Large, Simple Trials
Policy Needs: Ethics, Trial Processes

Conflicts

- I have and continue to conduct simple and complex trials funded by industry, NIH and foundations
- Industry relations can be found at www.dcri.org/about-us/conflict-of-interest
- I am PI of the Coordinating Center for the Health Systems Research Collaboratory, dedicated to pragmatic EHR based trials and Co-Chair of the Clinical Trials Transformation Initiative (CTTI) a public private partnership with FDA, academia, industry and patient advocates

Early Career

- As a Coronary Care physician I was fortunate to be around when we figured out that blood clots cause heart attacks
- A global effort quickly grew in which “tens of thousands” of people around the world were rapidly enrolled in RCTs to define the most effective treatments
- Enrollment in trials was expected of practitioners
- Risk of death from heart attack is 40% lower now than it was due to both new therapies and their implementation

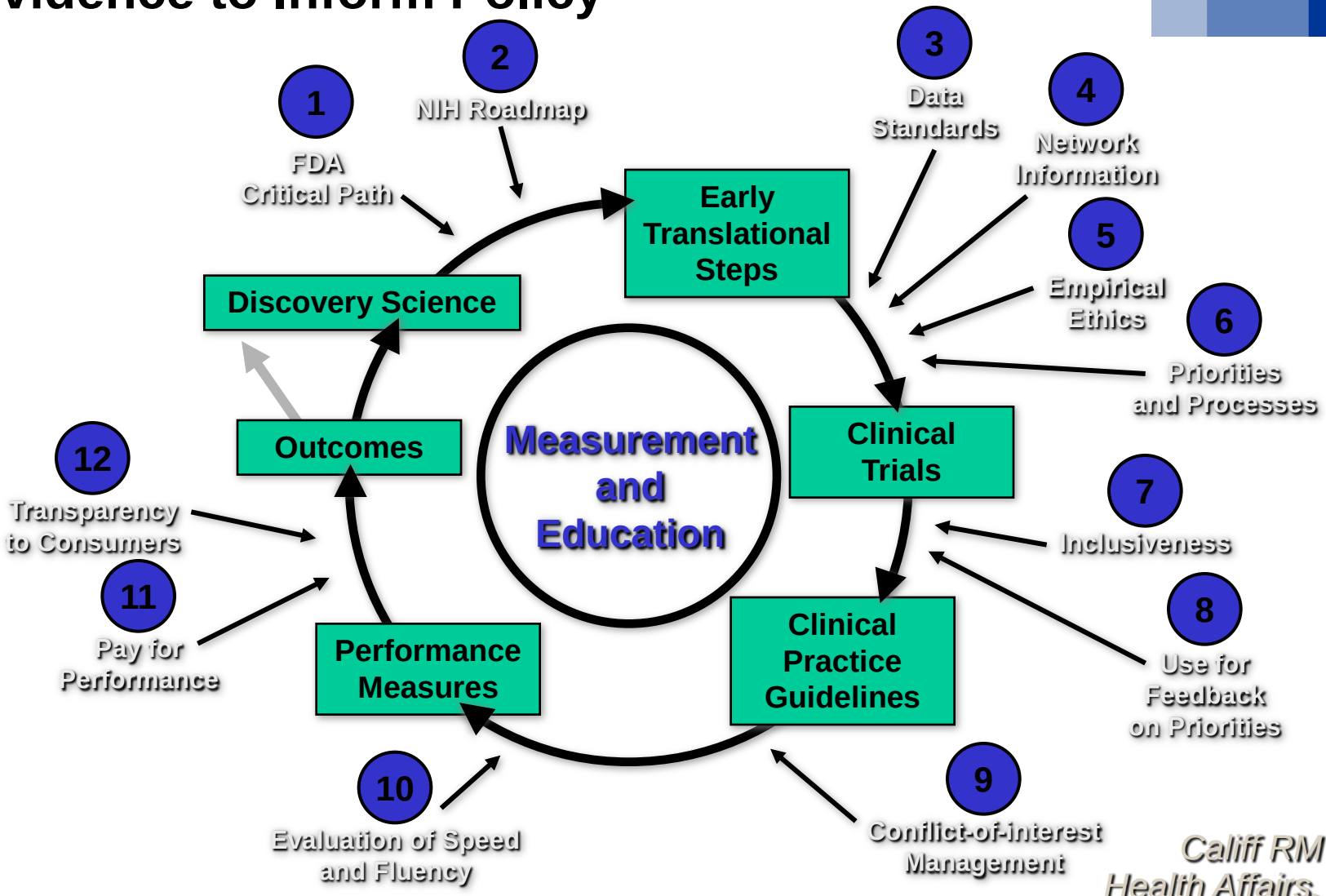
Re-engineering the Clinical Research Enterprise

