# Advisory Panel on Clinical Trials Spring 2015 Meeting

**Washington, DC**

May 28, 2015

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# Welcome and Plans for the Day

**Bryan Luce, PhD, MBA**

Chief Science Officer, PCORI

**Elizabeth A. Stuart, PhD, AM (Chair)**

Associate 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 |
|---|---|---|
| 8:30 a.m. | Welcome and Plans for the Day | B. Luce<br>E. Stuart<br>J. Lantos |
| 8:45 a.m. | Reports from Subcommittees | M. Michaels<br>M. Zwarenstein<br>A. Trontell |
| 10:15 a.m. | Break | |
| 10:30 a.m. | Methodology Standards for Clinical Trials | E. Stuart<br>D. Hickam |
| 11:45 a.m. | FY16 Budget | K. Odom Walker |
| 12:00 p.m. | Lunch | |
| 1:00 p.m. | Methods Consultation Panel for Pragmatic Clinical Studies: Evaluation and Recommendations | L. Forsythe<br>J. Gerson<br>L. Fayish |
| 1:30 p.m. | Trial Simulation and Response-Adaptive Platform Trials | B. Luce |

# Today's Agenda (cont'd.)

| Start Time | Item | Speaker |
|---|---|---|
| 2:30 p.m. | Break | |
| 2:45 p.m. | PCORI's DSMP Policy | J. Gerson |
| 3:30 p.m. | Potential Uses for Chatter | E. Djabali |
| 3:45 p.m. | Recap and Next Steps | B. Luce<br>E. Stuart<br>J. Lantos |
| 4:00 p.m. | Adjourn | |

# PCORI Scientific Leads to the Advisory Panel on Clinical Trials

- **Anne Trontell, MD, MPH – Senior Program Officer in the Clinical Effectiveness Research Program**

Before joining PCORI, Trontell led two research portfolios at the Agency for Healthcare Research and Quality: the Clinical and Health Outcomes Initiative in Comparative Effectiveness (CHOICE) prospective studies in comparative effectiveness, and the Centers for Education and Research on Therapeutics. A pediatrician and former captain in the US Public Health Service, Trontell also helped lead drug safety activities at the US Food and Drug Administration, analyzed preventive services at the Health Care Financing Administration (now CMS), and served as an epidemic intelligence service officer with the Centers for Disease Control and Prevention. She is particularly interested in applied, user-driven research and its translation into clinical practice.

- **Jason Gerson, PhD – Associate Director for Comparative Effectiveness Research (CER) Methods and Infrastructure**

Before joining PCORI, Gerson was a senior officer at The Pew Charitable Trusts, where he led research activities on a number of drug safety and innovation issues. Before that, he was a commissioner's Fellow at the Food and Drug Administration (FDA), working in the Office of Pediatric Therapeutics on regulatory science, policy, and ethical issues related to pediatric medical product development. Prior to joining the FDA, Gerson was a faculty member in the Department of Epidemiology at the Johns Hopkins Bloomberg School of Public Health. During that time, he served as a co-investigator on a project assessing how evidence about the biological mechanisms underlying therapeutic interventions (drugs and devices) is incorporated into the broader evidence base for those interventions.

Earlier in his career, Gerson worked in the New York City Mayor's Office of Health Policy and the New York City Administration for Children's Services designing, implementing, and evaluating health services for a number of populations, including the city's foster care children.

# Reports from Subcommittees

# CTAP Subcommittees

- **Recruitment, Accrual, and Retention**
  - Margo Michaels, MPH, Executive Director/Founder, Education Network to Advance Cancer Clinical Trials
- **Standardization of Complex Concepts and their Terminology**
  - Merrick Zwarenstein, MBBCh, MSc, PhD, Director of the Centre for Studies in Family Medicine, Department of Family Medicine, Western University
- **Post-Award Subcommittee**
  - Anne Trontell, MD, MPH, Senior Program Officer, Clinical Effectiveness Research, PCORI

# Recruitment, Accrual, and Retention

Margo Michaels, MPH, Executive Director/Founder, Education Network to Advance Cancer Clinical Trials

# Subcommittee on Recruitment, Accrual, and Retention (RAR) – Purpose

- To inform PCORI Funding Announcements and related review criteria
- To guide PCORI monitoring of funded contracts by providing technical assistance and support
- To provide additional direction regarding the engagement of healthcare stakeholders around recruitment, accrual, and retention

# Subcommittee on Recruitment, Accrual, and Retention (RAR)

- Given PCORI's mandate to improve the quality and relevance of evidence available to help people make informed healthcare decisions, we must ensure that the ***research PCORI produces is truly representative of the affected population(s) and that funded studies serve both the study participants and the study research question(s) by achieving all necessary recruitment, accrual, and retention targets.***

# Areas of Exploration

- Methodology Standards
- Development of Letters of Intent/Funding Announcements (PFAs)
- Engagement Expectations/Engagement Monitoring
- Merit Review/Merit Review Training
- Contract Negotiation/Information Requests
- Program and Engagement Officers Monitoring Funded Projects
- PCORNET

# Subcommittee on Recruitment, Accrual, and Retention (RAR)

- **List of tasks/priorities for next 12-18 months**
  - Refine PCORI Methodology Standards on Patient-Centeredness to include definitions of and practices for "Patient-Centered Recruitment and Retention"
  - Provide technical assistance and support – ad hoc as needed by PCORI
    - Provide comments on new interim report template
    - Provide comments on Project Remediation SOP
    - Serve on Post-Award Advisory Subcommittee as recruitment and retention "experts"
  - Provide technical assistance and support – RAR tool kit for staff to monitor clinical trials
  - Advise on Scope of Work for Contractor to develop a tool kit/guide to monitor projects

# Subcommittee on Recruitment, Accrual, and Retention (RAR)

- **Members**
  - CTAP Members
    - Margo Michaels (chair)
    - Sanford Jeames
  - MC Member
    - David Meltzer
  - RDAP Member
    - Kate Lorig, DrPH
  - Outside Experts
    - Clair Meunier
    - Giselle Corbie-Smith, MD, MSc
    - Terrance Albrecht, PhD
    - Deborah Watkins Bruner, PhD, RN, FAAN
    - Consuelo Wilkins, MD, MSCI

# Standardization of Complex Concepts and their Terminology

Merrick Zwarenstein, MBBCh, MSc, PhD, Director of the Centre for Studies in Family Medicine, Department of Family Medicine, Western University

# Subcommittee on Standardization of Complex Concepts and their Terminology (SCCT) – SOW

- The CTAP Subcommittee on SCCT will provide guidance, as requested, on topics relating to the standardization of complex concepts and their terminology, which may include, but are not limited to:
  - Pragmatic
  - Mixed methods
  - Ideal level of detail with which investigators should describe their interventions and comparison conditions

# Subcommittee on Standardization of Complex Concepts and their Terminology (SCCT) – Principles

- Its work should not contradict any work already done by PCORI
- Its work should be coherent with the work done in the literature
- It will collaborate with the MC and vet its work through the committee
- Its first step will be to get consensus on terminologies included in PCORI materials (PFAs, Methodology Report, etc.) to provide clearer definitions to potential applicants for PCORI funding

# Subcommittee on Standardization of Complex Concepts and their Terminology (SCCT)

- **Members**
  - CTAP Member
    - Merrick Zwarenstein, MBBCh, MSc, PhD (chair)
  - MC Members
    - Robin Newhouse, PhD, RN
    - Mary Tinetti, MD
  - Outside Experts
    - Philip Posner, PhD
    - Sean Tunis, MSc, PhD
    - Jerry Krishnan, MD, PhD

# Subcommittee on Standardization of Complex Concepts and their Terminology (SCCT)

- **Update: Defining/Characterizing Pragmatic Clinical Trials**
  - Full subcommittee meeting (01/13): Introductions and going through SOW
  - Full subcommittee meeting (02/25): Introductions and going through SOW (for absentees at first meeting)
  - Review of sources (02/25 – 04/06)
  - Merrick meeting with PCORI staff (04/06): Workgroup on compiling sources
  - First version of the document drafted (04/06 – 04/23)
  - Full subcommittee meeting (04/23): Going over document with full subcommittee
  - Subcommittee comments incorporated into version 2 of the document
  - Document circulated to several PCORI staff

# Subcommittee on Standardization of Complex Concepts and their Terminology (SCCT)

- **PCORI Staff Involved**
  - Yen-Pin Chiang, PhD – Associate Director, Science, Clinical Effectiveness Research
  - Emily Evans, PhD, MPH – Program Officer, CER Methods and Infrastructure
  - Sarah Greene, MPH – Associate Director, CER Methods and Infrastructure
  - David Hickam, MD, MPH – Program Director, Clinical Effectiveness Research
  - Stanley Ip, MD – Senior Program Officer, Clinical Effectiveness Research
  - Shivonne L. Laird, PhD, MPH – Program Officer, Eugene Washington Engagement Awards Program
  - Bryan Luce, MBA, PhD – Chief Science Officer
  - Penny Mohr, MA – Senior Program Officer, Improving Healthcare Systems
  - Hal Sox, MD – Director, Research Portfolio Development, Office of the Chief Science Officer
  - Danielle Whicher, PhD, MHS – Program Officer, Clinical Effectiveness Research

# Subcommittee on Standardization of Complex Concepts and their Terminology (SCCT)

- **3 Potential Tasks for the Subcommittee:**
  - Review the Large Pragmatic Studies PFA for consistency with what PCORI is looking to fund
  - Present and propose to the Methodology Committee:
    - Minimal standard
    - Guidance document
  - Continue refining the document as a white paper/standalone thought piece that could be published in the literature and on PCORI's website

# Post-Award Subcommittee

Anne Trontell, MD, MPH, Senior Program Officer, Clinical Effectiveness Research, PCORI

# Post-Award Subcommittee

- **Purpose**
  - Address specific methodological designs of awarded applications that have already undergone PCORI's merit review process
  - Provide technical advice to the program staff monitoring the trials
  - Provide supplemental expertise in highly specialized areas that may be beyond the existing skill set of Science Program Officers
  - Help ensure that the study design and methodology are appropriate and consistent with the standards generated by the PCORI Methodology Committee
- **Process Overview**
  - Functions as a pool of experts available to PCORI staff on an ad hoc basis
  - Reports back, when appropriate, to the CTAP's two overarching subcommittees and to the full CTAP to inform their broad guidance to PCORI

# Post-Award Subcommittee

- **Process Steps**
  - Program staff submit a request describing nature of needed expertise
  - One or more subcommittee members are selected
  - Selected members are asked to carefully review PCORI's COI/confidentiality/nondisclosure policy and then proceed to look through the key personnel for potential COIs
  - Upon verification that the member(s) do not have a COI with particular projects, the program staff will be put in contact with members
  - Subcommittee members will receive awarded applications, study protocols, progress reports, and/or other relevant study documents
  - The frequency of the communication between the subcommittee members and the program staff will vary with the level of input needed on the study

# Post-Award Subcommittee

- **Nature of Advice**

  Could include, but is not limited to, issues associated with:

  - Statistical inference
  - Confounding
  - Complex methods
  - Defining “usual care”
  - Human subjects
  - Patient safety
  - Sample size and power calculations
  - Alignment of trial components for cross-study analyses
  - Recruitment, accrual, and retention
  - Patient engagement
  - Review of DSMB reports
  - Remediation of poor study performance
  - Clinical or patient expertise/experience

# Post-Award Subcommittee

- **Members: 29 total (including 5 CTAP members)**

| Name | Employer |
|---|---|
| Daniel Merenstein | Georgetown University |
| Daniel Sargent | Mayo Clinic |
| Charles McCulloch | University of California, San Francisco School of Medicine |
| Shelley Tworoger | Harvard University School of Public Health |
| Ronald Chen | University of North Carolina Chapel Hill |
| Peter Peduzzi | Yale University School of Public Health |
| Jason Roy | University of Pennsylvania Perelman School of Medicine |
| Wahed Abdus | University of Pittsburgh School of Public Health |
| Soko Setoguchi-Iwata | Duke University Clinical Research Institute |
| John Wong | Tufts University Medical Center |
| Tom Louis | Johns Hopkins Bloomberg School of Public Health |
| James O'Malley | Dartmouth Institute for Health Policy and Clinical Practice |
| Eloise Kaizar | Ohio State University |

| Name | Employer |
|---|---|
| Sanford Jeames | Eastside Memorial High School |
| Frank Rockhold | GlaxoSmithKline |
| Jason Connor | Berry Consultants |
| Merrick Zwarenstein | Western University |
| Margo Michaels | Founder, Education Network to Advance Cancer Clinical Trials |
| Elizabeth A. Chrischilles | University of Iowa College of Public Health |
| Constantine Gatsonis | Brown University School of Public Health |
| Kert Viele | Berry Consultants |
| Roger Lewis | University of California Los Angeles School of Medicine |
| Leslie Curtis | Duke University |
| William Crown | Optum Labs |
| David Kent | Tufts University Medical Center |
| Ravi Varadhan | Johns Hopkins University |
| Lisa Salberg | HCMA-Hypertrophic Cardiomyopathy Association |
| Ralph B. D`Agostino Jr. | Comprehensive Cancer Center, Wake Forest University School of Medicine |
| Bibhas Chakraborty | Duke-NUS Graduate Medical School |

