review
  - Substantial work, discussion, revisions, and ongoing debate
  - Documents still exist in draft form

Challenges of Pragmatic and RAR Workgroups

- Target audiences, purposes, work products, and publication type and authorship poorly defined at outset
- Changing interpretations over time have led to multiple revisions, lack of closure
- Considerable effort, expertise, and valuable contributions expended without a product or clear target

PCORI "Product" Opportunities for CTAP, Subcommittees, or Workgroups

- Incorporation of advice, recommendations, or language into PCORI Funding Announcements to direct applicants, merit reviewers, and funding decisions
- Inclusion into different articulations of PCORI policies and practices with definitions of the following nearing completion
  - Policies that address the rationale or framework of PCORI's work
  - Guidance documents
    - To interpret policies or governance in specific contexts
    - To document and support committee advice or decisions
  - Guidelines of non-mandatory suggestions of best practices or to clarify a policy or process
- Nomination of a Methodology standard
- Author independent publications or blog pieces of viewpoints or perspectives

New Opportunity: Study Advisory Committees

- New requirement of pragmatic and targeted clinical studies since 2015 Cycle 3 PFAs
  - Requirement moved from pre-award to post-award
  - Applicants to work with PCORI to establish a project SAC or its equivalent
- Includes relevant national stakeholder groups
  - SAC comprised of organizations of patients & families with lived experience, clinicians, payers, & health plans
  - Other representation may be included: **scientific and methodological experts**
- SAC activities
  - Advise/assist with refinement of study questions, outcomes, and protocol
  - Meet in person $\geq$ 2 times/year + virtual communications at other times

Study Advisory Committees

- An avenue for CTAP input on the design, conduct, and oversight of clinical trials
- Opportunity for committee and subcommittee members' direct advice on specific clinical studies

Summary of Ways for CTAP To Influence and Impact PCORI Work

- Expert advice and review through Committee and Subcommittee work
- Methodology standard input or recommendations
- Contributions to PCORI statements of policies, guidances, or guidelines
- Participation in Study Advisory Committees
- Independent scientific contributions related to PCORI work
- Other ideas or suggestions

Questions/Comments/Discussion

PCORI's Clinical Trials Portfolio

David Hickam, MD, MPH
Program Director, CER Methods, PCORI

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PCORI's Trajectory of Research Funding since 2013

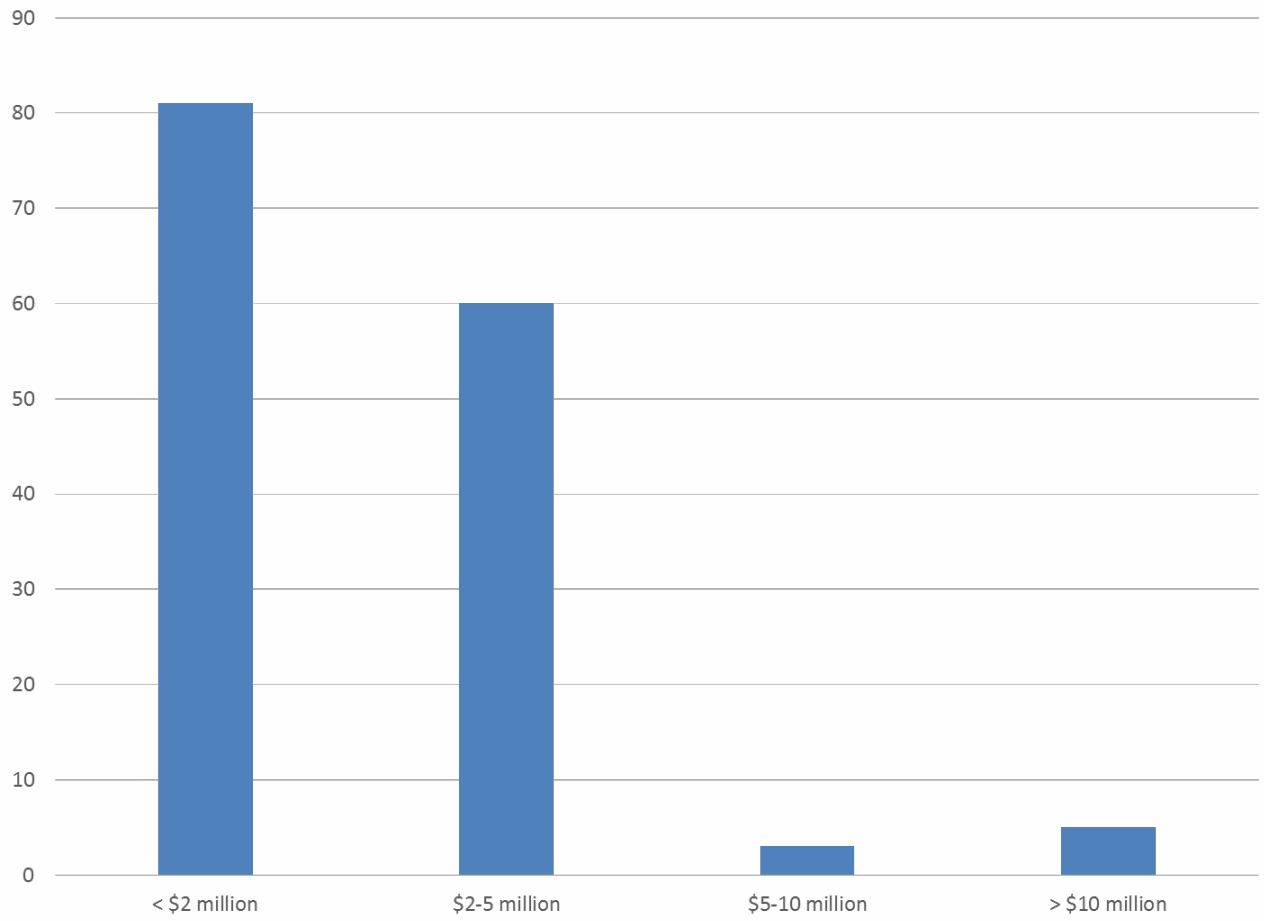
- Multiple funding cycles
  - Total of 359 research projects funded through multiple programs
    - APDTO
    - Improving Healthcare Systems
    - Addressing Disparities
    - Communications and Dissemination Research
    - Improving Methods for CER
    - Pragmatic Clinical Studies
    - Targeted Funding Announcements
  - 359 research projects awarded through the Spring 2015 PCS cycle
- This portfolio excludes more recently coded cycles, Pilots, MOUs, PPRN, and CCRN projects