Increasing Level of Difficulty

Plan and start a few demonstration networks Simplify complex regulatory systems – demonstration projects Plan for networks in place for all institutes	Funding mechanism to sustain national system through consensus of all constituents (“1% solution”) Simplified regulatory system in place for networks	**National Clinical Research System** creates effectiveness data that moves rapidly into the community AND data on outcomes and quality of care; sustained efficient infrastructure to rapidly initiate large clinical trials; scientific information for patients, families, advocacy groups
Establish repositories of biological specimens and standards for collection Standardize nomenclature, data standards, core data, forms for most major diseases Start a library of these elements shared between institutes and NLM Develop efficient network administration infrastructure at NIH Develop standards for capturing images for research	Data standards shared across NIH institutes Funding mechanisms evaluated to determine which are most efficient	ONE medical nomenclature with national data standards (agreed to by NIH, CMS, FDA, DOD, CDC) Data standards updated ‘in real time” through networks National repository of images and samples Critical national “problem list” Most efficient network funding mechanisms in place across NIH
Create NIH standards to provide “safe haven” for clinical research Inventory and evaluate existing public-private partnerships, networks, CR institutions, and regulatory systems Establish FORUM(S) of <u>all</u> stakeholders Establish standards for and pilot creation of a National Clinical Research Corps Demonstration/planning grants to enhance/evaluate/develop model networks	NIH standards for safe haven in place Regulations and ethics harmonized with FDA, CMS Public private partnership mechanisms in place 100,000 members of certified “Clinical Research Corps” Standards shared across NIH	Participation in research is a professional standard (taught in all health professions schools) Study, evaluation and training regarding clinical research a part of every medical school, nursing school, pharmacy school Clinical research practices documented and updated regularly to maintain safe haven Networks provide detailed training about network specific issues
1-3 years	4-7 years	8-10 years

