The PRAGMATIC CLINICAL TRIAL MEETS THE LEARNING HEALTHCARE SYSTEM

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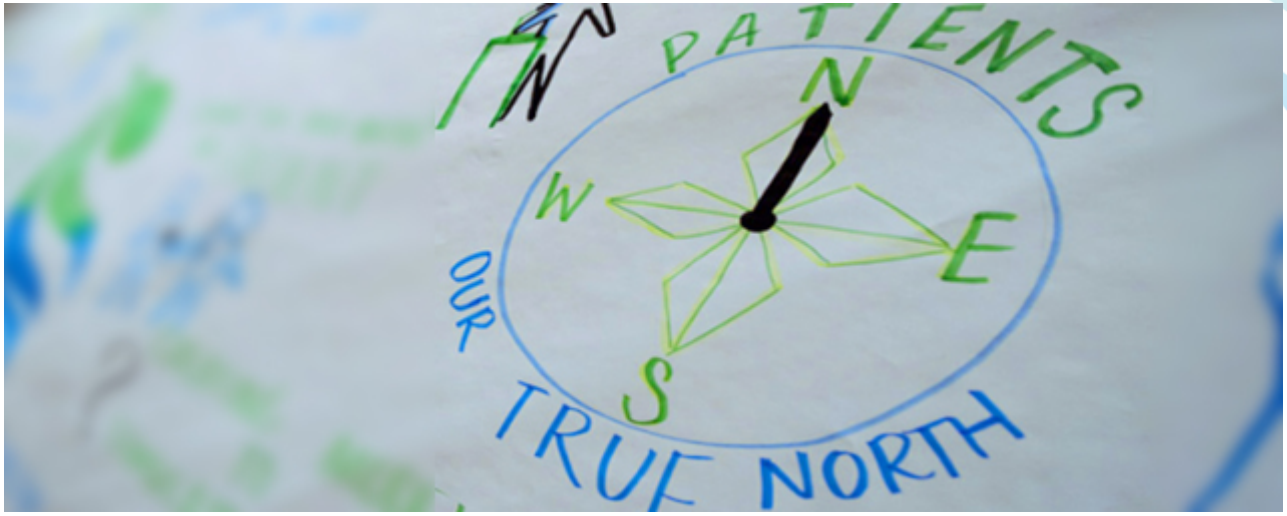
Organization of Talk

- Brief intro to PCORI, with focus on…
  - Pragmatic clinical studies (PCS) initiative
  - PCORnet (national clinical data research network of networks)
- Introduce the learning healthcare system concept
- Considerations for immediate future
  - Adapting adaptive techniques for PCSs
  - Embedding platform designs into PCORnet

About PCORI

- An independent research institute authorized by Congress in 2010 and governed by a 21-member Board of Governors representing the entire healthcare community
- Funds comparative clinical effectiveness research (CER) that engages patients and other stakeholders throughout the research process
- Seeks answers to real-world questions about what works best for patients based on their circumstances and concerns



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Pragmatic Clinical Studies

Seeks to produce information that can be directly adopted by providers:

- Compares two of more options for prevention, diagnosis, treatment, or management of a disease or symptom
- Addresses critical clinical choices faced by patients, caregivers, clinicians, and systems
- Often conducted in routine clinical settings
- Though often large, usually less complex protocols than traditional trials
- Topics of special interest from stakeholders, Institute of Medicine, Agency for Healthcare Research and Quality

Overview

- Anticipated Awards per Funding Cycle: Six to Nine
- Funds Available per Cycle: Up to $90 Million
- Maximum Project Duration: 5 Years
- Maximum Direct Costs per Project: $10 Million
- Embed PCTs into PCORnet

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Summary of PCT Features

- Randomization (individual, cluster)
- Comparative
- Real world setting
- Minimizes protocol-induced perturbations within clinical care
- Tends to answer the question “does it (an intervention) work” in routine clinical practice (the *effectiveness* question) vs. “can it work” under ideal conditions (the *efficacy* question)