Total Number of Randomized Controlled Trials

- The portfolio includes 149 RCTs (41.5% of the portfolio)
  - 4 RCTs in the Methods Program
  - RCTs comprise 50.7% of the portfolio, when Methods projects are excluded

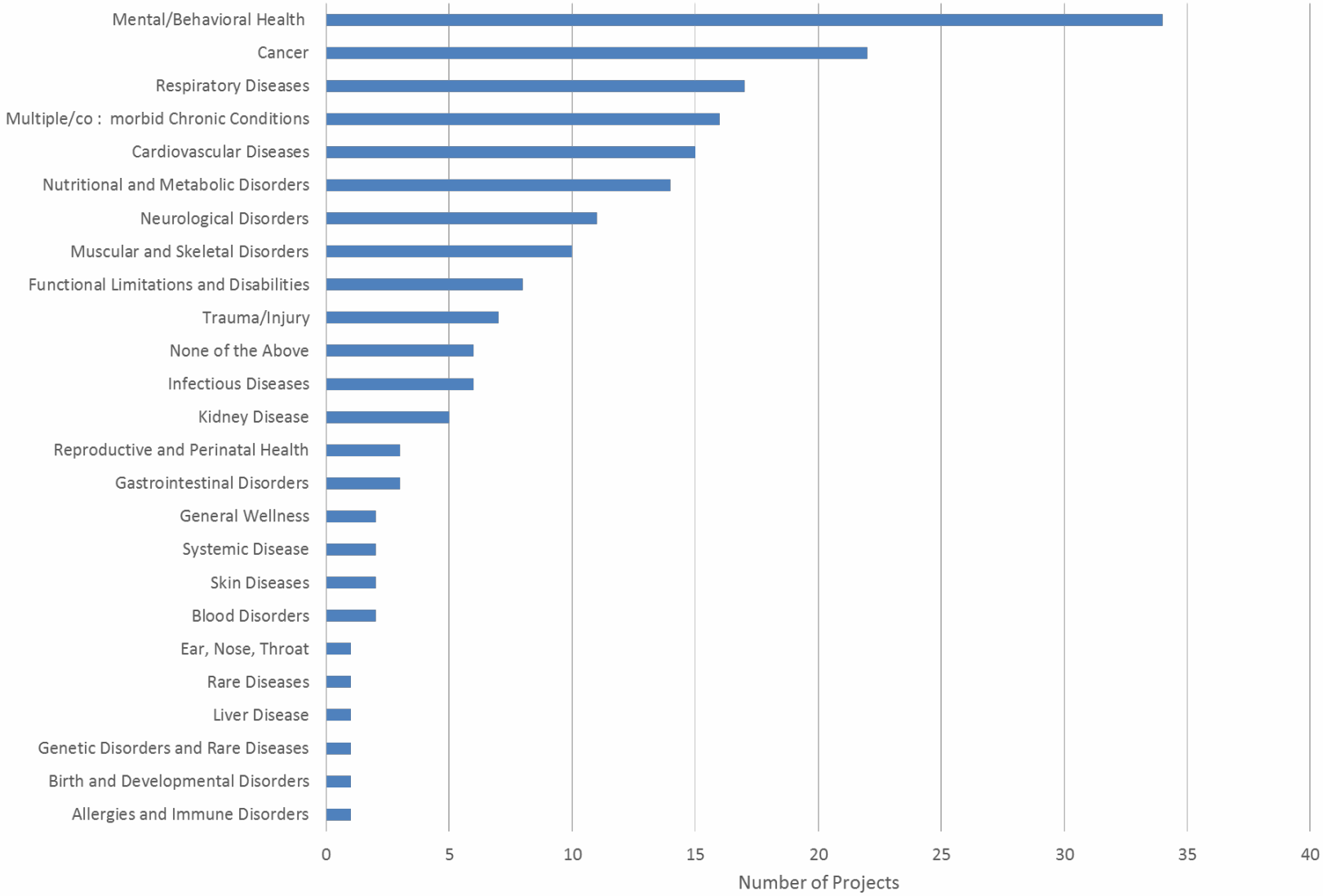
- Large number of RCTs in all of the other PCORI programs
  - AD = 41 projects
  - APDTO = 47 projects
  - CDR = 22 projects
  - IHS = 35 projects