Time

The Cycle of Quality: Generating Evidence to Inform Policy



Califf RM et al, Health Affairs, 2007

Conceptual Case

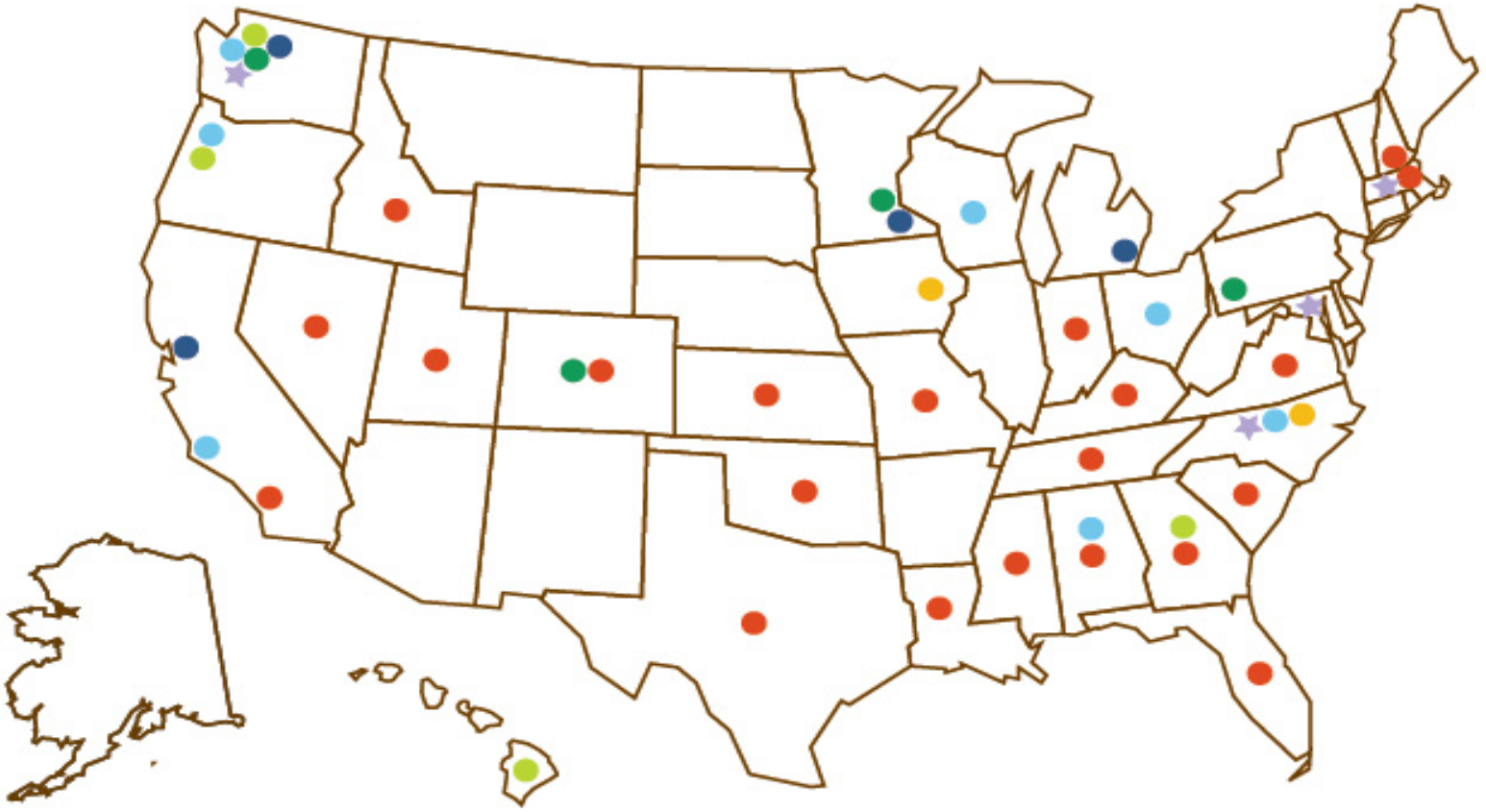
- Over 85% of clinical practice guideline recommendations are based on low quality evidence (Tricoci JAMA)
- The current clinical trials system could not possibly close the gap (Califf JAMA)
- Technology is no longer a limitation
- We know how to determine the best treatment and how to determine the best way to deliver it
- Why don’t we just do it?

Health Care Systems Collaboratory

A Virtual Home for Knowledge about Pragmatic Clinical Trials using Health Systems: www.theresearchcollaboratory.org