# Post-Award Subcommittee

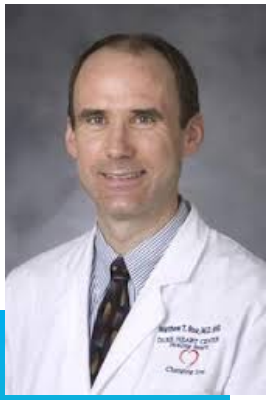
- **Members: 29 total (including 5 CTAP members)**
  - **Areas of expertise include, but are not limited to:**
    - Biostatistics
    - Epidemiology
    - Biomarkers
    - Pragmatic trials
    - Epidemiology
    - Missing data
    - Bayesian methods
    - Adaptive designs
    - Decision analysis
    - Screening
    - Generalizability
    - Sequential analysis
    - Rare events
    - Recruitment, accrual, and retention
    - Operational capacity
    - Interim analysis and the oversight of clinical trials (and DSMBs)
    - Statistical methodology (health econometrics, epidemiological models)
    - Data linkage methods
    - Heterogeneity of treatment effect/subgroup analysis
    - Ethical issues in research

# Post-Award Subcommittee

- **Research studies utilizing the subcommittee as of now:**

| Project Name | Funding Program | Stage | Input Requested | Number of Subcommittee Members |
|---|---|---|---|---|
| Aspirin Dosing: A Patient-Centric Trial Assessing Benefits and Long-term Effectiveness (ADAPTABLE) | PCORnet | • Post Merit Review<br>• Pre-selection Committee<br>• Continuing Post Board approval | • Review and provide verbal comment via teleconference to both the application research plan and study protocol<br>• Participate in ADAPTABLE team site visit all-day meeting to discuss concerns and potential solutions with applicant<br>• Review revised protocol (upcoming mid-June) | 4 |
| Project ACHIEVE (Achieving Patient-Centered Care and Optimized Health In Care Transitions by Evaluating the Value of Evidence) | Improving Healthcare Systems | 6 months underway | Review of study protocol for adequacy, appropriateness of design, and potential improvements | 2 |
| Improving Palliative and End-of-Life Care in Nursing Homes | Improving Healthcare Systems | 18 months underway (Cycle I) | Potential design changes and related methodology improvements | 2 |

# Aspirin Dosing: A Patient-Centric Trial Assessing Benefits and Long-term Effectiveness (ADAPTABLE)



## Potential Impact

- Demonstrate PCORnet's capability to conduct important CER efficiently and economically
- Identify the optimal dose of aspirin for secondary prevention of heart attacks and stroke in patients with heart disease

## Engagement

- ADAPTORS patient group involved throughout the trial, contributing to design, start-up, enrollment, follow-up, analysis, and dissemination

## Methods

- Individual-randomized pragmatic clinical trial to compare the effectiveness of two doses of aspirin, using the PCORnet Common Data Model as a key data source

An innovative pragmatic clinical trial conducted within the PCORnet infrastructure to determine the optimal daily aspirin dose (325 mg versus 81 mg) for patients with heart disease. The trial leverages existing electronic health records, which link to insurance claims. A web-based patient portal collects patient-reported outcomes and additional patient-encounter data. The trial engages patients, their healthcare providers, and researchers in using the infrastructure that PCORnet has developed and continues to refine.

*Matthew T. Roe, MD, MHS*
*Associate Professor of Medicine, Duke Cardiology*

*CER Methods and Infrastructure, awarded April 2015*

# Project ACHIEVE (Achieving Patient-Centered Care and Optimized Health In Care Transitions by Evaluating the Value of Evidence)

## Potential Impact

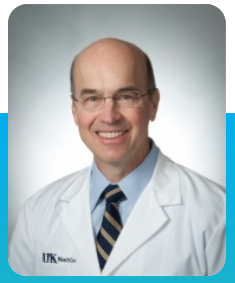
- Will provide tools for hospitals, community-based organizations, patients, caregivers, clinicians, and other stakeholders to help them make informed decisions about which transitional care services are most effective and how best to implement them in the context of their own community.

## Engagement

- Brings together, through multiple forums, the expertise of patients, caregivers, and stakeholders with national leaders in care transition research

## Methods

- Qualitative and quantitative methods, including site visits, surveys, and clinical and claims data to study historical, current, and future groups of patients, caregivers, and providers. The comparators will be hospitals and communities that have implemented different clusters of transitional care interventions.



Objective is to identify which transitional care services and outcomes matter most to patients and caregivers, evaluate the comparative effectiveness of ongoing multi-component efforts at improving care transitions, and develop recommendations on best practices for the design, implementation, and large-scale national spread of highly effective, patient-centered care transition programs.

*Mark V. Williams, MD*
*University of Kentucky*

*Improving Healthcare Systems, awarded January 2015*

# Improving Palliative and End-of-Life Care in Nursing Homes

## Engagement

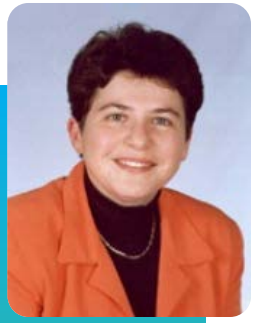
- Study measures outcomes from patient and provider perspectives and involves stakeholders including residents, family members, staff, and policy makers

## Potential Impact

- Could change practice by establishing the impact on residents and clinicians of palliative care teams in nursing homes

## Methods

- Randomized controlled trial



A randomized controlled trial to evaluate the impact of palliative care teams on resident and staff outcomes and care processes in nursing homes. Studies the impact of the intervention on both patient outcomes (e.g., shortness of breath, pain) and staff outcomes (e.g., care delivery skills, satisfaction).

*Helena Temkin-Greener, PhD*
*University of Rochester*
*Rochester, NY*

*Improving Healthcare Systems, awarded December 2012*

# Discussion

- What kind of reports from this subcommittee would be useful for the CTAP to provide general guidance to PCORI?
- How can PCORI evaluate this process?
- Any questions about the subcommittee and its function?

# Break

**10:15 – 10:30 a.m.**



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# New Methodology Standards for Study Designs Using Clusters

**David Hickam, MD, MPH**
Program Director, Clinical Effectiveness Research, PCORI

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# Overview of Process

- **Current Status**
  - A group of external experts, MC members, and staff met on April 7 to develop and refine a set of draft standards
  - The standards developed on April 7 were presented to MC on May 6
- **Next Steps**
  - Revisions based on MC feedback
  - Final approval of draft standards in summer 2015
  - Board approval for public comment period
  - Revisions based on public comments
- **MC Members:** Naomi Aronson, Cynthia Girman, Steve Goodman, Robert Kaplan, Sally Morton, Robin Newhouse, and Sebastian Schneeweiss
- **Experts:** Allan Donner, Thomas Koepsell, Ken Kleinman, David Murray

# About the Draft Standards

- CONSORT Statement used as background for drafting the standards
- These standards mostly include language only for randomized trial designs
  - The experts also had suggestions for standards on observational cluster designs
  - Plan to incorporate language on observational cluster designs into the standards

# Standard 1

Specify whether the study objectives, the interventions, and the primary outcomes pertain to the cluster level or individual level.

a) Describe the target population of clusters and individuals to which the study findings will be generalizable.
b) Describe the clusters to be randomized and the subjects to be enrolled in the trial.

# Standard 2

Justify the choice of cluster randomization. Describe the benefits and disadvantages of cluster randomization versus individual-level randomization for the proposed research. Cluster randomization should be substantiated by a sound theoretical and conceptual framework that describes the hypothesized causal pathway. Cluster randomization generally is applicable when*:

a) An intervention is delivered at the cluster level
b) An intervention changes the physical or social environment
c) An intervention involves group processes, or
d) An intervention cannot be delivered without a serious risk of contamination

*Logistical considerations can also justify cluster randomization, for example, to reduce costs or to improve participation, adherence, or administrative feasibility.

# Standard 3

The number of clusters, and the sample size per cluster, should provide adequate power since cluster trials are inherently not as statistically efficient as standard randomized trials.

# Standard 4

Power and sample size estimates must use appropriate methods to account for the dependence of observations within clusters. The methods used to reflect dependence should be clearly described. Sources should be provided for the methods and for the data used to estimate the degree of dependence. Sensitivity analyses incorporating different degrees of dependence must be reported.

a) For simpler designs, the dependence in the data can be reflected in the intraclass correlation.
b) Dependence can also be reflected in variance components.
c) Other factors that affect the power calculation include: the design of the study, the magnitude of the hypothesized intervention effect, the pre-specified primary analysis, and the desired Type I error rate.

# Standard 5

Data analyses must account for the dependence of observations within clusters regardless of its magnitude. Data analyses must also reflect the degrees of freedom available at the cluster level. Investigators must propose appropriate methods for data analyses with citations and sufficient detail to reproduce the analyses.

# Standard 6

Ethical dimensions of cluster randomized trials are complex. For all intervention studies, randomization is highly recommended. Research should conform to the Ottawa Statement on the Ethical Design and Conduct of Cluster Randomized Trials.

# Standard 7

Blinding should be used when feasible. Blinding of evaluation staff should be used even in situations for which subject and investigator blinding are not feasible. When blinding is not possible, the impact of lack of blinding on results should be discussed.

# Standard 8

Because cluster randomized trials often involve a limited number of groups or clusters, stratified randomization is recommended. Non-randomized intervention trials often involve a limited number of groups or clusters, and efforts should be made to balance treatment or study conditions on potential confounders.

a) The recommended stratification factors are those that are expected to be strongly correlated with the outcome or with the implementation of the intervention, such as:
    i. Baseline value of the outcome variable
    ii. Cluster size
    iii. Geographic area

# Definitions

- Baseline value of the outcome variable
- Contamination
- Degrees of freedom available at the cluster level
- Dependence
- Group processes
- Intraclass correlation
- Non-randomized intervention studies
- Observational studies: In a non-randomized study, the issue of bias due to potential confounding becomes very important.
- Randomized studies
- Variance components

# New Methodology Standards for Clinical Trials

**Elizabeth A. Stuart, PhD, AM (Chair)**

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

**David Hickam, MD, MPH**

Program Director, Clinical Effectiveness Research, PCORI


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# Potential Areas for Standards Development

- Issues of consent: assessing risk of participation in trials
- Endorsement of some portion of the EQUATOR guidelines
- Guidance on the issue of justifying the inclusion/exclusion criteria used in a trial
- Handling noncompliance
- Recruitment, accrual, and retention
- Criteria for determining "equivalence" criteria
- Methods to look at safety issues
- Benefit to risk modeling
- Key elements of data management plans
- Heterogeneity
- Use of networks
- Illustrations of useful Bayesian design/analyses

# CTAP Involvement

- Decisions on standards to develop?
- Development of standards?
- Review of scope of work for contractor?
- Review of standards developed by contractor?
- Presentation to the Methodology Committee?

# FY16 Activities

**Kara Odom Walker, MD, MPH, MSHS**
Deputy Chief Science Officer, PCORI

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# CTAP Budgeted Activities

| Activity | FY15 | FY16 |
|---|---|---|
| Spring 2015 Meeting | X | |
| Fall 2015 Meeting | | X |
| Winter 2016 Meeting | | X |
| Spring 2016 Meeting | | X |
| Landscape Review 1 – Methodology Standards | X | |
| Landscape Review 2 – Methodology Standards | X | |
| Landscape Review 3 – RAR Tool Kit | | X |
| Landscape Review 4 – TBD | | X |

# Lunch

**12:00 – 1:00 p.m.**

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# Methods Consultation Panel for Pragmatic Clinical Studies: Evaluation and Recommendations

**Laura Forsythe, PhD, MPH**
Senior Program Officer, PCORI
**Jason Gerson, PhD**
Associate Director, CER Methods and Infrastructure, PCORI
**Lauren Fayish, MPH**
Program Associate, PCORI


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# Overview

- Evaluation Rationale and Methods
- Evaluation Findings – Spring 2014 PCS
- Evaluation Update – Fall 2014 PCS
- Recommendations

# Purpose of Merit Review and Methods Consultation

## Merit Review

- Identify applications with potential to help patients and other stakeholders make informed decisions to improve health outcomes
- Elicit high-quality feedback from diverse perspectives to ensure that funded research:
  - meets the criteria for scientific rigor, and
  - reflects the interests of patients and those who care for them

## Methods Consultation Panel (MCP)

- Additional, focused assessment of methods
- Identify strengths, weaknesses, and recommended solutions for weaknesses
- Rate criticality of weaknesses and feasibility of solutions
- Inform funding decisions and PIR (PCORI information requests)

# Spring 2014 PCS Review: Guidance on Assessing Project Methods

## Merit Review

### Criterion 3: Technical Merit

The proposal has sufficient technical merit to ensure that the study goals will be met. It includes:

- A clear research plan with **rigorous methods** that **adhere to PCORI's Methodology Standards** and prevailing accepted best practices
- A clear and adequate justification for the **study design** choices in the proposed pragmatic trial
- A **realistic timeline** that includes specific scientific and engagement milestones
- A research team with the **necessary expertise** and an appropriate organizational structure
- A **research environment**, including the delivery systems that will host the study, that is well-resourced and highly supportive of the proposed study

## Methods Consultation

### Written Assessment Form

1. **Study Design**
   - Participants, interventions, outcomes, sample size, treatment assignment, blinding
2. **Study Conduct and Analyses**
   - Data and safety monitoring, data management, missing data, HTE, causal inference
3. **Overall Assessment of Application's Proposed Methods**
   - Is design adequate for study purpose?
   - Does healthcare decision that the study will inform match proposed design?
   - Are there any design dimensions that, if modified, would help the design better address the question proposed?