Budget Levels for RCT Projects*



N=149

Clinical Conditions in RCT Projects



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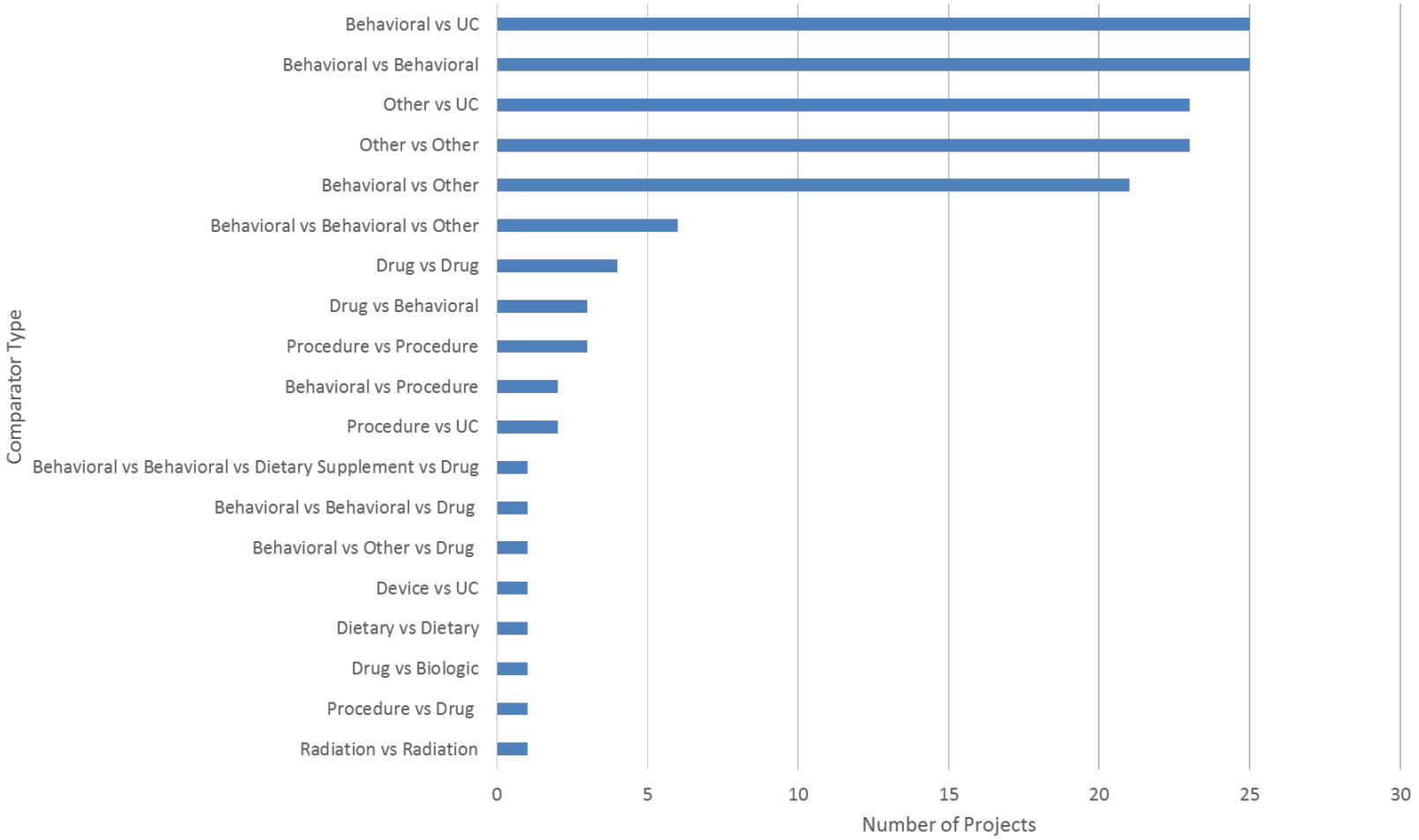
N=149 (includes Methods); coding was inclusive

Comparator Types in RCT Projects*



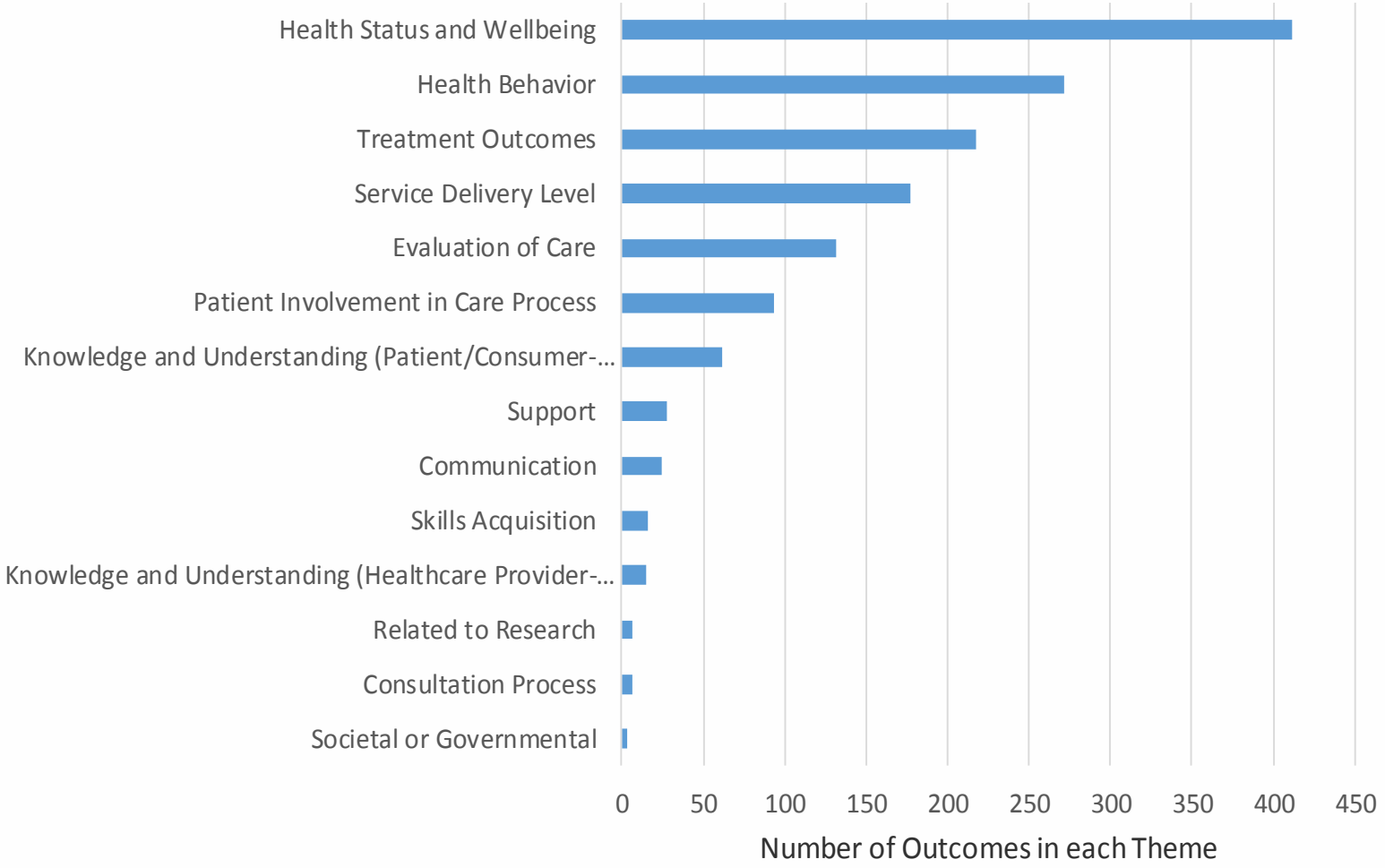
N=145 (excludes Methods)

