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
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. I.e., 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.
Flow of Information

- Demonstration Projects
- Cores/Working Groups
- Teleconferences
- Issue Tracker
- Steering Committee Meetings

Lessons

- Knowledge Repository & Living Textbook
- Grand Rounds & Presentations
- Guidance Documents & Manuscripts

PCORnet

Other
Demonstration Project Overview

10 Demonstration Projects spanning 12 NIH institutes and centers

1-year planning phase (UH2)

Implementation phase (UH3)
Baseline Severity of Participants

UH2s/UH3s by Severity and Intervention

More severe

Less severe

Therapeutic Mix

Type of Intervention

Operational/Educational

TiME

SPOT

PROVEN

ICD-Pieces

ABATE

TSOS

PPACT

STOP CRC

LIRE

NIH Collaboratory
Health Care Systems Research Collaboratory

Rethinking Clinical Trials
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
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
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
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