First 14 PCORI Funded PCTs

- **Breast cancer screening tailored to individual risk and preferences vs. annual mammography** for detecting breast cancer and minimizing screening-related harms in women 40-80.
- **Annual vs. biennial surveillance CT scanning** in patients found to have small, potentially cancerous growths on initial CT scan.
- **Standing order entry system for guiding use of colony stimulating factor vs. usual oncology practice** for reducing over- and underuse of this medication and preventing complications in patients with breast, lung, colorectal cancer.
- **Comprehensive transitional care program of early discharge and in-home support services vs. usual care** in improving' functional status and preventing hospital readmissions and mortality in stroke survivors?
- **Primary care plus prompt referral to physical therapy and cognitive behavioral therapy vs. usual primary care** to prevent acute back pain from becoming chronic.

First 14 PCORI Pragmatic Clinical Studies

Healthy lifestyle intervention plus metformin therapy vs. health lifestyle intervention alone for reducing weight gain and metabolic problems associated with certain antipsychotic medications in youth with bipolar disorders?

Anti-TNF factor vs. anti-TNF plus low dose of methotrexate in children with Crohn's disease for induction, maintenance of remission, patient-reported outcomes, and adverse events?

Nerve blocking regional anesthesia vs general anesthesia in older adults undergoing surgery for hip fracture on acute post-operative pain, satisfaction with care, inpatient morbidity, and ability walk without assistance at 60 and 180 days, health and disability, pain, ability to return home after fracture, and mortality.

Exercise coaching program vs. usual care for older adults who have experienced a low-impact fracture as a result of a fall for preventing further injuries and improving health.

Proton-beam vs. photon-beam radiation therapy post-mastectomy in women with Stage II or III for outcomes of recurrence, mortality and cardiovascular disease complications of radiation therapy.

First 14 PCORI Pragmatic Clinical Studies

Comparing Outcomes of Antibiotics first vs Appendectomy first

Integrated Versus Referral Care for Complex Psychiatric Disorders in Rural Federally Qualified Health Centers (FQHCs)

Comparative Effectiveness of Pulmonary Embolism Prevention after Hip and Knee Replacement (PEPPER): Balancing Safety and Effectiveness

Alternative Approaches to Integrate Behavioral Health and Primary Care

PCT Design-Related Issues with which PCORI is Grappling

- PCSs pose unique challenges:
  - (Optimally) conducted within 'real world' clinical settings
  - Data systems, patients, clinicians, practice patterns highly heterogeneous
  - "usual care" (whatever that is!) is a common "comparator" arm
- Relatively few experienced PCT investigators
- How to integrate research within a living system such that it learns and adapts?
- Few have experience in applying adaptive techniques to PCTs

PCT Adaptive Initiative Under Consideration

- PCORI's Methodology Standards report includes a standard for adaptive trials
- PCORI's funding announcements encourage the submission of pragmatic trials with adaptive designs, but to date….
  - …we receive little to no adaptive designed submissions
- We surmise that:
  - Many PCT applications may benefit from considering novel trial designs
  - There may be a dearth of trialists/statisticians with such experience and/or expertise
  - Investigators with expertise may be reluctant to submit novel designs due to concern that PCORI merit review may not fully appreciate the technical approach

Types of Design Issues Under Consideration

- Trial design simulation
  - May be particularly useful for power estimation of complex designs or trials with high uncertainty across multiple key parameters
- Bayesian and other adaptive designs
  - E.g. trials with 3 (or greater) arm trials; likely new innovations and/or changing practice patterns during trial

PCORI Trial Design Initiative

- More explicitly encourage the previously-noted designs (in PFAs)
- Recruit a cadre of trial design experts: PCORI Adaptive Trial Expert Research Network "PATERN"
- Evaluate (employing PATERN) highly-scoring traditionally-designed submissions as possible candidates for a "re-design phase"
- Work with selected PIs to consider a re-design phase while….
  - …offering to fund the consultation and redesign effort, including providing extra time (e.g. 6 months)

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The National Patient-Centered Clinical Research Network

The National Patient-Centered Clinical Research Network (PCORnet)

