NIH Collaboratory
Rethinking Clinical Trials®
Health Care Systems Research Collaboratory

The NIH Collaboratory: Working with grantees and stakeholders to strengthen research”

Outline

- What is the NIH Collaboratory
  - Why it exists
  - Overview of organization
- Biostatistics and Study Design Core/Workgroup
  - Membership
  - Interaction
  - Examples of activities
- Conclusions

Background

- Traditional Explanatory (Efficacy) trials are Costly, Time-Consuming, and not Generalizable
- Results of these trials are often not implemented into clinical care
- General recognition that a more PRAGMATIC approach is needed – one that is:
  - Less Costly
  - Less Time Consuming
  - More Generalizable
  - More Sustainable

Dialogues Clin Neurosci. 2011 Jun; 13(2): 209–215.

Key features of most PCTs

Use of electronic health records (EHRs)

- EHRs allow efficient and cost-effective, recruitment, participant communication & monitoring, data collection, and follow up

Randomization at clinic or provider level

- (Cluster randomization) Protocols can be tailored to local sites and can adapt to changes in a dynamic health care environment

The Collaboratory Vision

Strengthen the national capacity to implement **cost-effective large-scale** research studies that **engage healthcare delivery organizations** as research partners

Specific Aim 1

To develop, adapt, and adopt technical and policy guidelines and best practices for the effective conduct of research studies in partnership with healthcare systems

ie, leveraging healthcare systems data and infrastructure, establish more efficient and practical systems for clinical research

Specific Aim 2

To work collaboratively with Demonstration Project teams, including their partnering healthcare systems, to develop and test an implementation plan for the proposed Demonstration Projects while providing technical, design, and coordination support

ie, launch demonstration projects in collaborative effort to "get it right"

Specific Aim 3

To disseminate Collaboratory-endorsed policies and practices and lessons learned in the Demonstration Projects to inform best practice for broad participation of healthcare systems and their patients, practitioners, and staff in research studies to improve health and care delivery