Note: Projects with more than 2 comparisons of the same type (e.g. behavioral vs behavioral vs behavioral) were truncated to 2 comparators (e.g. behavioral vs. behavioral), for summary purposes

Outcomes in RCT Projects

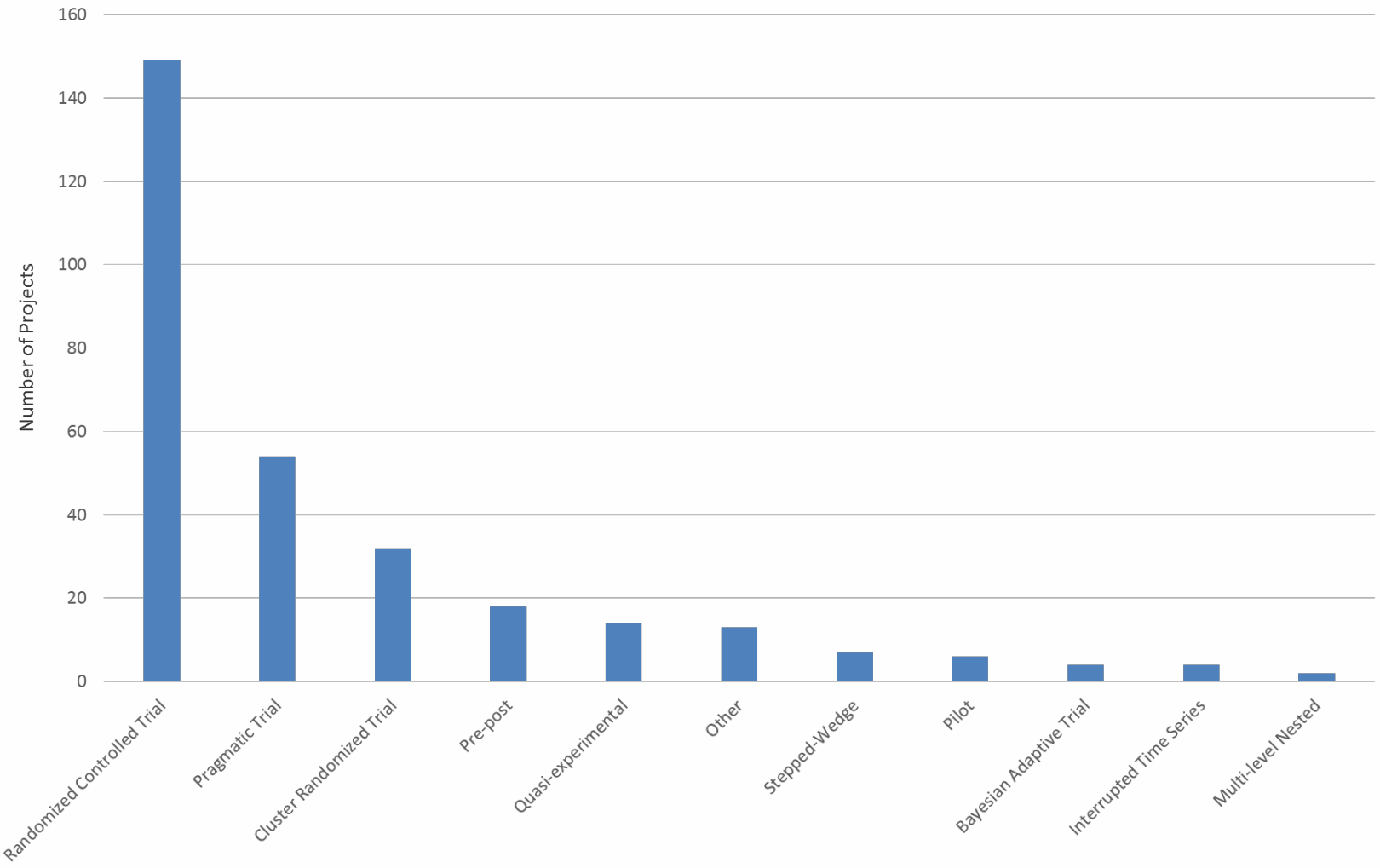
- Each project was coded for up to 30 outcomes cited in research plans. As such, the number of outcomes far exceeds the number of projects.
- Outcomes are presented as high level themes.