11 Clinical Data Research Networks (71 health systems)

Health system-based networks, such as hospital systems; $76.8 million awarded

18 Patient-Powered Research Networks (80 organizations)

Patients with a single condition form a research network; $16.8 million awarded

Coordinating Center

Provides technical and logistical assistance under the direction of a steering committee and PCORI staff

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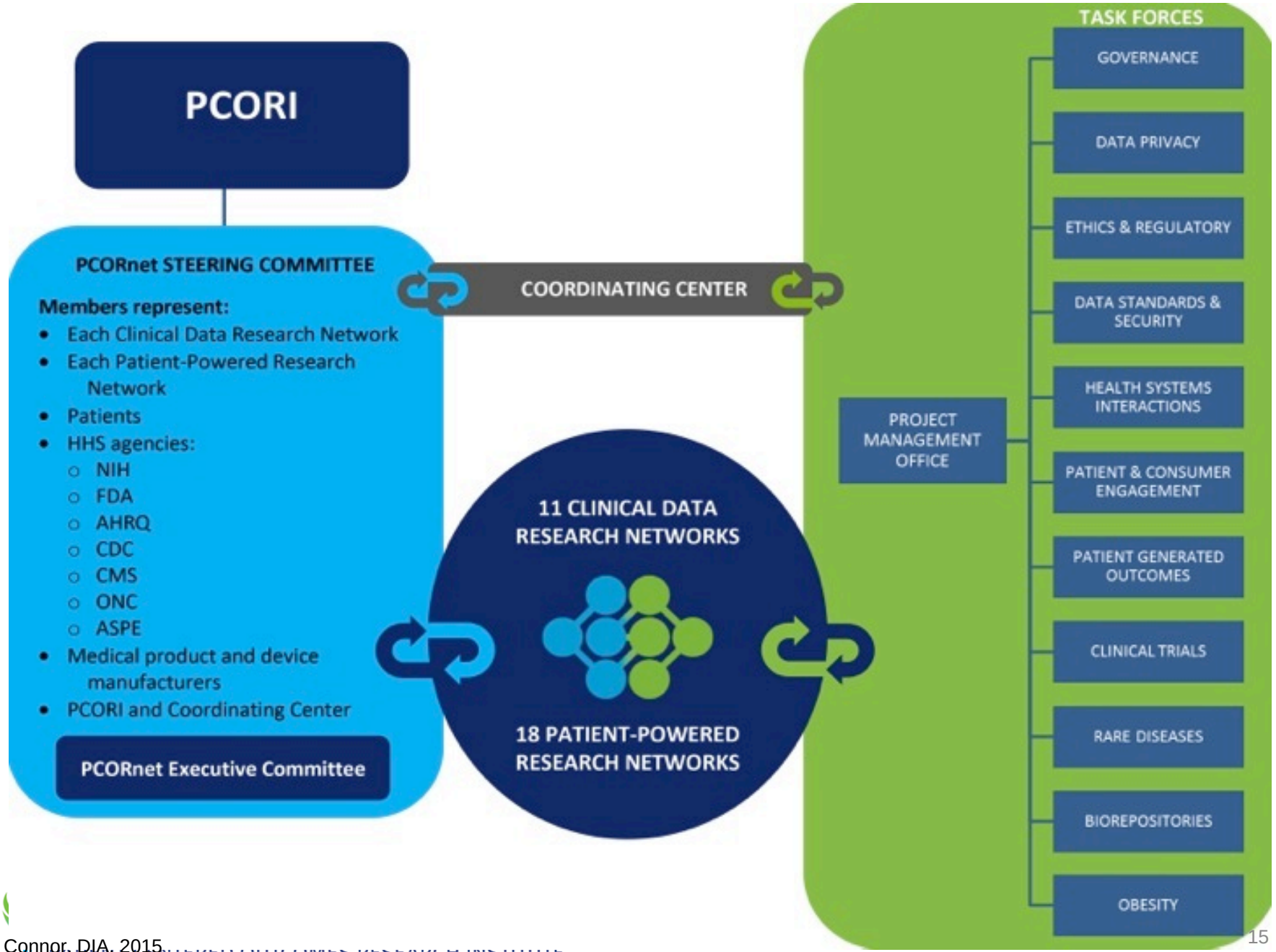
The National Patient-Centered Clinical Research Network



Connor, DIA, 2015

PCORnet:
The World's First Network Infrastructure To:

- Be based primarily on EHR data, rather than claims data
- Support both large observational studies and embedded randomized pragmatic clinical trials
- Involve patients, clinicians, and health systems leaders in governance and use of the network

PCORnet Vision

- To enable rapid, large-scale, patient-centered clinical research in real-world care delivery systems and communities.