# Evaluation Approach: Quantitative and Qualitative Information

- **Tracking Applications in Review Processes:**
  - # projects sent for Methods Consultation
  - # projects funded conditionally or not funded based on Methods Consultation

- **Written Reviewer Assessments:**
  - # and type of changes recommended (e.g., sample size, outcome measures)
  - Uniqueness relative to the Merit Review
  - Method Consultation Panelists' rating of the importance and feasibility of recommended changes

- **Staff and Methods Consultation Panelist Debriefs:**
  - Procedural feedback
  - Perceptions of the impact of the consultation
  - Incorporating recommendations from consultation with applicants

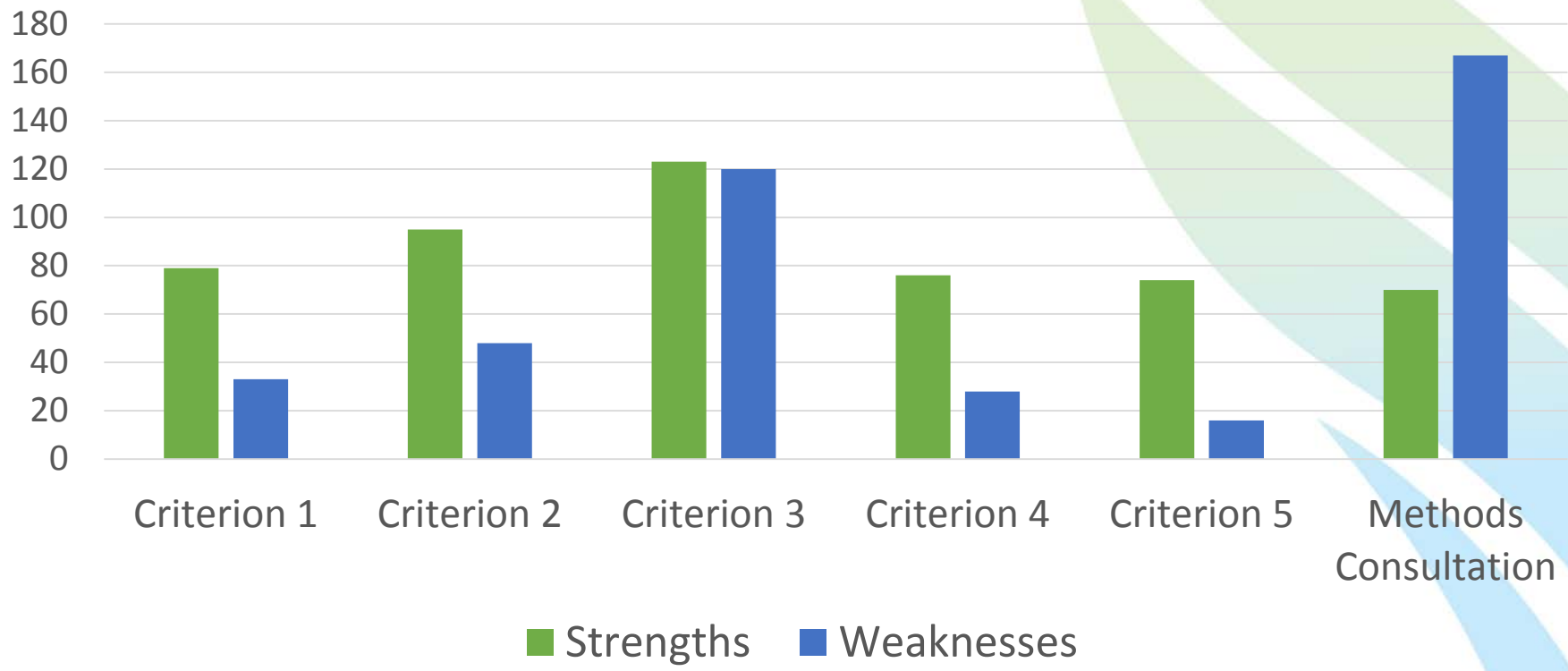
# Methods: Qualitative Analysis (Spring 2014)

- **Sampled 10 of 22 applications based on funding status and Merit Review scores**

- **Data Extraction (Strengths & Weaknesses)**
  - Methods Consultation: comments from Section 1 (Design) and Section 2 (Study Conduct and Analyses)
  - Merit Review: comments from the Technical Merit Criterion section for the three Scientific Reviewers

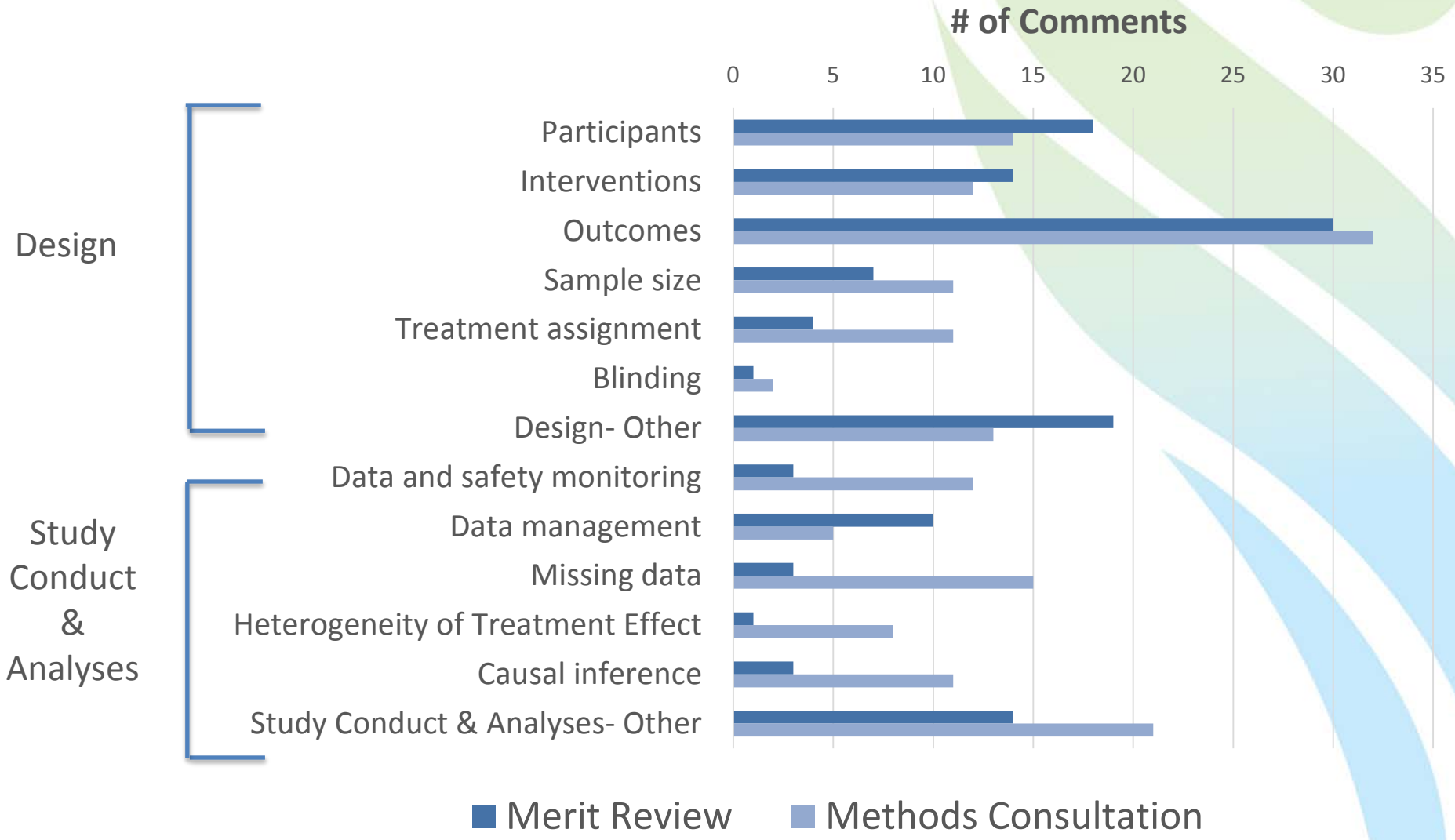
- **Data Coding (Weaknesses)**
  - Created a predetermined list of weakness categories from Methods Consultation written assessment template
  - Compared Merit Review and Methods Consultation weakness comments for uniqueness

# Number of Strengths & Weaknesses Identified by Scientist Reviewers in Merit Review and Methods Consultation (Spring 2014)




*N= 10 sampled applications*
*Criteria 1-5 from Merit Review (3 Scientific Reviewers)*
*Methods Consultation (1 Scientific Reviewer)*

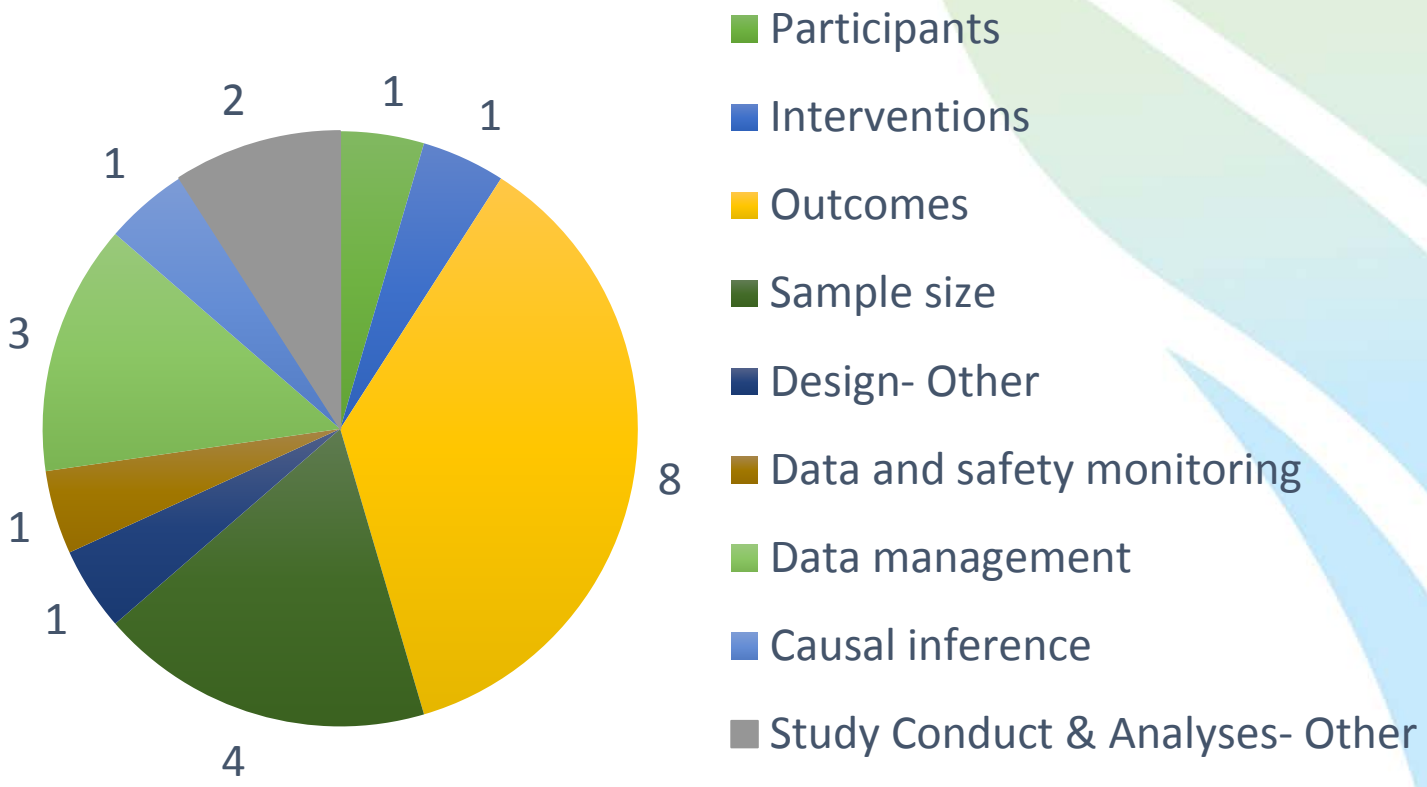
# Categorizing Comments on Methodological Weaknesses (Spring 2014)