Themes of Outcomes in RCT Projects

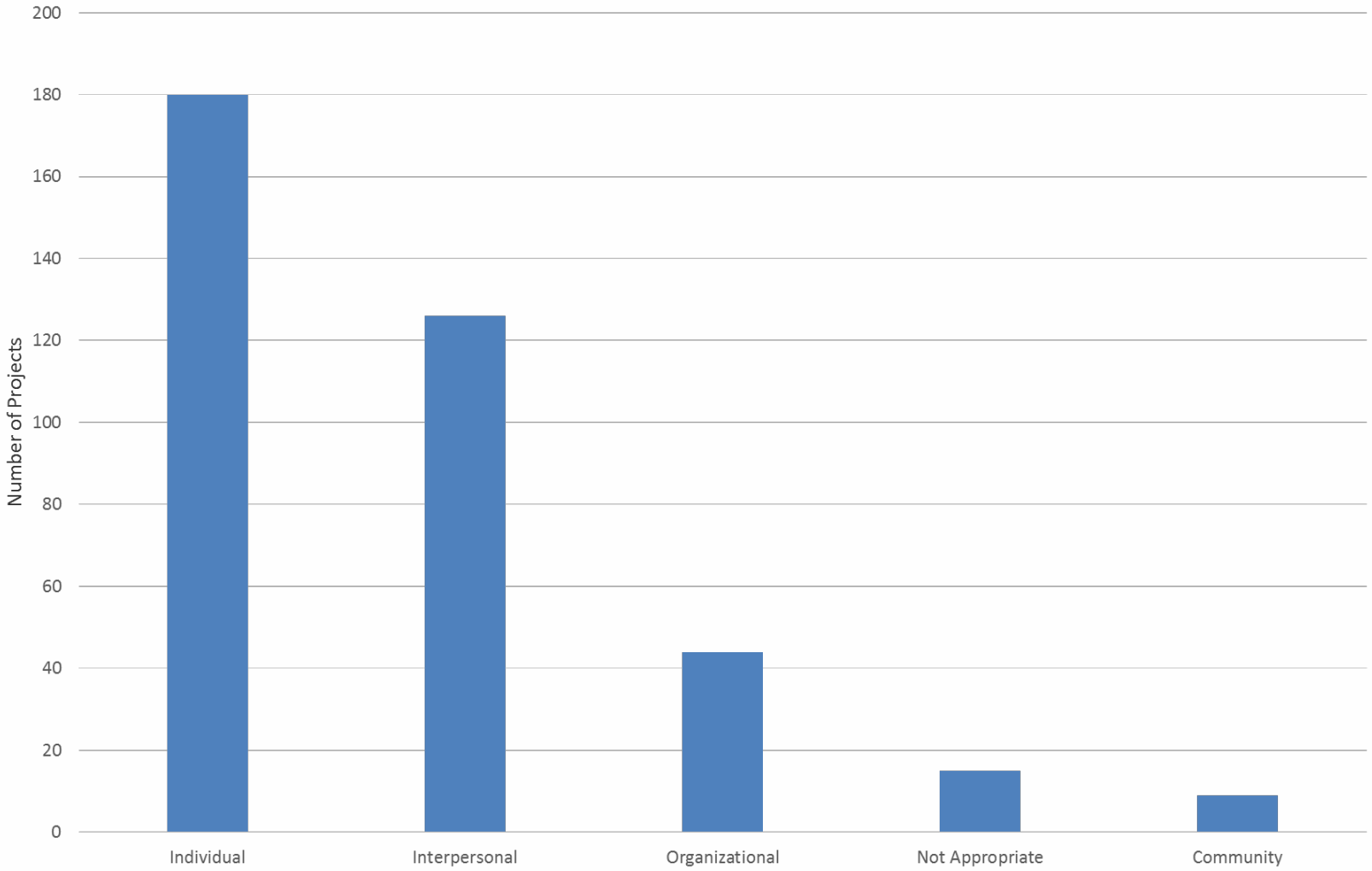


N=149 (includes Methods)

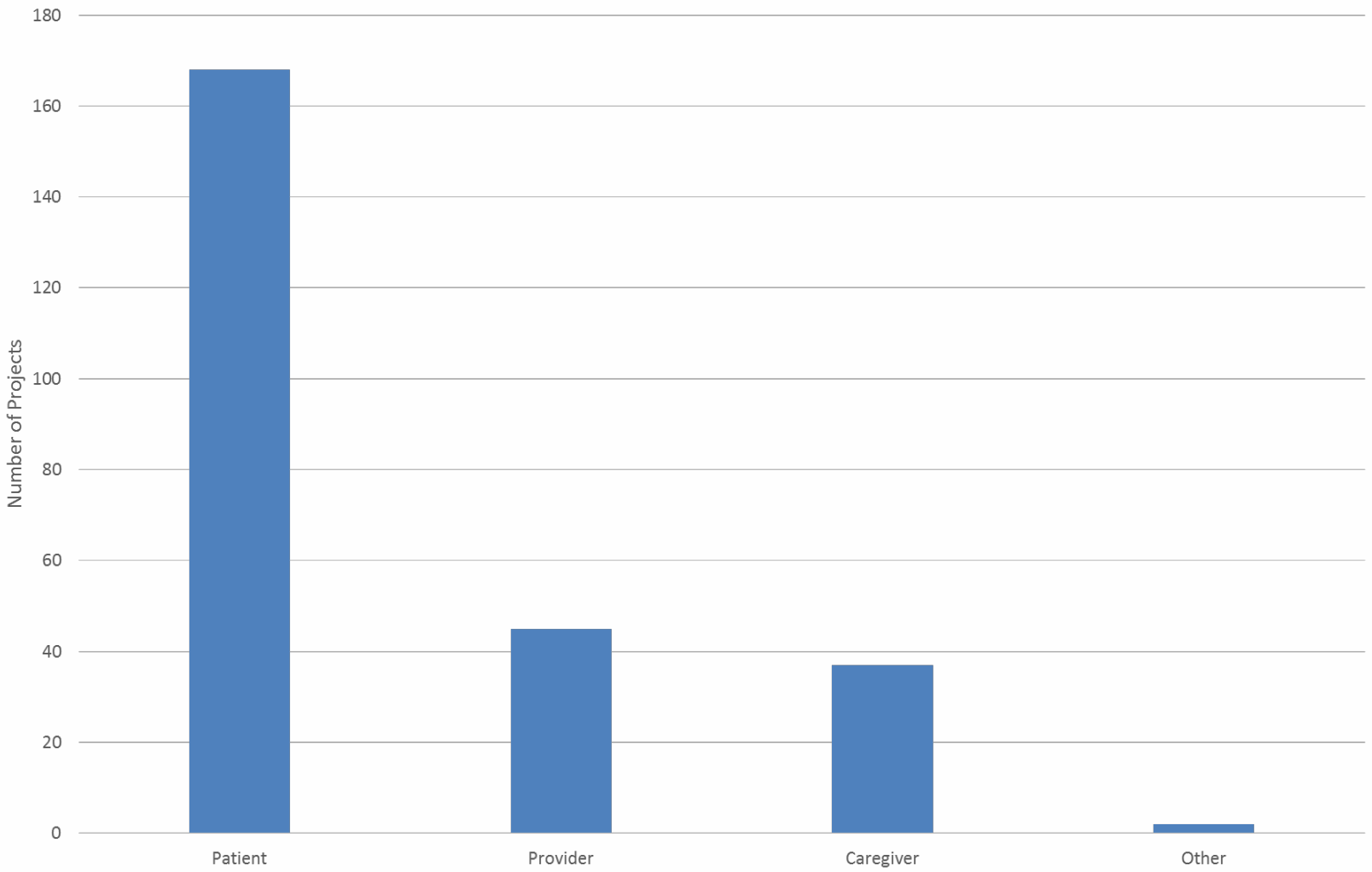
Interventional Designs in PCORI's Portfolio