The Collaboratory

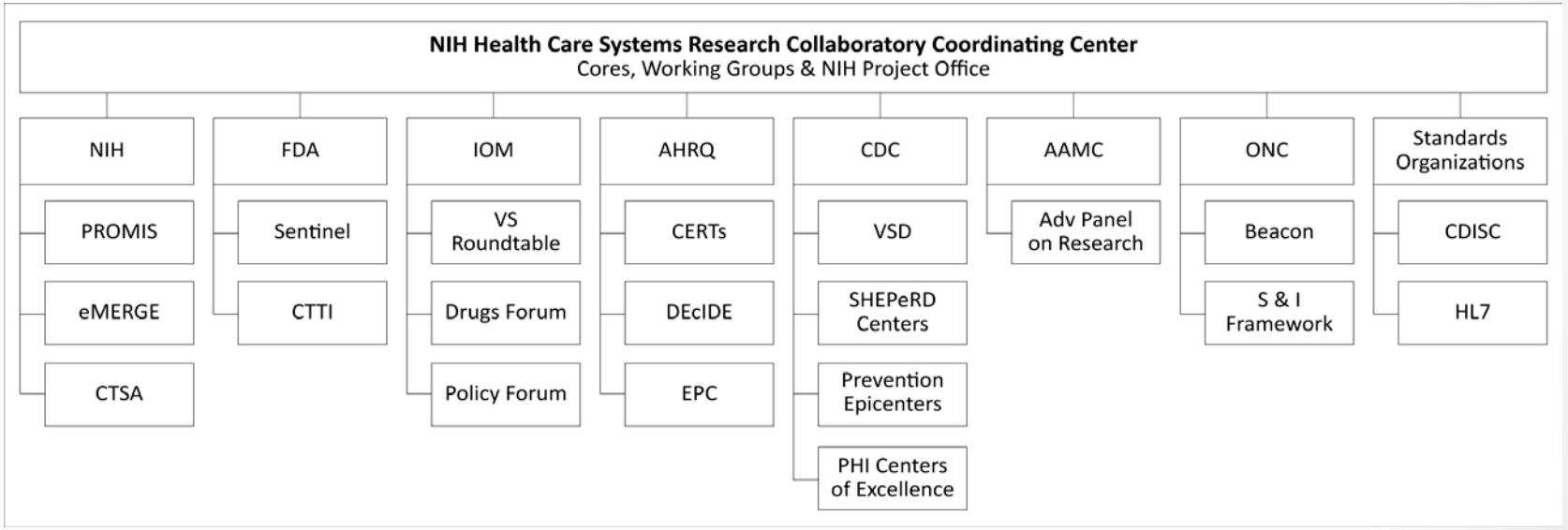
NIH Health Care System Collaboratory



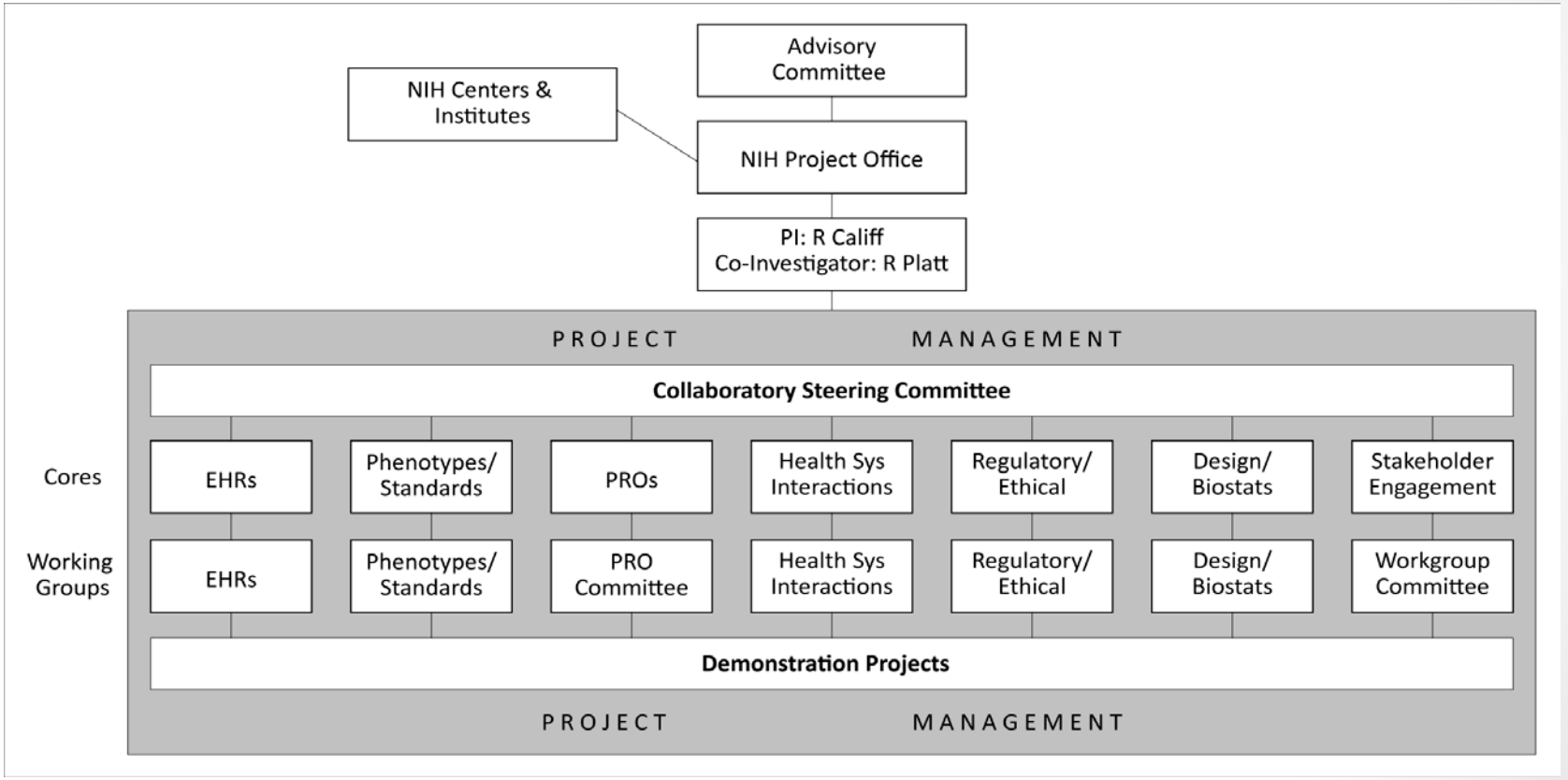
- Collaboratory Coordinating Center
- Nighttime Dose of Anti-Hypertensive Medications
- Prevent Suicide Attempt
- Reduce Mortality in End Stage Renal Disease (sites to be selected from units across all 50 states)
- Stop Colon Cancer in Priority Populations
- Chronic Pain in Primary Care
- Reduce Infections and Readmissions
- Lumbar Image Reporting and Epidemiology