"Research *Infrastructure* Done Differently"

PCORnet

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

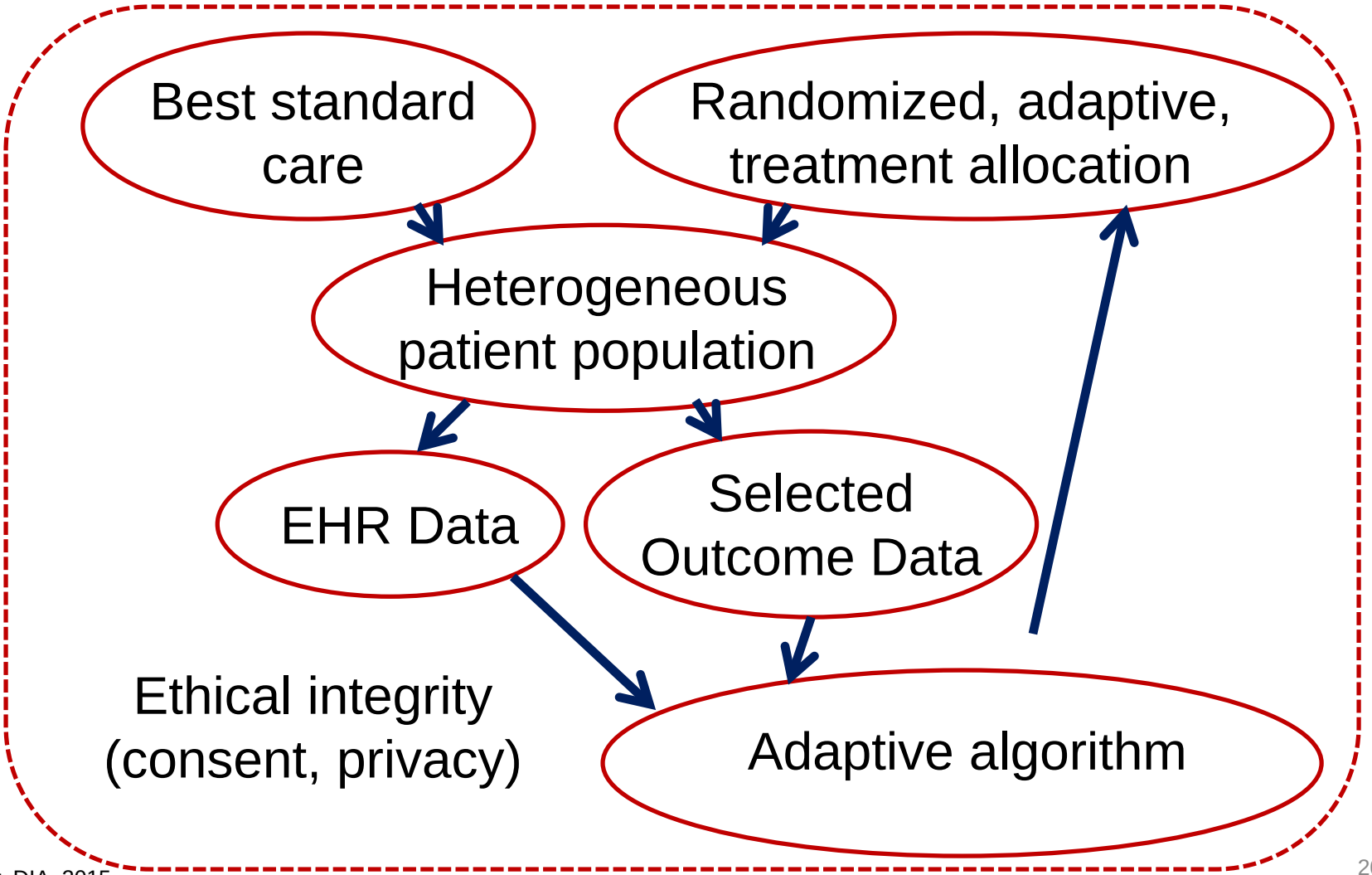
- Study Aims:
  - Compare effectiveness of two daily doses of Aspirin (81mg vs 235mg) in reducing composite of all-cause death and hospitalization for nonfatal MI, or nonfatal stroke in high-risk patients with a history of MI or documented CAD. Primary safety endpoint is major bleeding complications.
  - Develop and refine PCORnet infrastructure for conducting faster, cheaper clinical trials
- Study Design: Individual RCT
- Sample Size/Priority Population: 20,000 high-risk patients with CAD
- Outcomes:
  - Composite endpoint of all-cause mortality and hospitalization for nonfatal MI, or nonfatal stroke
  - Major bleeding complications
  - PROs
- Maximum Follow-up Time: 30 months
- Total Budget: $14,016,506