ie, to translate and make accessible lessons learned

Advisory Panel

NIH Project Officers

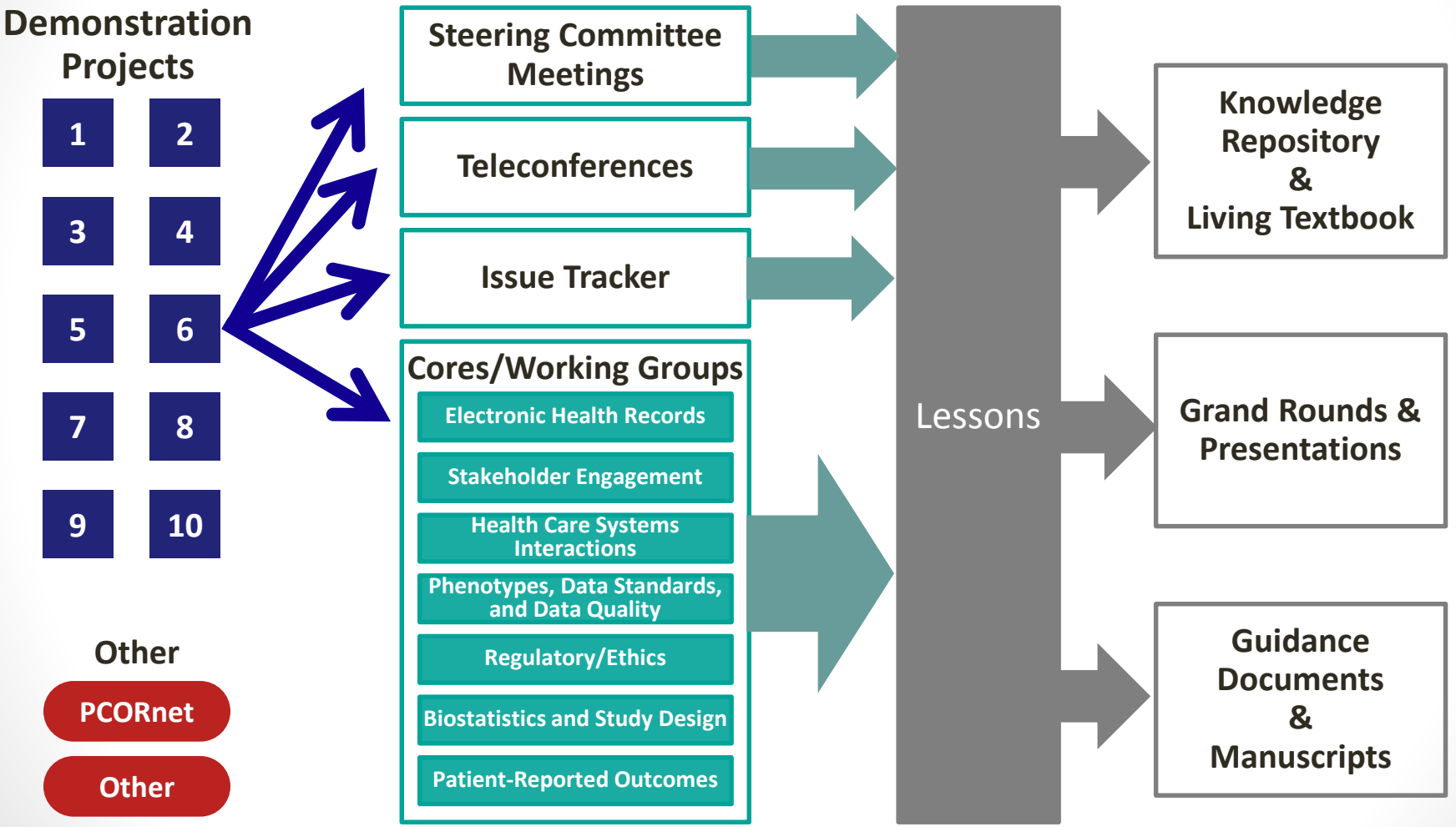
Demonstration Projects

Steering Committee

Cores/Workgroups

Coordinating Center

Flow of Information



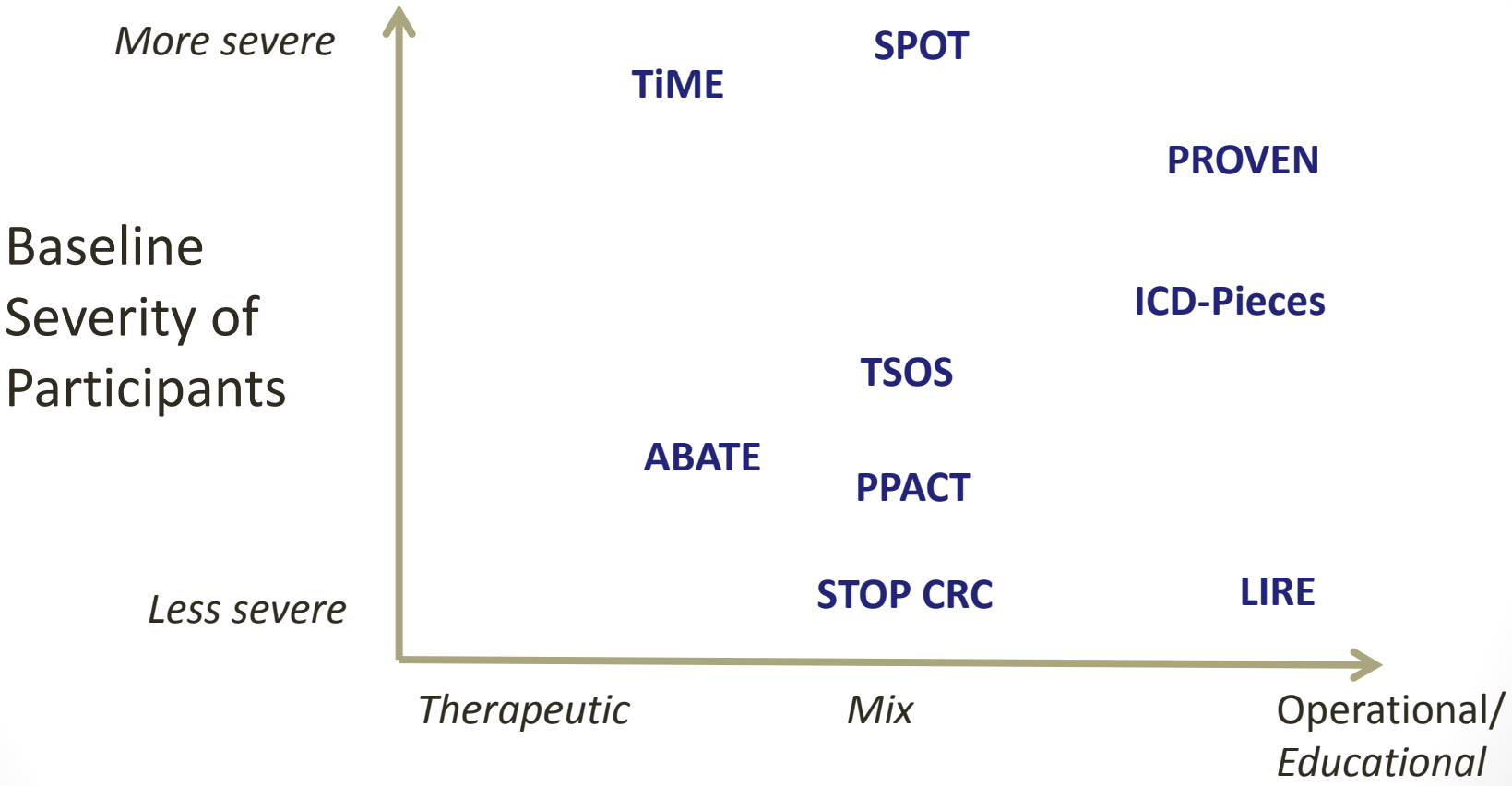
Demonstration Project Overview

10 Demonstration Projects spanning 12 NIH institutes and centers

1-year planning phase (UH2)

Implementation phase (UH3)

UH2s/UH3s by Severity and Intervention



Cores/Working Groups

- Guide and support Demonstration Projects
- Disseminate knowledge
- Chair from Coordinating Center and representatives from NIH and Demonstration Projects

Electronic Health Records

Stakeholder Engagement

Health Care Systems Interactions

Phenotypes, Data Standards, and Data Quality

Regulatory/Ethics

Biostatistics and Study Design

Patient-Reported Outcomes

Biostatistics and Study Design Core

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Who we are and our respective roles

- **Three members from Central Coordinating Center, including myself**
  - Andrea Cook, Group Health and University of Washington
  - Jessica Young, Department of Population Medicine at Harvard Medical School and the Harvard Pilgrim Health Care Institute.
  - Responsible for overall direction and cohesiveness/consistency of approach
  - Charged with ensuring communication among projects, determining best practices, and dissemination more widely
- **At least one Biostatistician from each of the demonstration projects**
  - Responsible for design and analysis of respective individual demonstration projects
  - Charged with communication and adoption of common practices across projects

Key Issues

- Study Design: Can this study be implemented with a pragmatic trial approach?
  - Is it “real world” enough to be generalized?
  - Is it practical enough to be sustained?
- Methods:
  - Cluster design
    - Unit of randomization – trade-off between contamination and sample size
    - Changes in practice over time
  - Type of randomization scheme
    - Simple, Stratified, Paired, Constrained
    - Relative power and Type I error
  - Feasibility and completeness of outcome ascertainment

Objectives

- Work with Demonstration Projects to address gaps and limitations in their statistical plans and study designs during the U2 planning phase
  - **Example**: Trade-off between risk of contamination and sample size
    - Effective sample size strongly influenced by ICC and number of clusters being randomized
    - One study changed from randomizing providers to randomizing clinics because of overlapping staff and clinic procedures (ICD-Pieces)
    - One went the other direction after preliminary assessment of potential contamination/ correlation of outcomes (PPACT)