*N= 10 sampled applications*

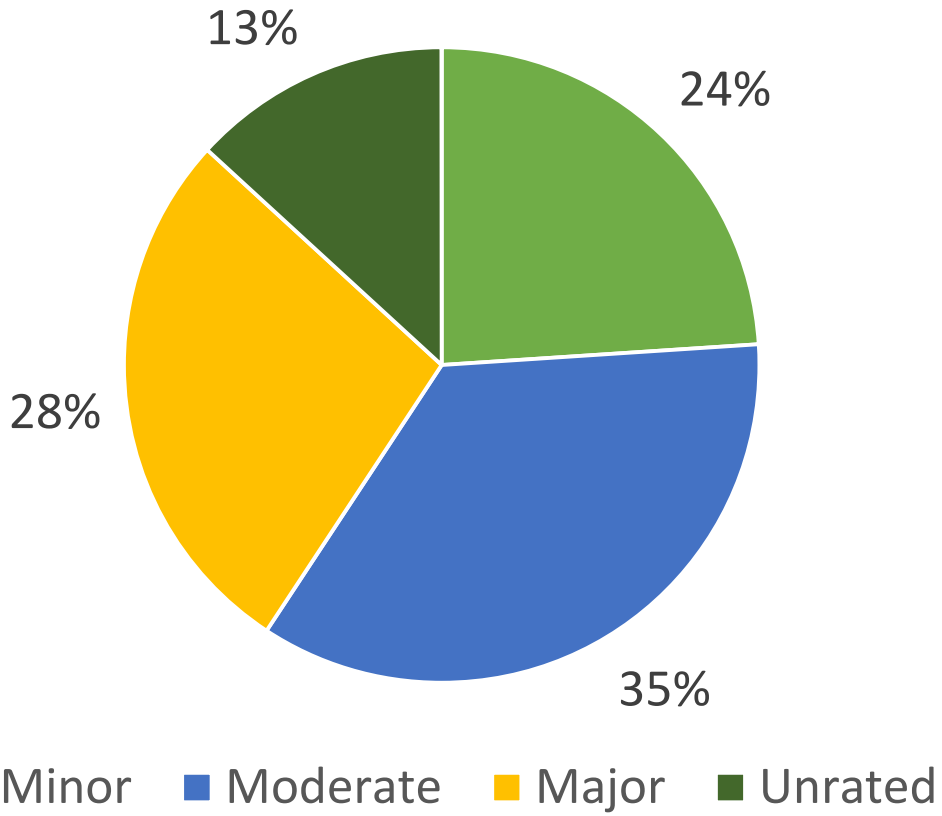
# Methods Consultation Weaknesses that Duplicated Merit Review Weaknesses

84% of the weaknesses from the Methods Consultation were unique from the Merit Review




*N= 22 Duplicative Weaknesses*

# Methods Consultants' Rating of Importance of Weaknesses




*N= 167 Weakness Comments*

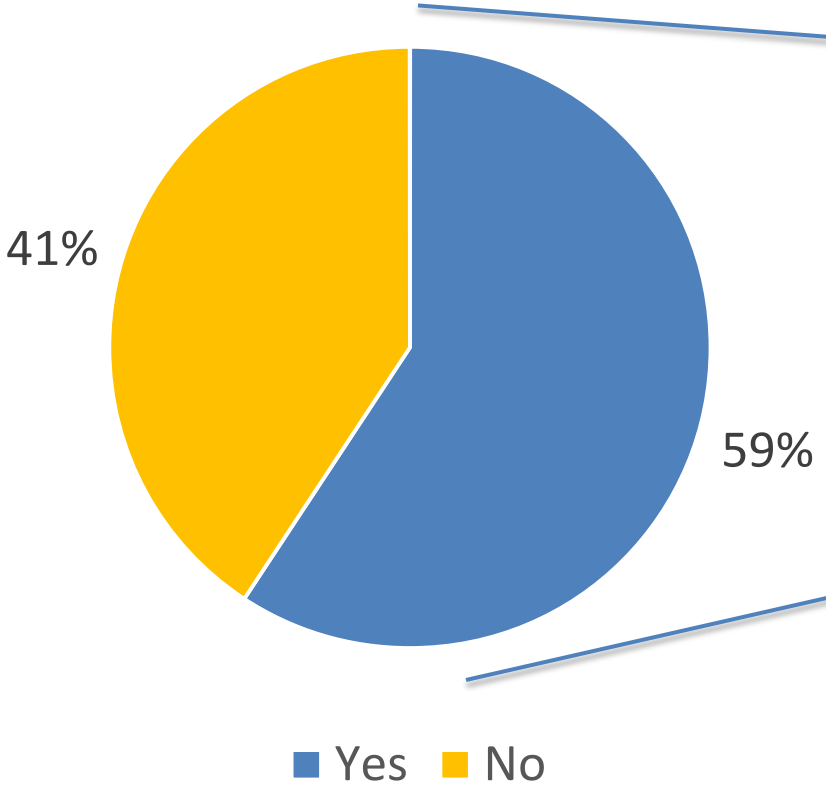
***Minor**: the validity of the study result is unlikely to materially change*

***Moderate**: the validity of the study result could be materially affected*

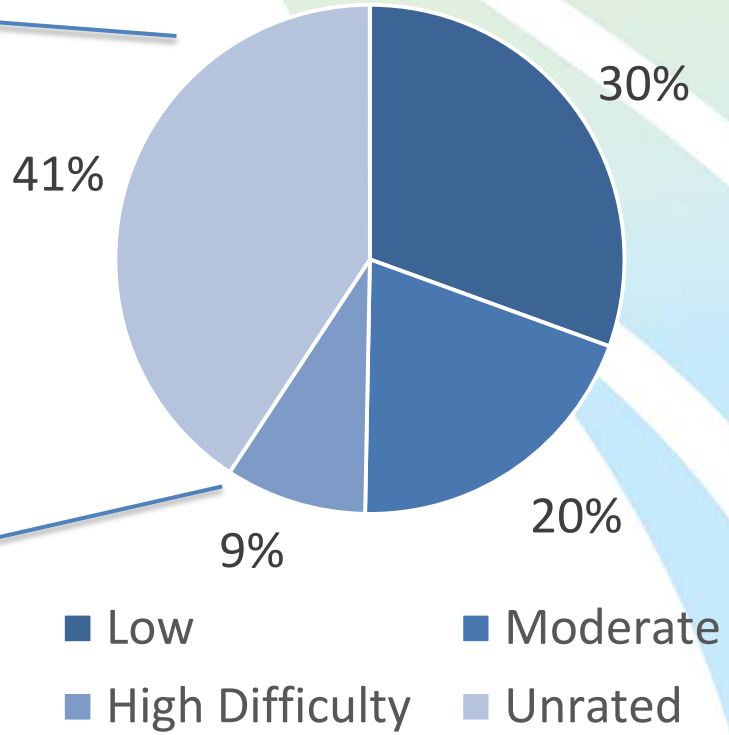
***Major**: the validity of the study result is seriously threatened; the study probably should not be done if this isn't addressed*

# Methods Consultation: Recommendations

Recommendations were provided for 98 (59%) of the weaknesses identified.




Panelists' Ratings of Difficulty to Implement Recommendations




*N= 98 Recommendations*

# Use of Feedback from Methods Consultations

**Process:**

- Incorporated into PCORI Information Requests (PIR)
- Conversations between program staff and PI
- Option of additional consultation with methods consultants

**Outcomes reported by PCORI staff:**

- Opportunity to carefully consider and discuss rationale for decisions
- Increased communication between PCORI staff and PIs
- Higher confidence in methods decisions
- In some cases, changes to study design

# Feedback from the Methods Consultation Panelists

- More guidance needed regarding the scope of their review
- Requests to receive all application materials and appendices
- Most reviewers liked receiving the Merit Review critiques and saw value in identifying new issues or validating their own views
- Recommendations for Merit Review
  - More statistical expertise on review panels
  - More space in applications to describe study design

# Feedback from PCORI Staff – 1

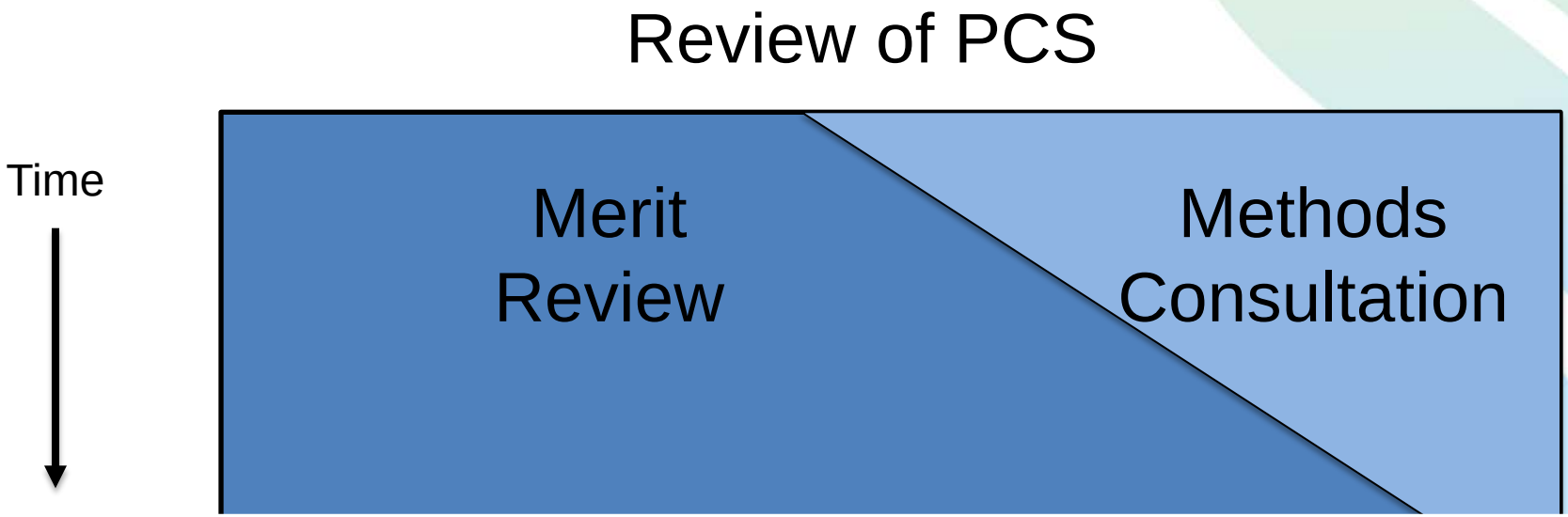
- Consultation yielded high-quality critiques and additional useful information about study methods
- Consultation didn't find any fatal flaws that changed funding decisions
- Recommended solutions have the potential to be a major value added
- Importance of getting strong methodological reviewers in the merit review

# Feedback from PCORI Staff – 2

- Clarity needed regarding the purpose and scope
- Obtain consultation for a targeted set of applications with specific methodological questions/concerns
- Merit Review critiques should be used to steer the Methods Consultation
  - Goal is not an “independent” second review
- Need more time to consider which applications need Methods Consultation

# Recommendations: Consider a Phased Approach

- Methods Consultation can adapt as Merit Review process is refined



# Fall 2014 PCS

Understanding differences compared to Spring 2014

# Fall 2014 PCS: Technical Merit Criterion

- Is there a clear research plan with rigorous methods that adhere to PCORI's Methodology Standards and prevailing accepted best practices?
- Is there a clear comparison condition that is a realistic option in standard practice? Is the comparator sufficiently described to reasonably compare the two or more conditions in the trial?
- Are the proposed comparative conditions currently in use? Is there prior evidence of efficacy or effectiveness for the interventions being compared?
- Is there evidence that the outcome measures are sufficiently sensitive to identify differences between groups?
- Is the study conducted in a patient population that is relevant to the majority of patients with a condition or to a previously understudied subgroup?
- Are the pre-specified subgroups reasonable given the proposed interventions and condition?
- Are the subgroups sufficiently large to allow a rigorous and valid comparative analysis?
- Is the budget appropriate for the proposed research?
- Is there a clear and adequate justification for the study design choices in the proposed pragmatic trial?
- Is there an adequate plan for protection of human subjects participating in this study?
- Do the applicants provide evidence of study feasibility based on availability of participants and experienced staff for efficient start-up?
- Does the project include a realistic timeline that includes clear and specific scientific and engagement milestones?
- Does the research team have the necessary expertise and prior experience conducting large-scale multicenter trials and an appropriate organizational structure to successfully complete the study?
- Is the research environment, including the delivery systems that will host the study, well-resourced and highly supportive of the proposed study?