The Learning Healthcare System

"The nation needs a healthcare system that learns." (IOM 2007)

- Adaptation to the pace of change
- New clinical research paradigm
- Universal electronic health records and clinical decision support systems
- Narrowing the research-practice divide

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



VIEWPOINT

The Platform Trial
An Efficient Strategy for Evaluating Multiple Treatments

Berry, Connor, Lewis

JAMA Published online March 23, 2015

Platform Trial

- An experimental infrastructure to evaluate multiple treatments, often for a group of diseases, and intended to function continually and be productive beyond the evaluation of any individual treatment
  - Designed around a group of related diseases rather than a single treatment
  - Dynamic list of available treatments, assigned with response-adaptive randomization
  - Preferred treatments may depend on health system, patient, or disease-level characteristics

From: **The Platform Trial: An Efficient Strategy for Evaluating Multiple Treatments**

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

Table. General Characteristics of Traditional and Platform Trials[a]

Characteristic	Traditional Trial	Platform Trial
Scope	Efficacy of a single agent in a homogeneous population	Evaluating efficacy of multiple agents in a heterogeneous population; explicitly assumes treatment effects may be heterogeneous
Duration	Finite, based on time required to answer the single primary question	Potentially long-term, as long as there are suitable treatments requiring evaluation
No. of treatment groups	Prespecified and generally limited	Multiple treatment groups; the number of treatment groups and the specific treatments may change over time
Stopping rules	The entire trial may be stopped early for success or futility or harm, based on the apparent efficacy of the single experimental treatment	Individual treatment groups may be removed from the trial, based on demonstrated efficacy or futility or harm, but the trial continues, perhaps with the addition of new experimental treatment(s)
Allocation strategy	Fixed randomization	Response-adaptive randomization
Sponsor support	Supported by a single federal or industrial sponsor	The trial infrastructure may be supported by multiple federal or industrial sponsors or a combination

[a] Platform trials and similar trials may also be called basket, bucket, umbrella, or standing trials.

Table Title:

General Characteristics of Traditional and Platform Trials[a]

Key Components

- Healthcare systems with informatics systems, leadership, and commitment to learn
  - Veterans Health Administration
  - European PREPARE Consortium
  - PCORI National Patient-Centered Clinical Research Network (PCORnet)
- Multiple treatment domains and factors to be investigated
- Flexible, adaptive trial algorithm for assigning treatments, evaluating effects, and drawing conclusions (“platform trial”)

Thus, for PCORI, When the Issue is …

- …"what works best for whom under what circumstances?" across a *condition* (e.g. diabetes) of interest, as opposed to which of two interventions to employ…
- …. a response-adaptive platform design may be indicated, and…
- …may be particularly applicable for a PCORnet study

In which case….

- …PCORI *may well* be interested in talking!

THANK YOU!

Questions? Comments? Discussion?

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