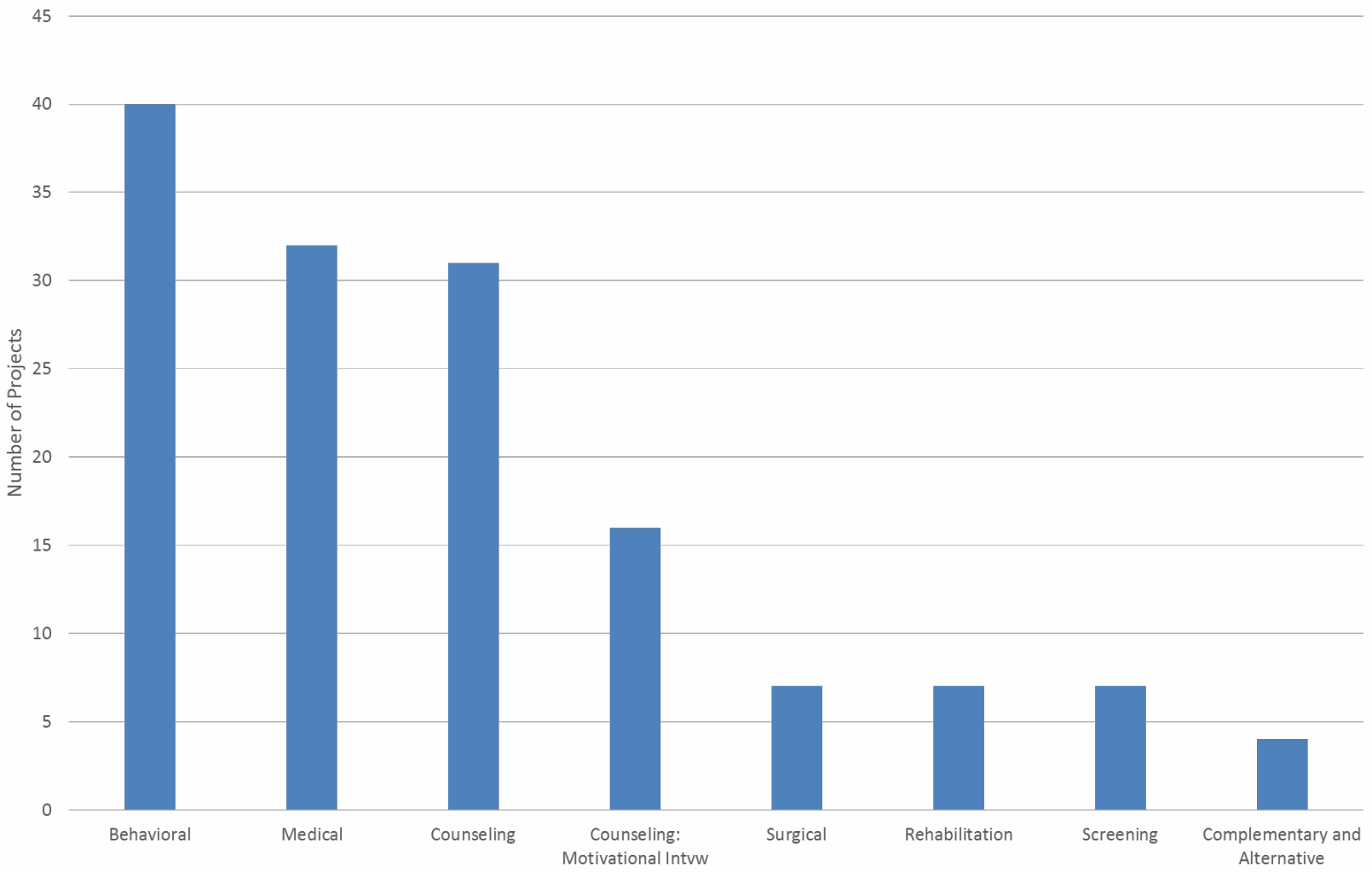
Intervention Level for Projects with Interventional Designs



Individuals Targeted in Interventional Projects



Intervention Strategies in Interventional Projects



Break

10:40 – 11:00 a.m.

