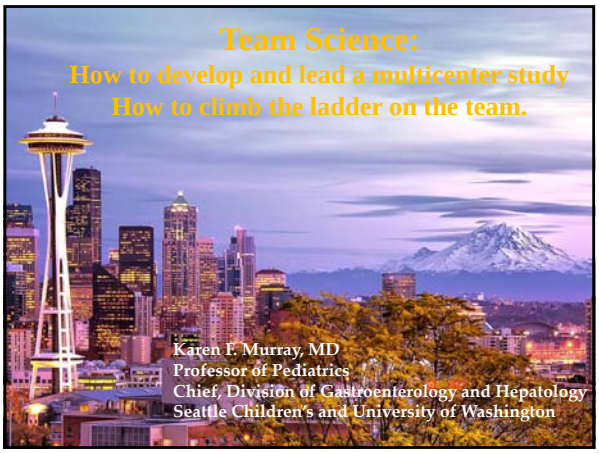


Disclosures

In the past 12 months I have had the following financial relationships relevant to this CME activity:

- NIH/NIDDK- Grant support (including salary support)
- Gilead
  - Research contract
  - Consulting contract with Seattle Children's (for DMC activity)
- Vertex- Research contract
- Merck- Stock

I do not intend to discuss any unapproved or investigational product

Multi-center Trials

- Types, advantages of, and requirements for
- Centrally sponsored multi-site, versus cooperative multi-centered
- Most common NIDDK mechanisms
- Structures of *large* federal multi-center trials
- DCCs and DMCs/DSMBs
- Pitfalls- learnings from the NCS
- Getting started and involved…my thoughts!

Multi-site/center Trials

Common Types

- Small Investigator-initiated
  - R01/R21 (NIDDK < 3 sites)
  - corporate, other
- Foundation initiated and sponsored
- Large Corporate initiated and funded
- Larger federally funded (NIDDK ≥ 3)
  - implementation planning phase (U34)
  - cooperative agreement (U01)

Multicenter Trials

Key advantages

- **Collaboration across sites**
- **Ability to recruit more subjects**
- **Inclusion of a wider diversity of subjects**
- **Potential for "power" in data collection**

Multicenter Trials

Key requirements

- **Focused aims with achievable plans**
- **Collaborative sites**
- **Standardization across sites**
- **Uniformity of procedures**
- **High Data quality and oversight**
- **Coordination, governance, and oversight plans**

	Centrally sponsored, multi-site	Cooperative, multi-center
Protocol development	Centralized	Investigators
Data control	Centralized	Investigators
Data analysis, manuscript development	Centralized	Investigators
Responsibility for quality, training	Centralized	Investigators
Site Investigators	"Contractors"	"co-Investigators"
Site collaboration needed	low	high

NIDDK Multi-Center Grants

- Hypothesis-driven
- Focused on a disease relevant to the mission of NIDDK
- Expected to improve understanding, diagnosis, prevention or treatment of the disease being studied.
- Expected to change clinical practice after 5-year funding period

- **R21/R01: Individual, few sites (NIDDK < 3)**
- **U34: Administrative establishment of U01**
- **U01: Multi-center cooperative study group agreement**

NIH- Individual or few sites

R01

- To support a discrete, specified, circumscribed project
- NIH's most commonly used grant program
- Usually no specific dollar limit (more stringent funding threshold for >500K)
- Generally awarded for 3 -5 years

R21

- Encourages new, exploratory and developmental research projects
- Pilot and feasibility studies
- Up to two years of funding
- Funding cap

Applications:

- General-use Parent Announcement (unsolicited application)
- Funding Opportunity Announcements (FOA)

NIH- Planning and Development
U34

- To support administrative activities required to begin recruitment of subjects into a multi-center trial (Protocol already final):
  - establishing the research team
  - developing the tools for data management and oversight
  - defining recruitment strategies
  - investigators brochure, manual of operations
  - establishing a data and safety monitoring plan
- Expected to result in an invitation to submit an U01 application to conduct the clinical study if U34 milestones achieved.

NIH- Cooperative Agreement
U01

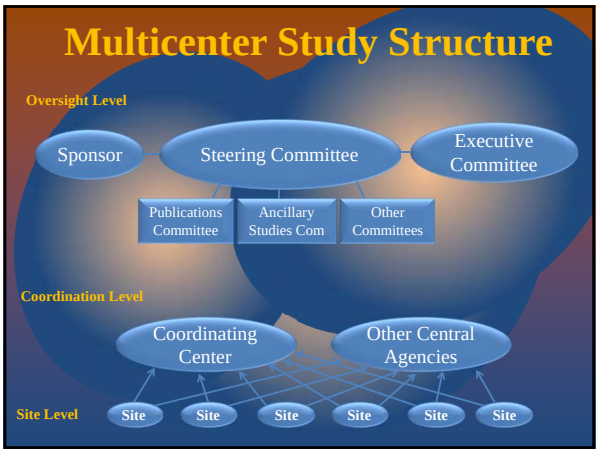
- Supports discrete, specified, circumscribed projects
- Used when substantial programmatic involvement is anticipated between the awarding Institute and Centers
- No specific dollar limit unless specified in Funding Opportunity Announcement