Blood Pressure Medication Timing Study (BPMedTime): Value of UH2 Period

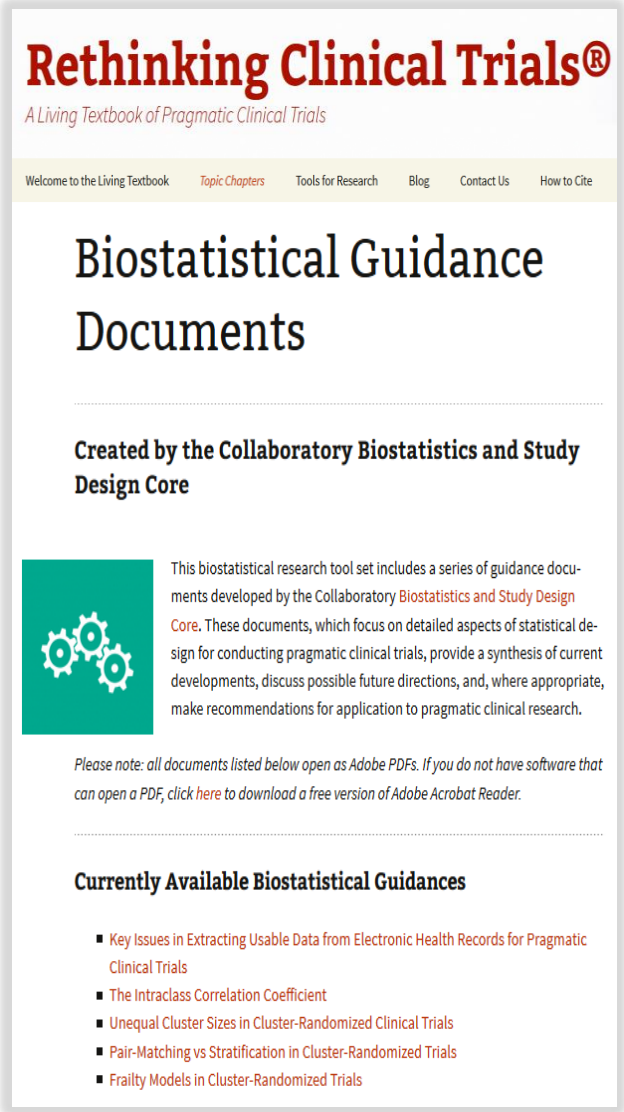
- *Randomized PCT to evaluate the risk of adverse cardiovascular events in patients who are instructed to take their currently prescribed once-daily antihypertensive medications at bedtime compared with patients who continue to take their once-daily antihypertensive medications in the morning or afternoon*
- Sample size needed was determined to be 5000 vs the original 1000 to detect lower effect rate; difficult to budget within Collaboratory
  - Alternative design and analysis plans not deemed acceptable
- Concern that potency of intervention not significant enough to re-introduce change in behavior
- Potentially better suited as a larger trial for network like PCORnet
- PI had positive feedback for the Coordinating Center, Core/Working Groups, and Collaboratory concept

Objectives

- Gather information on key methodological issues and make it accessible to the research community
- Identify areas in need of methods development and work to address these methodology challenges
- Generate new knowledge by studying the application of statistical techniques (e.g., constrained randomization) in pragmatic and cluster-randomized trial designs

Contributions to the website

- Published 5 “info sheets” on statistical considerations for PCTs (available on Knowledge Repository and Living Textbook)
  - Frailty Models in Cluster-Randomized Trials
  - Unequal Cluster Sizes in Cluster-Randomized Clinical Trials
  - Pair-Matching vs Stratification in Cluster-Randomized Trials
  - The Intraclass Correlation Coefficient (ICC)
  - Key Issues in Extracting Usable Data from Electronic Health Records for Pragmatic Clinical Trials
- Provided content for the Health Care Systems Interactions Core’s Introductory Toolkit