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Application Enhancement

Evelyn P. Whitlock, MD, MPH

Chief Science Officer, PCORI

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Application Enhancement

- Based on input from multiple workgroups and outside contractors, PCORI is undertaking a considered revision of its application process (PCORI 2.0)
- Change management suggests bundling refinements into this effort to be rolled out over the next two funding cycles
- Opportunities for contributions to improve proposals (PFAs) and their review (materials to support merit review)
  - Sample size assumptions and sensitivity of these
  - Recruitment assurance
  - Assurance of implementability of design
  - Within-trial pilots
  - Data management minimal specifications

Open Science Update

Jason Gerson, PhD

Senior Program Officer, CER Methods, PCORI

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PCORI Open Science Working Group

- The Working Group was convened to revise the Draft Policy on Open Science and to make recommendations for how to operationalize that policy.
- The Working Group is comprised of senior staff members from Science, Legal and Information Technology (Aggarwal, Chiang, Convery, Evans, Gerson, Gurgol, Moscou-Jackson, Peters)
- Today, we will update you on our efforts and apprise you of our activities
  - PCORI's consultation with national experts
  - Pilot project to test data sharing approaches
  - Data management plans

Consultation with National Experts

- Members of PCORI's Open Science Working Group have spoken with a number of leading national experts about some of the operational and technical challenges of implementing an Open Science policy. These conversations have addressed a number of critical considerations, including, but not limited to:
  - operational challenges of building and maintaining data repositories;
  - making key decisions about centralized versus federated models;
  - challenges regarding de-identification of data;
  - the development and enforcement of data use agreements;
  - issues of informed consent; and
  - ascertaining participant perspectives on data sharing

- We have formed an expert advisory group that will be convened as needed.

Draft PCORI Open Science Policy

- The Open Science Working Group has drawn on the insights gathered from our interviews and the plenary session, and developed a revised Policy for Open Science and Data Sharing.

- The broad goal of the draft policy is to articulate PCORI's commitment and vision for open science and to signal expectations for applicants, awardees and other stakeholders.

- The purpose of the policy is to: (a) facilitate reproduction of original analyses to increase the integrity of PCORI-funded research findings; and (b) promote data sharing to enable conduct of additional analyses using data from PCORI-funded studies, thereby augmenting the knowledge generated from the original study.

Draft PCORI Open Science Policy (2)

- The draft policy is organized around three sets of requirements:
  - Applicants: must demonstrate a willingness to support open science and describe planned activities that will enable Data Sharing in their application
  - Awardees: must prepare for possible future requests for Data Sharing by developing a data management and data sharing plan in a manner consistent with applicable privacy, security and other legal requirements
  - Data Sharing Requests: such requests may originate from third party researchers and/or PCORI program staff

- The policy is drafted in a manner that will enable PCORI to incorporate additional operational details and procedures over time, based on learning from a pilot phase and decisions informed by experts.

Open Science: Piloting Data Sharing Approaches

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Piloting Data Sharing Approaches: Overview

Goals of Pilot:

- Overarching goal is to have repositories and PCORI awardees "play in the same sandbox" for a limited time in order to learn:
  - Which features and capabilities of repositories (e.g., data models, governance structure, security, staffing, experience with health data/IPD) are most critical for depositing and sharing of clinical data.
  - What time/effort is needed for awardees to prepare data package for sharing
  - What are the challenges/concerns for PCORI awardees and their institutions and how they can be addressed in a manner consistent with PCORI's commitment to open science.
  - What PCORI resources (staff and funding) are required to support data sharing.

Key Outcomes:

- Depositing of data and a data use agreement between repository and the PI/institution.
- PCORI will develop criteria for acceptable repository practices.

Duration:

- Pilot will last approximately 9 months and will include evaluation component.

Open Science: Data Management Plans

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Data Management Plans: Expectations and Guidance for Applicants and Awardees

- PFAs have signaled PCORI's broad expectations regarding open science.
- Revisions to PCORI's draft Open Science Policy have underscored the need to provide more specific guidance to ensure applicants and awardees are prepared to create and preserve research project data and data documentation.
- Recommendations based on discussions with experts and review of data management plans required by other funders:
  - Revise the "Replication and Reproducibility of Research and Data Sharing" sections of the Application Guidelines and Research Plan Template for upcoming funding cycle.
  - Require applicants to complete a "PCORI Data Management and Sharing Plan Template."
  - Structured data management plans include the elements necessary for ensuring research integrity, transparency, and reproducibility

Request for CTAP Input

- Are there elements of the Open Science Work Group's activities about which you have comments or questions?
- Any feedback about the Draft Policy or the planned pilot would be most welcome.

Lunch & Recognition of Panelists

12:00 – 1:00 p.m.

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Methodology Standards for Clinical Trials

David Hickam, MD, MPH

Program Directory, CER Methods, PCORI

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PCORI's Methodology Standards

- 12 Categories of Standards
  - 5 categories of "cross-cutting" standards (Research Questions, Patient Centeredness, Missing Data, Heterogeneity of Treatment effects, Data Integrity)
  - 2 categories addressing specific issues in clinical trials
    - Adaptive trials
    - Cluster designs
  - 3 categories on observational designs
    - Registries
    - Data networks
    - Causal inference
  - Diagnostic test standards
  - Standards for systematic reviews
- Standards on complex interventions are under development