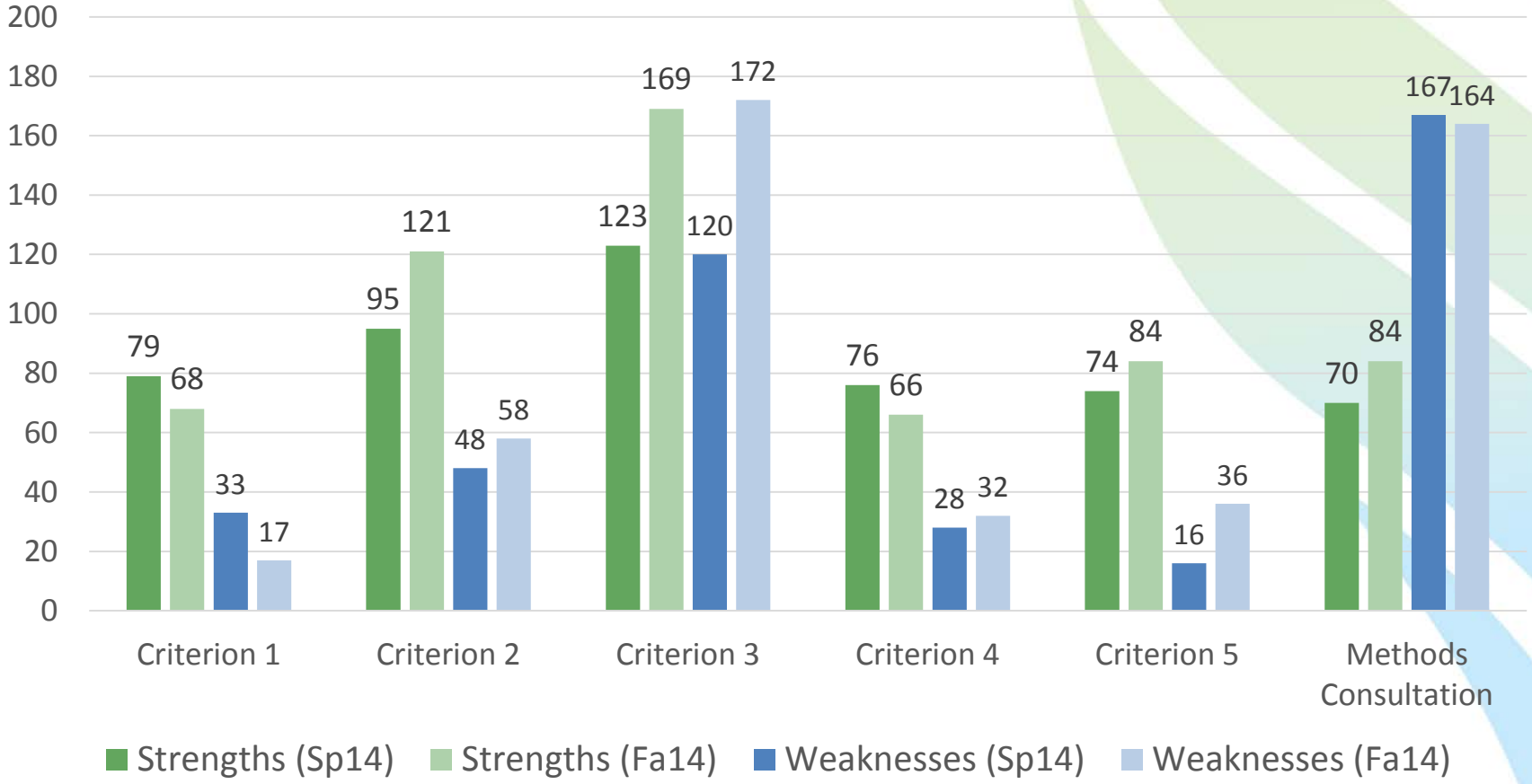
# Methods: Qualitative Analysis (Fall 2014)

- **Sampled 10 of 16 applications** based on funding status and Merit Review scores

- **Data Extraction (Strengths and Weaknesses)**
  - Methods Consultation: comments from Section 1 (Design) and Section 2 (Study Conduct and Analyses)
  - Merit Review: comments from the Technical Merit Criterion section for the three Scientific Reviewers

- **Data Coding (Strengths and Weaknesses)**
  - Identified comments from Spring and Fall 2014 Merit Review Critiques on
    - Heterogeneity of Treatment Effect (subgroup analyses)
    - Data and Safety Monitoring

# Strengths & Weaknesses Identified by Scientist Reviewers in Merit Review and Methods Consultation By Review Cycle




*N= 10 sampled applications*
*Criteria 1-5 from Merit Review (3 Scientific Reviewers)*
*Methods Consultation (1 Scientific Reviewer)*

# Summary of Findings:

- Methods Consultation identified additional methodological weaknesses and provided value for PCORI program staff

- More clarity on the scope and purpose needed
  - Focus on projects likely to be funded and opportunities for enhancement of project methods
  - Opportunity to address specific concerns from Merit Review or PCORI staff

- Indications that modifications to Merit Review can enhance review of proposal methods

# Recommendations: Methods Consultation

- Be clear with staff, merit reviewers, and methods consultants about the purpose and scope of Merit Review and Methods Consultation, including how the information will be used

- Use Methods Consultation for **targeted** consultation on methodological issues and solutions for specific concerns or questions identified in Merit Review or by PCORI program staff

- Allow time for Program Staff to thoughtfully identify applications for Methods Consultation

- Provide Methods Consultants with the Merit Review critiques (all reviewers, including patient/stakeholders) and summary statements to provide full context for methodological questions/concerns

# Other Implications

- What do we **ask for** in our Merit Review? Do we get it?
- What do we **want** from our Merit Review? Is this what we ask for?
- Revisiting guidance to applicants—are we clear in our expectations regarding methodological rigor and study design?

# Appendix

# Coding Taxonomy: Study Design

| Category | Examples |
|---|---|
| *Participants* | Study eligibility criteria, enrollment issues, recruitment settings |
| *Interventions* | Comparator intervention, timeline for implementing intervention, treatment leakage (e*xposure to multiple interventions*), treatment fidelity, intervention feasibility |
| *Outcomes* | Outcome ascertainment (f*ollow-up methods, lag time*), determination of baseline characteristics, detection bias |
| *Sample size* | Power analysis, detection of effect |
| *Treatment assignment* | Randomization, stratification variables |
| *Blinding* | Allocation concealment |
| *Design - other* | External validity/generalizability, study complexity, lack of clarity or rationale for design decisions, challenges for implementation, incentives |

# Coding Taxonomy: Study Conduct & Analyses

| Category | Examples |
|---|---|
| *Data and safety monitoring* | DSMB expertise (*particularly biostatistics*), procedures for safety monitoring |
| *Data management* | Logistical data collection issues*, d*ata cleaning, use of technology (e*lectronic medical records*), data management team expertise |
| *Statistics: missing data* | Loss to follow-up, analytic methods for handling missing data |
| *Statistics*: h*eterogeneity of treatment effect* | Treatment heterogeneity, subgroup analyses |
| *Statistics*: c*ausal inference* | Confounding, Type I & Type II error |
| *Study conduct & analyses - other* | Lack of information for analysis plan and statistical methods, specific proposed statistical methods |

# Trial Simulation and Response – Adaptive Platform Trials

**Bryan Luce, PhD, MBA**
Chief Science Officer, PCORI
**Jason Connor, PhD**
Director and Senior Statistical Scientist, Berry Consultants

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# Simulation

- **Execute trial millions of times before it is actually run**
  - Most things are done by trial and error
  - But not feasible or ethical in clinical trials, unless you simulate them
  - It's as though design team is testing every variation they can think of
  - The first time you run a trial shouldn't be the actual time you run the trial

# Simulation

- **Sample size software rarely allows for sensitivity analysis**
  - Accrual rate / accrual pattern
    - Calculate distribution for key analysis times
    - Understand what you'll know at DMC meeting times
  - Recruitment pattern
    - Is trial sensitive to filling up with Type A pts and lacking Type B
  - Role of stratification
  - Retention
  - Missing data
    - Differential missingness between arms
  - Crossovers
  - Non-proportional hazards
    - Related to when you choose to do the analysis
  - Sensitivity / specificity of test used for outcomes
  - Site-specific variation in effect size

# Simulation

- **Incredible learning tool**
  - Shows examples and process to MDs & stakeholders
  - Check decisions / common sense of execution
  - Great for debugging
  - Makes you write analysis code before any patients in
  - Makes you think about missing data, etc., sooner
  - What's the smallest effect that is significant?
    - 90% power isn't always better, if we're just identifying significant but irrelevant effects
  - Used to understand trials & trial robustness
    - Not a tool for trial prediction
    - For trialists not for Wall Street

# Simulation

- **Incredible learning tool**
  - Shows examples and process to MDs & stakeholders
  - Check decisions / common sense of execution
  - Great for debugging
  - Makes you write analysis code b[illegible]
  - Makes you think abou[illegible] sooner
  - What's the[illegible] is significant?

100% of these relevant to simple, fixed trials

always better, if we're just identifying significant but irrelevant

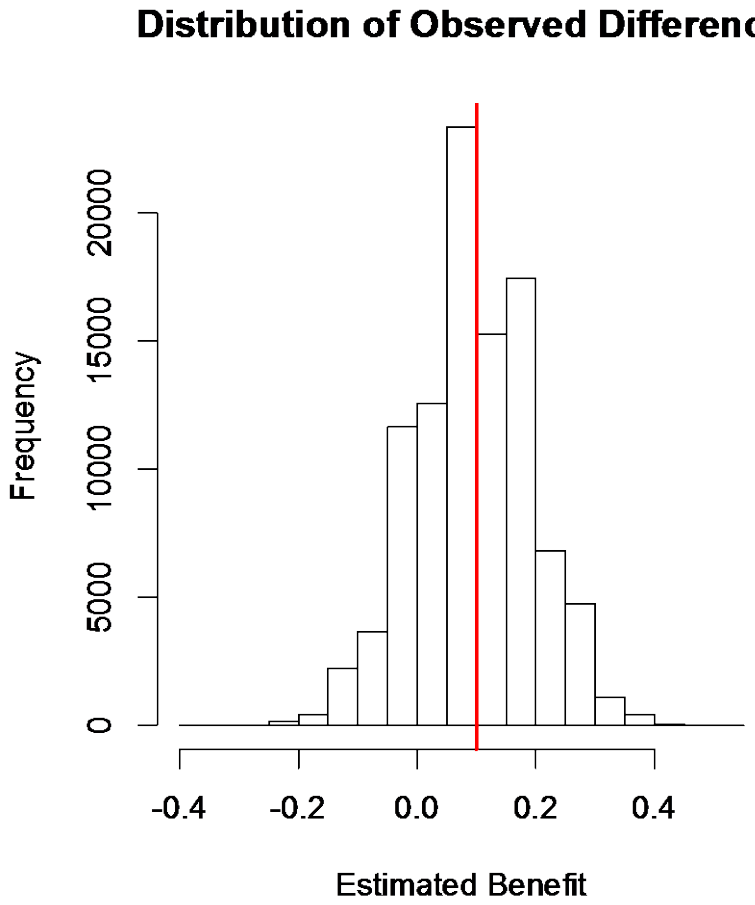
sed to understand trials & trial robustness

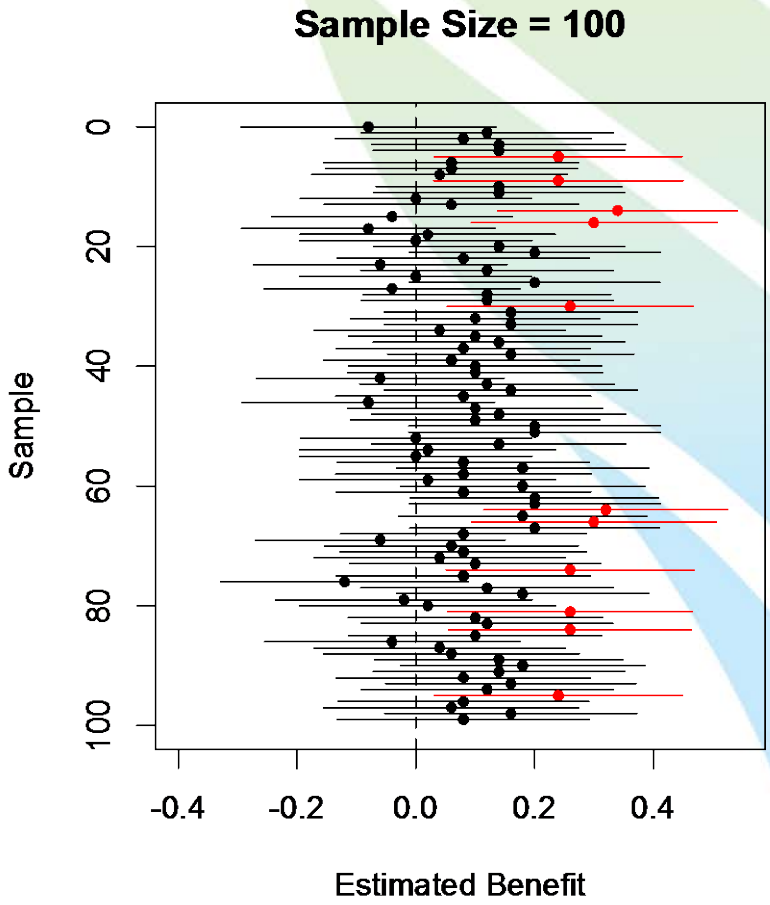
  - Not a tool for trial prediction
  - For trialists not for Wall Street

# Simulation

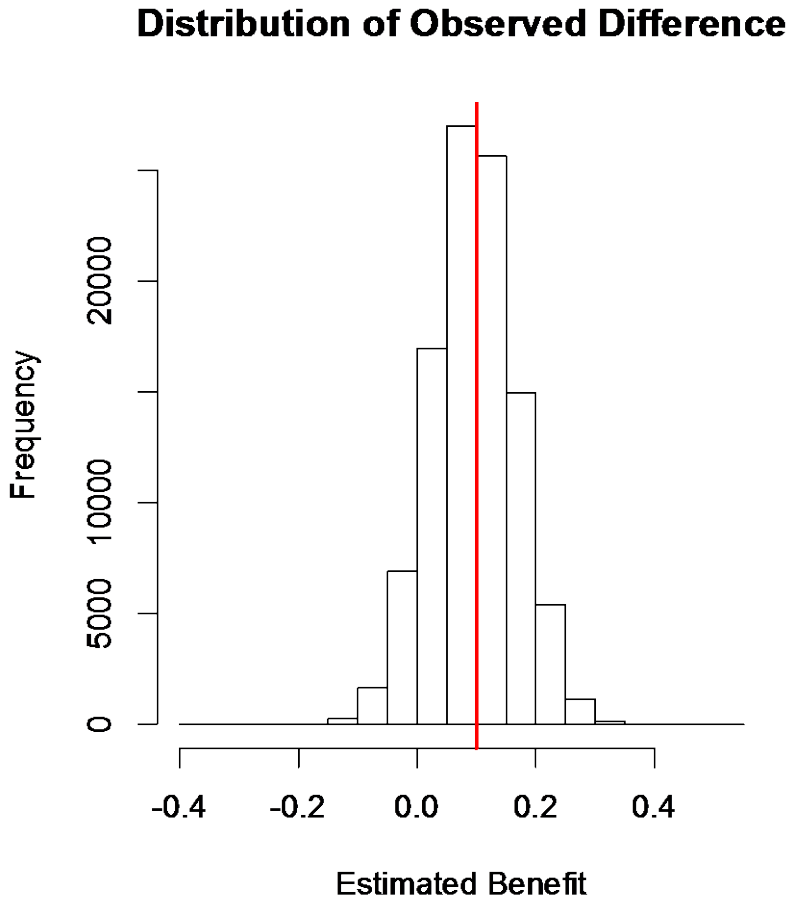
- Control:  40% response rate
- Treatment:  50% response rate
- What sample size for 90% power?