Applications:
- Linked to U34
- Funding Opportunity Announcements

Establishing the Multi-Center Trial Group
NIH and you

- Convergence of opportunities- ideas and funding
- Network of like-minded clinical sites more effective
- The Team
  - By competitive application or between collaborators
  - Collaborative reputation
  - Reputation for recruitment and retention
  - Inclusion of special talents/needs
- Data management plan
  - Need for a Data Coordinating Center
- Governance and oversight plan

Multicenter Study Structure



Data Coordinating Center

Conducts and coordinates the pre-, during, and post-study administrative needs of the research group, including:

- Protocol, manuals, regulatory documentation
- Site communication and meetings
- Monitors data quality
- Monitors and reports safety events
- Prepares Sponsor and DSMB Reports
- Helps with data analysis
- Helps with Manuscript preparation

Data Safety Monitoring Board

DSMB - Data Safety Monitoring Board (NIH)
DMC - Data Monitoring Committee (FDA)

Group of individuals with pertinent expertise that reviews on a regular basis accumulating clinical trial data.

Advises the sponsor regarding the continuing:

- Safety of trial subjects and those yet to be recruited
- Data quality, completeness, and timeliness
- Performance of individual centers
- Validity of the trial
- Scientific merit of the trial

Heart Special Project Committee 1967. Organization, Review and Administration of Cooperative Studies (Greenberg Report). *Contr Clin Trials*, 1988;9:137-148
Ellenberg *et al*. Practical Issues in Data Monitoring of Clinical Trials. *Stat Med* 1993;12:415-616

Data Safety Monitoring Board

All clinical trials require safety monitoring, but not all trials require monitoring by a formal committee that may be external to the trial organizers, sponsors, and investigators.

Need for a DMC/DSMB:

1. When interim analysis will improve safety:
   - a highly favorable or unfavorable result, might ethically require premature termination
   - There are safety concerns e.g. invasive treatments, expected serious toxicity
   - Studying a fragile population e.g. children, pregnant women, elderly, terminally ill, of diminished mental capacity, at elevated risk of death or other serious outcomes
   - The study is large, of long duration, and multi-center.
2. When practical
3. When can help assure scientific validity

The Establishment and Operation of Clinical Trial Data Monitoring Committees for Clinical Trial Sponsors. **DHHS, FDA, CBER, CDER, CDRH. Exp 10/31/2015**

Data Safety Monitoring Board

Usage is increasing in industry-sponsored trials because:

- Growing number with mortality or major morbidity endpoints
- Increasing collaboration between industry and government in sponsoring major clinical trials
- Heightened awareness of problems in clinical trial conduct and analysis that could lead to:
  - inaccurate and/or biased results
  - bias in determining early termination for efficacy
- Concerns of IRBs regarding ongoing trial monitoring and patient safety in multicenter trials.

Pitfalls for Multicenter trials

Learning from the National Children's Study

The NCS was a longitudinal birth cohort study examining the influence of environmental and biological factors on the health and development of children.

- Aims, scope unlikely to achieve goals
- Design too complex to achieve goals
- Not scientifically valid with new biological insights
- Investigative team not suited to tasks
  - Could not gain scientific consensus
- Management oversight not effective

Children's' Health Act of 2000 authorized NICHD to establish
Reviewed in 2008 and 2014, NRCIM, National Academic Press

Team Science: getting started

- Support of supervisor/mentor
  - Time
  - Invited as co-I, sub-I, or Trainee
    - Partner with PI in subject recruitment
    - Submit an ancillary project
  - Granted Site Principle Investigatorship
  - Introductions (the Corporate "list" and the NIH "list")
- Invited to participate in multicenter trial

  or
- Have an idea that is novel and requires more than 1 site to do

Multi-Centered Trials
Getting involved

- Secure Funding (Principle Investigator):
  - Apply for R21/R01, U34
  - Respond to RFA to U01
  - Corporate: contact sponsor of anticipated study
- Coordinator support available

Mentorship is fundamental:
inclusion, introductions, ideas and support

Multi-Center Trials
Summary

- Doing collaborative research has many advantages, but to do it well there must be significant organization and oversight.
- They can be time-intensive; junior faculty/trainees must
  - Publication authorship
  - Building reputation
  - Experience
- Getting started is about seizing or making the opportunity.

Discuss your ideas with mentors, ask for help, seek mentorship!