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Objectives

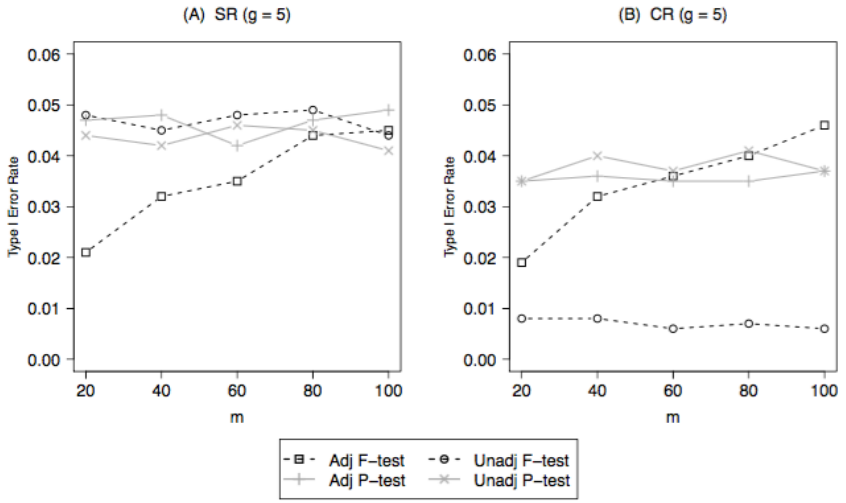
- Identify areas in need of methods development and work to address these methodology challenges
- Generate new knowledge by studying the application of statistical techniques (e.g., constrained randomization) in pragmatic and cluster-randomized trial designs

Generation of New Knowledge: Constrained Randomization

- Crude randomization risks major imbalances with smaller number of clusters
- How to balance between-cluster differences?
  - Paired
    - How to choose the pairs best to control for important predictors?
    - Implications for analyses and interpretation
  - Stratification
    - Stratify analysis on a small set of predictors
    - Ignore in analyses stage after stratifying?
  - Constrained randomization
    - Achieving balance among known potential confounders by "constraining" the possible randomization schemes to a set for which each scheme is suitably balanced, then randomly selecting one of these schemes
    - Is it an effective mechanism for controlling confounding?
    - What types of analyses work best in terms of Type 1 error and power?

Simulation studies

Lessons re: design & analysis



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To determine whether constrained randomization by itself could provide design-based control of group-level potential confounders

- What are the performance characteristics of constrained randomization (design-based randomization) with and without model-based adjustment
- Does constrained randomization have advantages over standard simple randomization?
- How many randomization schemes are needed to be able to conduct valid inference?
- How do different analysis strategies compare?
  - Model-based analysis with and without controlling for potential confounding
  - Permutation inference, both adjusted and unadjusted

Bottom line:

- **The adjusted F-test and the permutation test perform similarly and slightly better for constrained randomization relative to simple**
- **randomization in terms of power**
- Power under constrained randomization improves with decreasing candidate set size, as long as that is not too small
- Any unadjusted permutation test can still be improved by using additional analysis-based adjustment, even under constrained randomization
- In practice, investigators may desire to control more group-level characteristics than the available handful of groups will support for a model-based analysis. In these cases, permutation analysis represents a more practical alternative to the mixed-model methods.
- Constrained randomization by itself can offer design-based control of group-level potential confounders if one uses the unadjusted permutation analysis

Current and future activities

- Additional “info sheets”
  - Individual versus group-level analyses
  - GEE vs GLMM
  - ITT versus missing values
- Follow-up on constrained randomization for binary outcomes
- Continued interactions with demonstration projects

Conclusions

- Pragmatic Trials are important to be able to move research quickly into practice
- Pragmatic Trials add Complications
  - First Question: Can this study be answered using a pragmatic trial approach??
  - Study Design is essential and needs to be flexible
  - Using EHR data is valuable, but understanding the performance of all measures is important
  - Appropriate analysis taking into account design, randomization, and outcome ascertainment is key
- Lot's of open statistical questions still to be addressed

An Additional Conclusion

- The UH2/UH3 Process worked well
  - Pilot studies couldn't have been carried out without initial funding
  - The Uh2 pilot phase provided evidence that the study could be implemented
  - The simultaneous Work Group discussions provided additional input and guidance
  - Funding studies that are unlikely to be able to recruit the necessary sites/patients or to implement the intervention was avoided

Constrained Randomization (CR)
(design-based control)

- Unadjusted F-test too conservative
- Both adjusted and unadjusted Permutation tests maintain Type 1 error
- **Permutation test needs to be referenced to appropriate distribution**
- Adjusted F-test yields highest power, but adjusted permutation test is close
- Both adjusted F and adjusted permutation more powerful than unadjusted counterparts

Simple Randomization (SR)
(model-based control)

- Both F and permutation tests maintain Type 1 error rate
- Little difference in performance between F-test and permutation test
- Power of adjusted F-test competitive with adjusted tests under CR