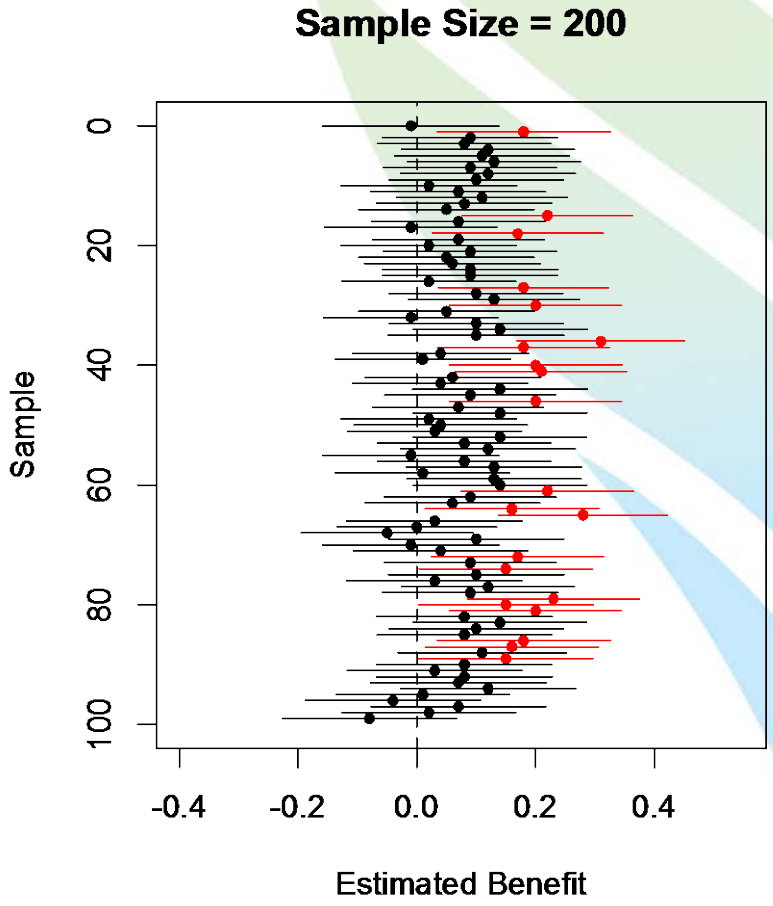
# 100 Patient Trial → 17% Power



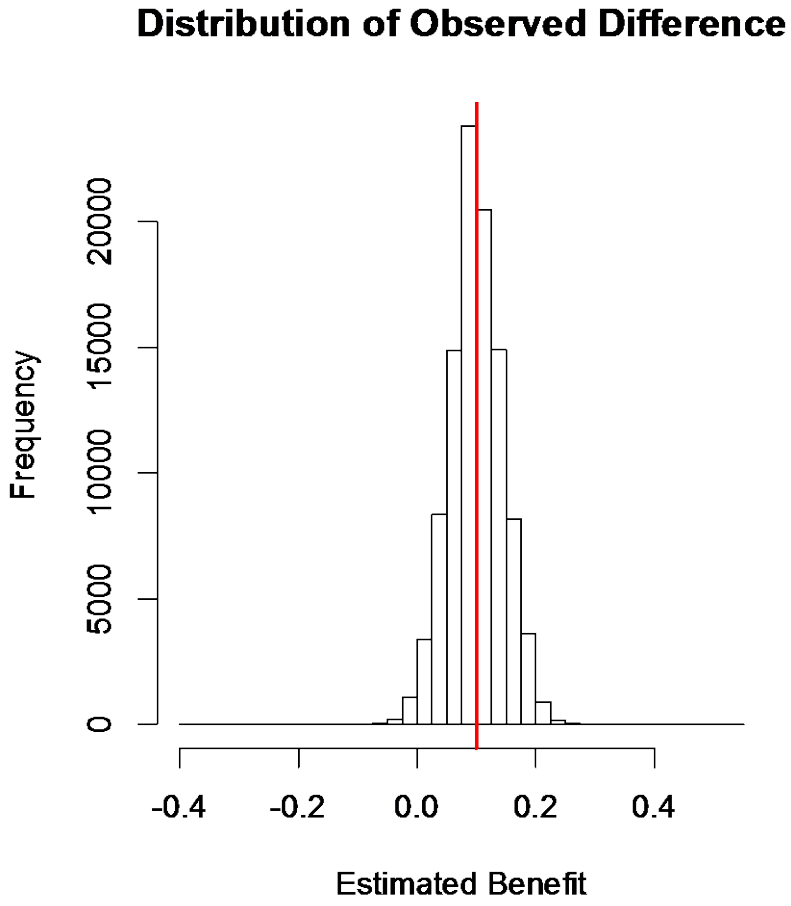



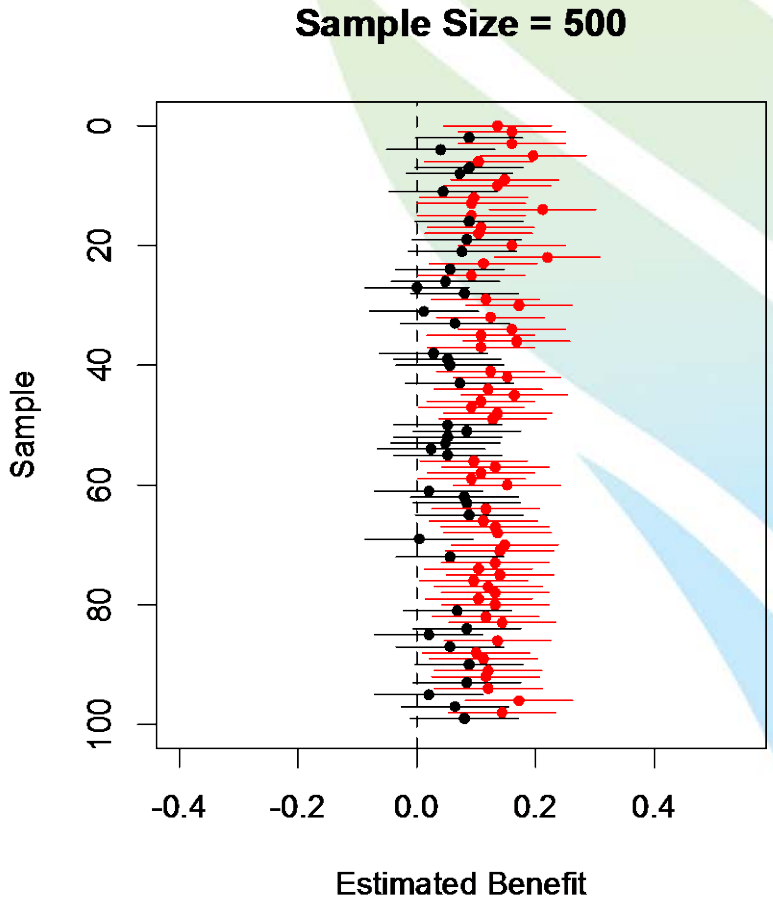
# 200 Patient Trial → 29% Power



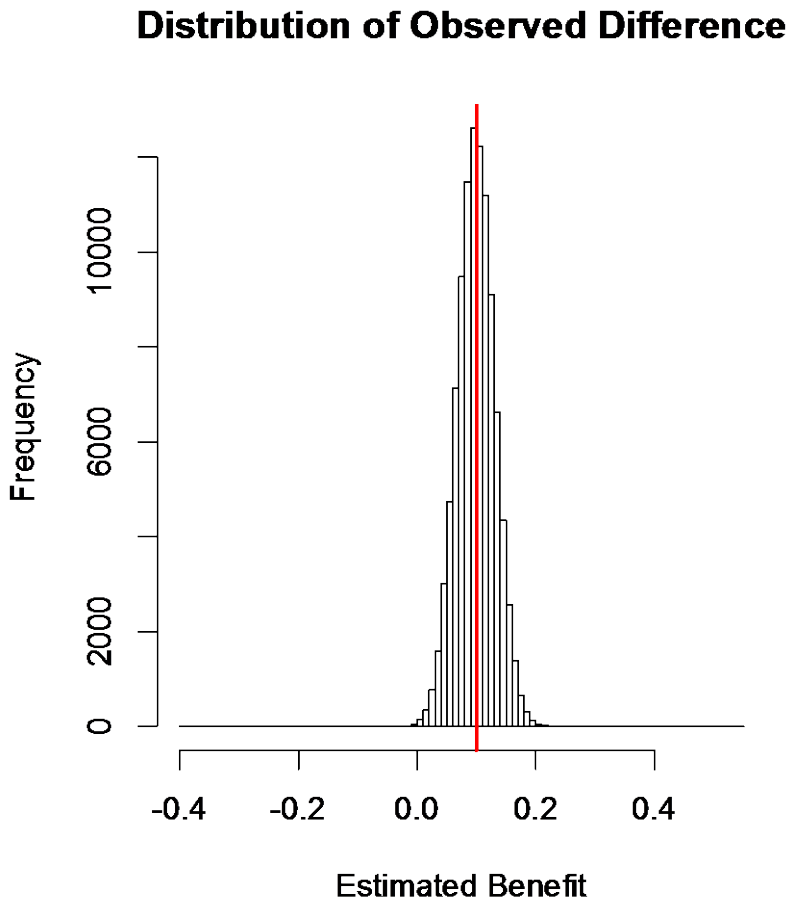



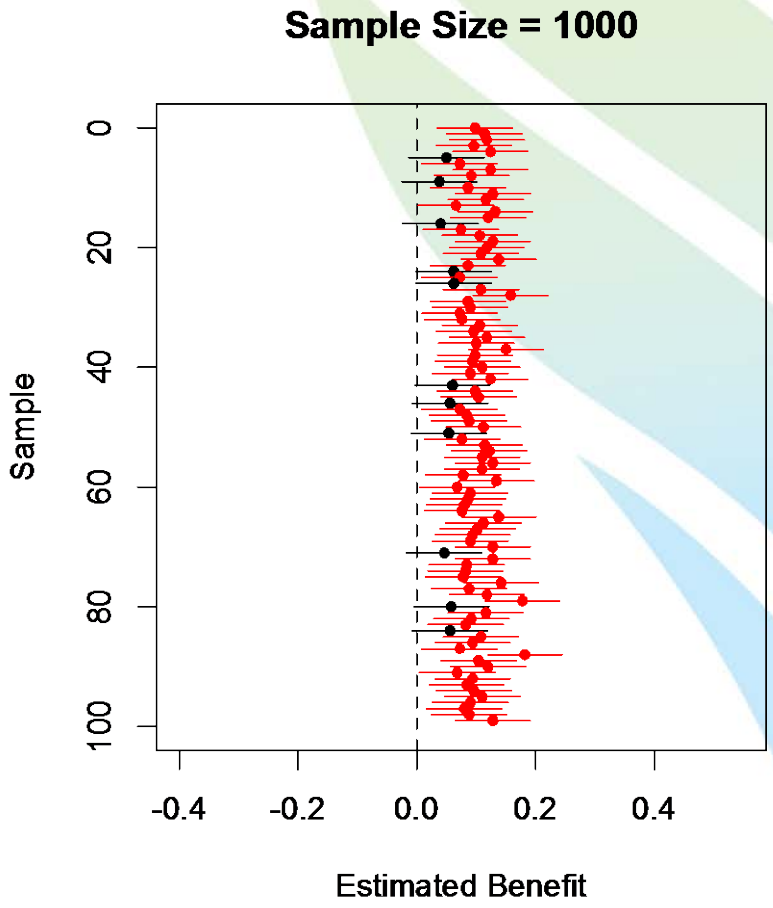
# 500 Patient Trial → 61% Power



# 1000 Patient Trial → 90% Power



# Importance of “Well Understood” Adaptations

- Real, currently enrolling NIH-funded trial
- Frequentist design uses 5 OBFs looks
  - Well understood according to 2010 FDA Draft Guidance
- Uses blinded sample size re-estimation prior to first OBF interim analysis
  - Gould & Shih Stats in Med 1998
  - Well understood, Gould & Shih Stats in Med 1998
  - Pc = 0.25 vs. Pt = 0.32 Power = 0.83
  - Pc = 0.46 vs. Pt = 0.53 Power = 0.75
  - Increase sample size if pooled rate > 31%
- What happens if there is a big effect?