Additional sites to be determined

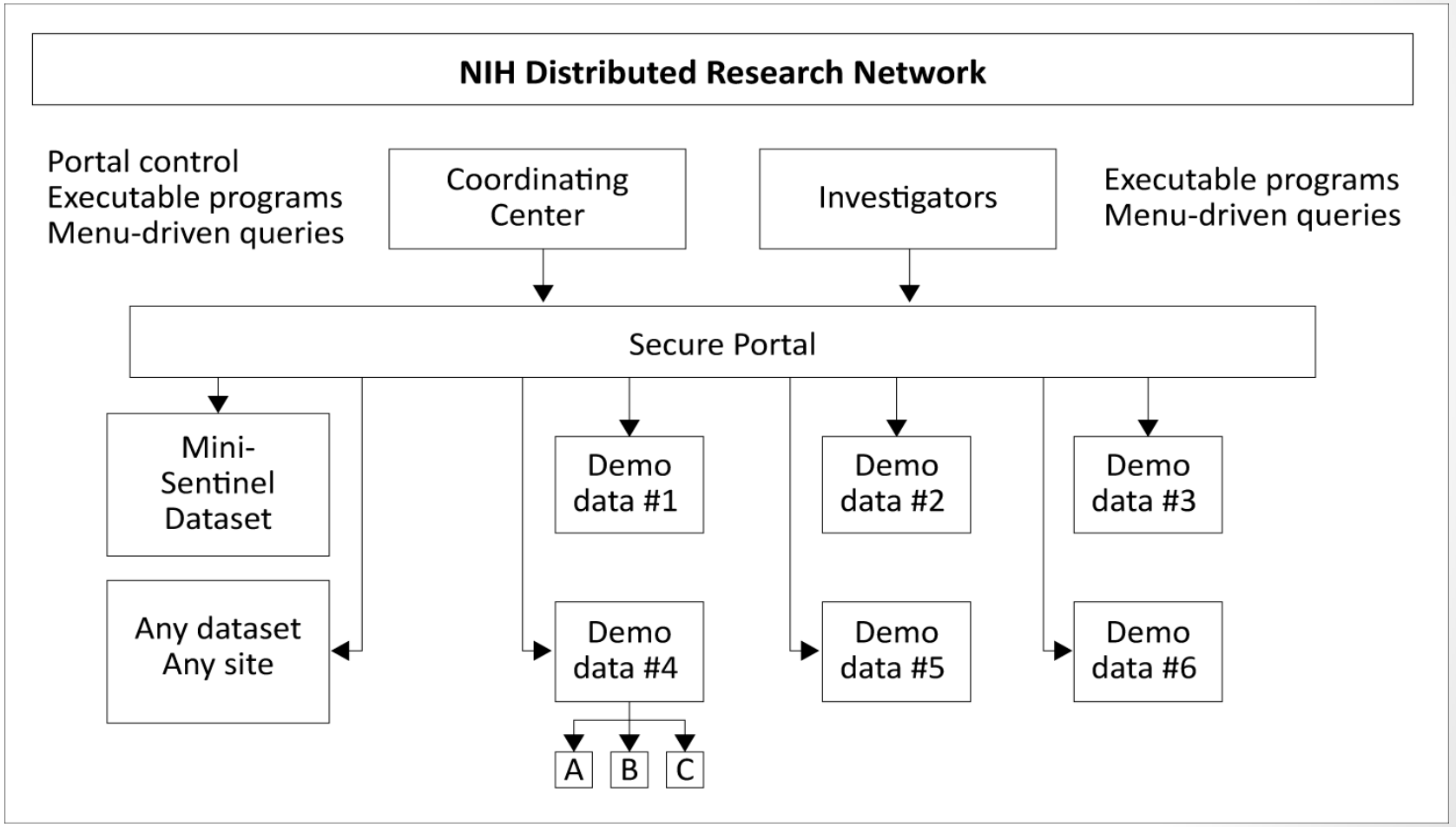
Collaboratory Coordinating Center and Stakeholder Organizations



Collaboratory Organization



NIH Distributed Research Network



A Policy Window?

- Interest expressed by leadership of
  - NIH
  - FDA
  - PCORI
  - Multiple European Governments and China
- Experience with practitioners
  - Very willing to participate if the study answers a question important to them and they don't lose money
- Experience with potential trial participants
  - Majority will participate if asked

Policy Issues--Technical

- Can we aggregate electronic records on a broad scale?
  - Yes, mini-sentinel has 130 million records and its working
- Can we identify “phenotypes” using current electronic records?
  - Yes, an increasing number of studies are doing this, but…
- What policies will move us more quickly to collection of standardized, reliable data that will serve as the backbone for a learning system, including LST’s?

Health System Interactions

- What policies will increase the motivation of health system administrators to participate in trials?
- What policies will increase the probability that trial designs are addressing questions of interest to providers and patients?
- If relevant trials are designed, what policies will increase the motivation of providers to participate in trials?

Regulatory

- Can ethical review and institutional requirements for oversight of research be streamlined without creating the perception or reality of putting research participants at risk?
- Can FDA actively encourage streamlining to get reliable answers to questions of risk benefit balance of therapeutics?
- Will key Federal agencies (NIH, CDC, VA, DOD, PCORI and OHRP) encourage novel approaches to IRB and consent approaches and involvement of patients?

Ethics

- When comparisons are made between therapies or strategies already in use and it is not known which is better and cluster randomization is used, is individual consent required?
- When comparisons are made using individual randomization, can we directly address the question of optimal consent procedures?
- Given that we now know that many people are harmed because we fail to answer obvious, critical questions about which therapies and strategies are most effective for which patients, is the underlying construct of separation of research and practice appropriate and reasonable?

Policy Window?

- The theory of the learning health system and the role of trials with adequate power to define most effective and efficient care is mature
- In theory there is no difference between theory and practice. In practice there is.
  - Yogi Berra