PCORI Methodology Standards for Clinical Trials – Survey Results

	Highly relevant	Very relevant	Somewhat relevant	Not relevant
RQ-1	28.6%	42.9%	28.6%	0.0%
RQ-2	85.7%	14.3%	0.0%	0.0%
RQ-3	57.1%	28.6%	14.3%	0.0%
RQ-4	57.1%	42.9%	0.0%	0.0%
RQ-5	85.7%	14.3%	0.0%	0.0%
RQ-6	85.7%	14.3%	0.0%	0.0%
PC-1	71.4%	28.6%	0.0%	0.0%
PC-2	85.7%	14.3%	0.0%	0.0%
PC-3	42.9%	42.9%	14.3%	0.0%
PC-4	85.7%	14.3%	0.0%	0.0%
IR-1	75.0%	25.0%	0.0%	0.0%
IR-2	42.9%	42.9%	14.3%	0.0%
IR-3	28.6%	57.1%	0.0%	14.3%
IR-4	57.1%	42.9%	0.0%	0.0%
IR-5	50.0%	50.0%	0.0%	0.0%
New IR-6	85.7%	14.3%	0.0%	0.0%

PCORI Methodology Standards for Clinical Trials – Survey Results

	Highly relevant	Very relevant	Somewhat relevant	Not relevant
MD-1	71.4%	28.6%	0.0%	0.0%
MD-2	66.7%	16.7%	16.7%	0.0%
MD-3	71.4%	14.3%	14.3%	0.0%
MD-4	66.7%	16.7%	16.7%	0.0%
HT-1	60.0%	20.0%	20.0%	0.0%
HT-2	50.0%	50.0%	0.0%	0.0%
HT-3	66.7%	33.3%	0.0%	0.0%
DR-1	28.6%	14.3%	42.9%	14.3%
DR-2	28.6%	14.3%	42.9%	14.3%
DR-3	57.1%	0.0%	28.6%	14.3%
DR-4	28.6%	14.3%	28.6%	28.6%
DN-1	50.0%	16.7%	33.3%	0.0%
DN-2	50.0%	0.0%	33.3%	16.7%
CI-1	16.7%	66.7%	0.0%	16.7%
CI-2	66.7%	16.7%	0.0%	16.7%
CI-3	60.0%	0.0%	20.0%	20.0%
CI-4	33.3%	33.3%	33.3%	0.0%
CI-5	16.7%	0.0%	50.0%	33.3%
CI-6	16.7%	16.7%	33.3%	33.3%

PCORI Methodology Standards for Clinical Trials – Survey Results

	Highly relevant	Very relevant	Somewhat relevant	Not relevant
AT-1	66.7%	16.7%	16.7%	0.0%
AT-2	66.7%	16.7%	16.7%	0.0%
AT-3	66.7%	33.3%	0.0%	0.0%
AT-4	66.7%	33.3%	0.0%	0.0%
DT-1	50.0%	16.7%	16.7%	16.7%
DT-2	50.0%	16.7%	16.7%	16.7%
DT-3	66.7%	16.7%	0.0%	16.7%
SR-1	33.3%	33.3%	33.3%	0.0%
RC-1	85.7%	14.3%	0.0%	0.0%
RC-2	100.0%	0.0%	0.0%	0.0%
RC-3	71.4%	14.3%	14.3%	0.0%
RC-4	60.0%	40.0%	0.0%	0.0%
RC-5	50.0%	50.0%	0.0%	0.0%

Issues not Currently Addressed in the Standards

- Reporting of results (Consort, etc.)
- Recruitment and retention
- Fidelity of interventions

n-of-1 Designs

Evelyn P. Whitlock, MD, MPH
Chief Science Officer, PCORI

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n-of-1 Designs: Background

- In the context of a PPRN demonstration project, the PCORI Board of Governors has asked for methodological input on n-of-1 designs
- PCORI is receiving more applications related to this type of design (clinical as well as methodology proposals)
- PCORI is requesting input from the CTAP as follows:
  - To outline the history and development of this methods;
  - To characterize the current maturity of this method for stand-alone clinical research
  - To define parameters for clinical research if the method is sufficiently developed (see next slide)

n-of-1 Designs: Request for Input from the CTAP

- For what types of conditions are n-of-1 designs applicable?
- What are the minimal requirements for good n-of-1 designs?
- How robust is the methodological development for this type of design?
- How well has this design been validated against other types of research for specific conditions?
- How robust are quantitative methods for synthesizing results from n-of-1 trials?
- What are criteria for distinguishing between a study that addresses treatment optimization for the individual versus creation of generalizable knowledge?

Break

2:15 – 2:30 p.m.

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Advisory Panel on Clinical Trials Charter Update

David Hickam, MD, MPH

Program Director, CER Methods, PCORI

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Legislation on Clinical Trials Advisory Panel

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PCORI's Authorizing Legislation

Specific statutory provision that mandates the appointment of expert advisory panels for clinical trials (at (d)(4)(A)(ii):

"(ii) EXPERT ADVISORY PANELS FOR CLINICAL TRIALS.—The Institute shall appoint expert advisory panels in carrying out randomized clinical trials under the research project agenda under paragraph (2)(A)(ii). Such expert advisory panels shall advise the Institute and the agency, instrumentality, or entity conducting the research on the research question involved and the research design or protocol, including important patient subgroups and other parameters of the research. Such panels shall be available as a resource for technical questions that may arise during the conduct of such research.

Interpretation: CTAP will be the primary way that PCORI fulfills its legislative mandate and that subcommittees can be formed for purposes of addressing focused issued and needs.

Panel Discussion

Elizabeth A. Stuart, PhD, AM (Chair)

Professor of Mental Health and Biostatistics, The Johns Hopkins Bloomberg School of Public Health

John D. Lantos, MD (Co-Chair)

Professor of Pediatrics, Children's Mercy Hospital

Recap and Next Steps

Elizabeth A. Stuart, PhD, AM (Chair)

Professor of Mental Health and Biostatistics, The Johns Hopkins Bloomberg School of Public Health

John D. Lantos, MD (Co-Chair)

Professor of Pediatrics, Children's Mercy Hospital

Anne Trontell, MD, MPH

Senior Program Officer, Clinical Effectiveness Research, PCORI

Jason Gerson, PhD

Senior Program Officer, CER Methods, PCORI

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Thank You!

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