# Be Careful Combining Features

- Large effect size → High pooled rate
  - 30% vs. 50% (but sample size analysis is unblinded, observe 40%)
- High pooled rate → Increase in sample size
  - From 1400 to 1650
- Increase in sample size → Delay 1st interim look
  - From 700 with data to 825 with data
  - About 4 months
- Delay 1st interim look --> Delay early stopping

# Be Careful Combining Features

- Large effect size → High pooled rate
  - 30% vs. 50% (but sample size analysis is unblinded, observe 40%)
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- UNDERSTAND effects of combining features
- SIMULATE trials

# Conclusion

- We never understand something until we do it
- We never *truly* understand something until we've explained it to someone else

# Conclusion

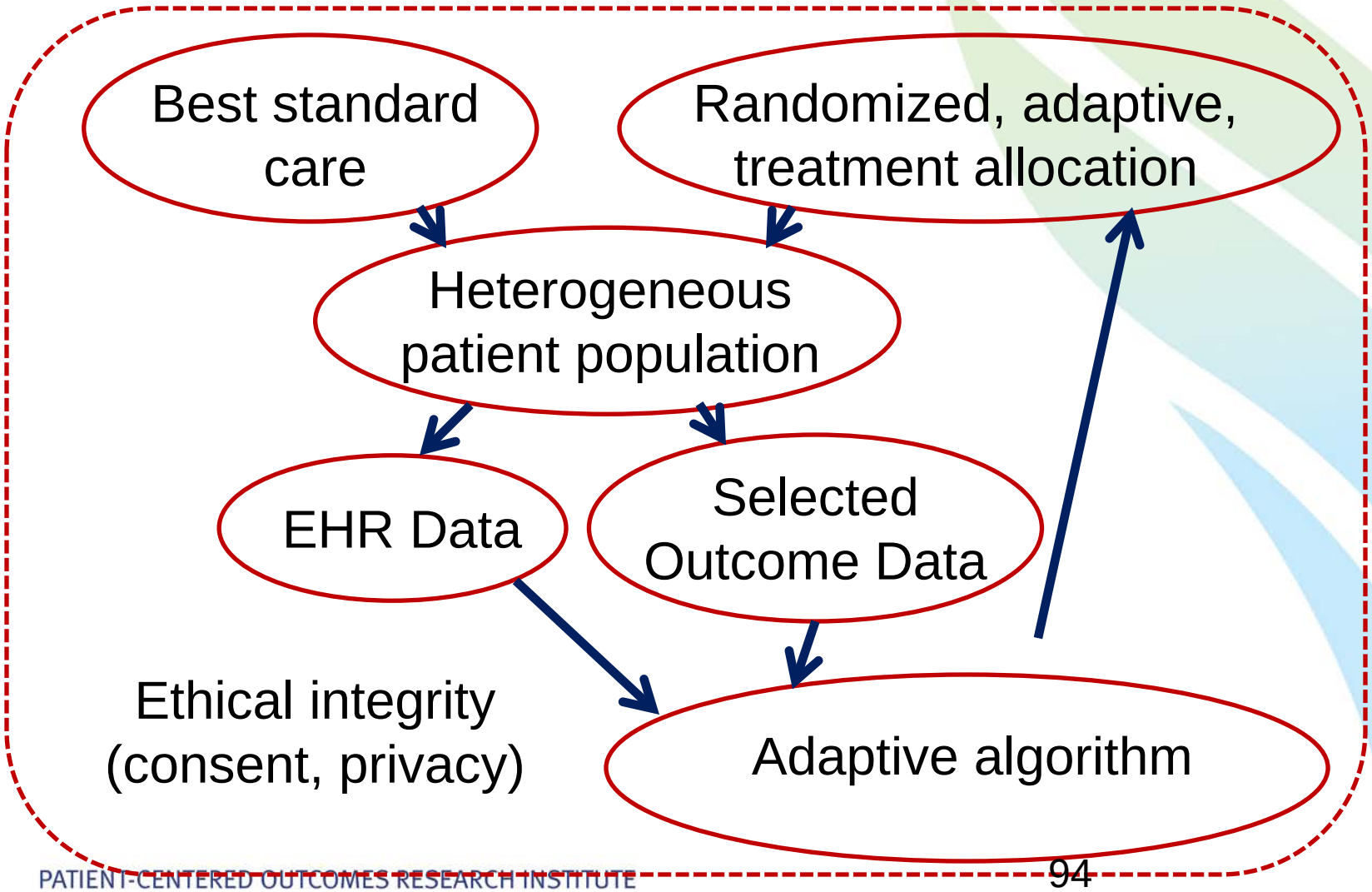
- We never understand something until we do it
- We never *truly* understand something until we've explained it to someone else
- We never understand our trial designs until we execute them
- We never *truly* understand our trial designs until we explain them to experts
- We shouldn't wait until we've spent millions of dollars and exposed 100s/1000s of patients and have no chance to improve our design to understand our trial design

# Asking the Right Question

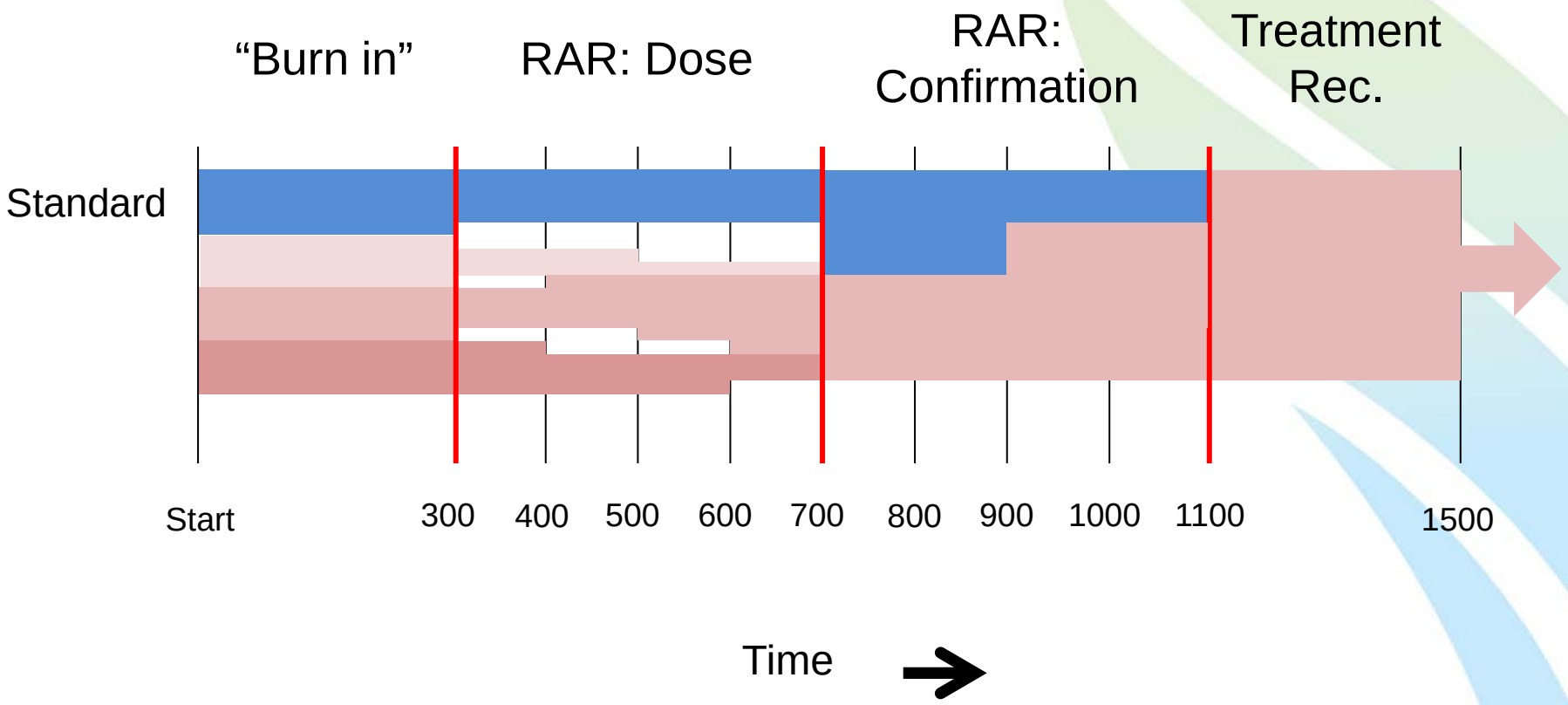
- Current Clinical Trials
- Is Drug A Effective and Safe?

- Correction Question
- What is the best treatment for Patient Z?

# The 40,000 Ft View of a Pragmatic Trial in a LHS



# Example of Learning Strategy



VIEWPOINT

# The Platform Trial
## An Efficient Strategy for Evaluating Multiple Treatments

**Scott M. Berry, PhD**
Berry Consultants LLC, Austin, Texas; and Department of Biostatistics, University of Kansas Medical Center, Kansas City.

**Jason T. Connor, PhD**
Berry Consultants LLC, Austin, Texas; and University of Central Florida College of Medicine, Orlando.

**Roger J. Lewis, MD, PhD**
Department of Emergency Medicine, Harbor-UCLA Medical Center, Torrance, California; and Berry Consultants LLC, Austin, Texas.

**The drug development enterprise** is struggling. The development of new therapies is limited by high costs, slow progress, and a high failure rate, even in the late stages of development. Clinical trials are most commonly based on a "one population, one drug, one disease" strategy, in which the clinical trial infrastructure is created to test a single treatment in a homogeneous population.

This approach has been largely unsuccessful for multiple diseases, including sepsis, dementia, and stroke. Despite promising preclinical and early human trials, there have been numerous negative phase 3 trials of treatments for Alzheimer disease[1] and more than 40 negative phase 3 trials of neuroprotectants for stroke.[2] Effective treatments for such diseases will likely require combining treatments to affect multiple targets in complex cellular pathways and, perhaps, tailoring treatments to subgroups defined by genetic, proteomic, metabolomic, or other markers.[3]

There has been increasing interest in efficient trial strategies designed to evaluate multiple treatments and combinations of treatments, in heterogeneous patient

benefits when evaluating potentially synergistic combination treatments (eg, treatment A, treatment B, treatment C, and all combinations) if the starting point is the testing of each treatment in isolation.

### What Is a Platform Trial?

A platform trial is defined by the broad goal of finding the best treatment for a disease by simultaneously investigating multiple treatments, using specialized statistical tools for allocating patients and analyzing results. The focus is on the disease rather than any particular experimental therapy. A platform trial is often intended to continue beyond the evaluation of the initial treatments and to investigate treatment combinations, to quantify differences in treatment effects in subgroups, and to treat patients as effectively as possible within the trial. Although some of the statistical tools used in platform trials are frequently used in other settings and some less so, it is the integrated application of multiple tools that allows a platform trial to address its multiple goals. The **Table** summarizes the general differences between a traditional clinical trial and a platform trial



JAMA. Published online March 23, 2015. doi:10.1001/jama.2015.2316

# Challenges in Platform Trials

- Complexity in trial implementation and planning
- Collaborations across sponsors—who initiates the planning?
- Timely communication between participating sites and data coordinating units
- Sponsors sacrifice autonomy in running the trial
- Determining shared costs
- Identifying what to report when
- iSpy2 has rules for “graduating”
- When to report subgroup results broadly?

# Platform Trial Efficiencies

- Useful for evaluating combinations of treatments and for direct comparisons between competing treatments
- Do not require a new trial infrastructure for every treatment under investigation
- Implemented or planned in many diseases
  - Breast cancer
  - Lung cancer
  - Brain cancer
  - Pandemic influenza
  - Community acquired pneumonia
  - Alzheimer's
  - Ebola
  - Melanoma
  - Scleroderma
  - President's Council of Advisors on Science and Technology (PCAST) included a call for antibiotic platform trials

# The PREPARE Consortium

- **P**latform fo**R** **E**uropean **P**reparedness **A**gainst (**R**e)emerging **E**pidemics
  - 25 million euro FP7 strategic award
- Work Package #4 – ALI$^4$CE
  - Antivirals for influenza-Like Illness? An rCt of Clinical and Cost effectiveness in primary CarE

PREPARE is funded by the European Commission under grant number 602525

# Scope of PREPARE FLU

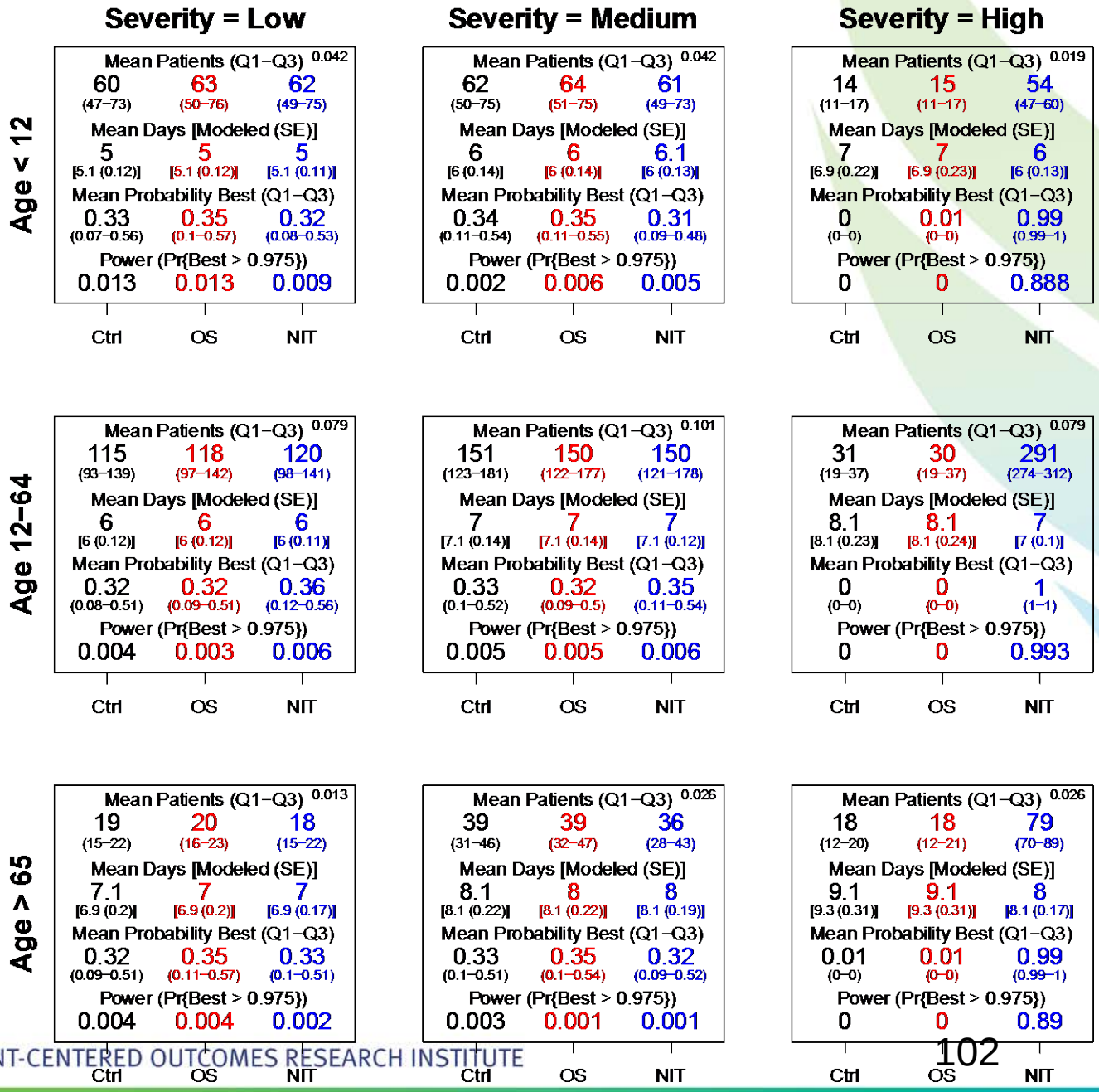
- Simultaneously considers
  - Standard of care (Paracetamol)
  - Historical antiviral (Tamiflu)
  - Newer antiviral (TBD)
- Design stratifies by different subgroups
  - Age
  - Severity
  - Duration of flu
  - Patient comorbidities
- 3x3x2x2 = 36 subgroups x 3 treatments

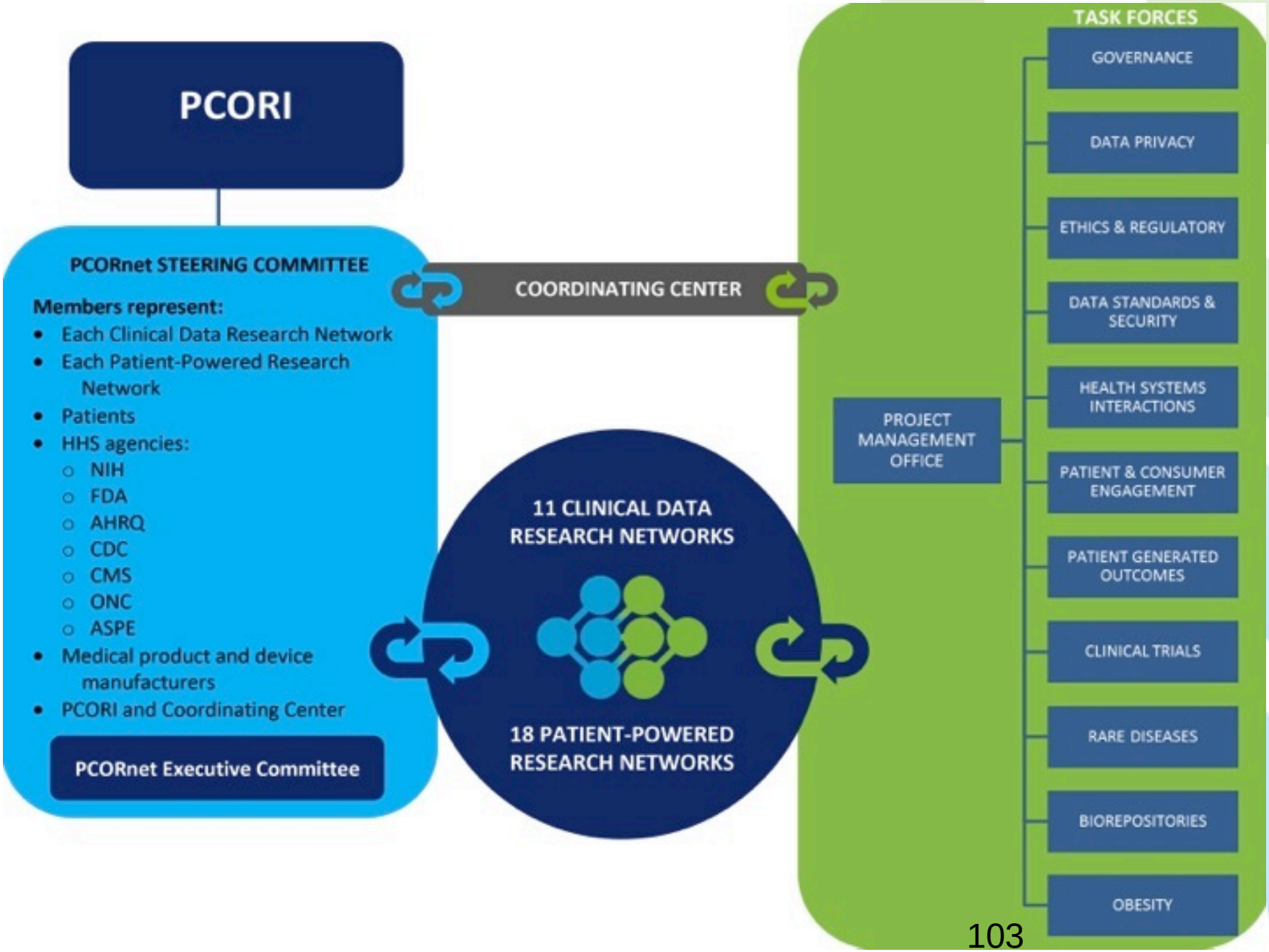
# PREPARE FLU

- Identify best treatment for each subgroup
- 4500 patients over 3 years
- Update every ~750 patients, 1 flu season
- Model time to return to usual activities
  - Shares data with smaller subgroups
- Adaptively randomize within each subgroup
  - Only after 30 patients in subgroup 10:10:10
  - Minimum 10% rand prob until 100 patients

$$R_{s,t} \propto \sqrt{\frac{\Pr(t \text{ best in } s) V(\theta_{s,t})}{n_{s,t}+1}}$$

# Operating Characteristics




PCORI
PCORnet STEERING COMMITTEE
Members represent:
Each Clinical Data Research Network
Each Patient-Powered Research Network
Patients
HHS agencies:
NIH
FDA
AHRQ
CDC
CMS
ONC
ASPE
Medical product and device manufacturers
PCORI and Coordinating Center
PCORnet Executive Committee
COORDINATING CENTER
11 CLINICAL DATA RESEARCH NETWORKS
18 PATIENT-POWERED RESEARCH NETWORKS
PROJECT MANAGEMENT OFFICE
TASK FORCES
GOVERNANCE
DATA PRIVACY
ETHICS & REGULATORY
DATA STANDARDS & SECURITY
HEALTH SYSTEMS INTERACTIONS
PATIENT & CONSUMER ENGAGEMENT
PATIENT GENERATED OUTCOMES
CLINICAL TRIALS
RARE DISEASES
BIOREPOSITORIES
OBESITY

# PCORI's Data and Safety Monitoring Plan (DSMP) Policy

**Jason Gerson, PhD**

Associate Director, CER Methods and Infrastructure, PCORI

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# Presentation Overview

- Background and context
- PCORI as funder—not sponsor—of research
- Overview of PCORI's Draft DSMP Policy
- When DSMBs are required
- Reporting DSMBs, IRBS, and PCORI
- DSMB Membership
- DSMB Meetings and PCORI Program Staff
- Request for CTAP's Input

# Background and Context

- Draft policy under development by PCORI staff in consultation with legal, IRB, and other human subjects protection experts.
- Policy does not usurp the role of Institutional Review Boards (IRBs) or other monitoring or regulatory bodies with jurisdiction over a particular research study.
- Already studies underway that have DSMPs—policy will not require existing DSMPs to be changed.

# PCORI as Funder – Not Sponsor – of Research

- Awardee institutions are responsible for the conduct of research studies funded by PCORI, including fulfilling applicable regulatory requirements (e.g., FDA) and requirements of the IRBs.

- Awardee institution should ensure that PCORI's role as the funder of the research study is accurately described in the DSMP.

- Awardee institution is responsible for ensuring that PCORI, as funder of the research study, is informed in timely manner of all recommendations/decisions/steps taken emanating from DSMP activities.

# Overview of PCORI's Draft DSMP Policy

- PCORI requires awardee institution to ensure there is a DSMP for the research study commensurate with the study's potential risks, nature, size, and complexity.
- DSMP for PCORI-funded research must be approved by the applicable IRB.
- Policy articulates minimal requirements for DSMP to: (1) identify who is responsible for monitoring study, and (2) describe DSM procedures (e.g., minimizing research-associated risk; protecting confidentiality of data; reporting adverse events and unanticipated problems)

# When DSMBs Are Required

- At a minimum, PCORI expects awardees to appoint a DSMB as part of the DSMP when:
  - An IRB or regulatory agency requires appointment of a DSMB;
  - The research study involves a high-risk intervention;
  - The research study includes a vulnerable research subject population; or
  - The research study is a multi-center trial or otherwise includes a research network.

# Reporting to DSMBs, IRBs, and PCORI

- PCORI expects awardees to notify their DSMBs and IRBs of adverse events and unanticipated problems without delay.
- PCORI expects to be kept informed of DSMP activities.
  - Every 12 months in our interim report form will be a primary mechanism for keeping PCORI apprised of DSMP-related issues.

# DSMB Membership

- Each DSMB must have members who are independent of the research study and generally have expertise in biostatistics, epidemiology, clinical trials, bioethics, and key subject areas involved in the research.
- Additionally, PCORI strongly recommends the inclusion of a patient or family representative who is independent of the research study on the DSMB.

# DSMB Meetings and PCORI Program Staff

- As the funder, PCORI is interested in the work of the DSMB that is overseeing the study. However, PCORI won't have formal representation on DSMB.
- Types of DSMB meetings: open, closed, executive.
  - Open: PCORI staff may attend, unless DSMB Chair decides their presence will inhibit discussion or compromise DSMB's independence.
  - Closed and executive: at discretion of DSMB Chair.

# Request for CTAP's Input

- Strength of recommendation to have independent patient or family representative on DSMB.
- Appropriateness of PCORI staff attending DSMB meetings.
- Other questions or comments?

# Potential Uses for Chatter

**Emma Djabali**

Program Associate, Office of the Chief Science Officer, PCORI


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# Recap and Next Steps

**Bryan Luce, PhD, MBA**

Chief Science Officer, PCORI

**Elizabeth A. Stuart, PhD, AM (Chair)**

Associate 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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# Thank You!


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