Team Science:
How to develop and lead a multicenter study
How to climb the ladder on the team.

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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)
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- Planning and Development
U34

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

NIH- Cooperative Agreement
U01

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

**Oversight Level**
- Sponsor
- Steering Committee
- Executive Committee

**Coordination Level**
- Publications Committee
- Ancillary Studies Comm.
- Other Committees

**Site Level**
- Coordinating Center
- Other Central Agencies

### 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

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
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, or 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

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
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 REA 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

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

Building reputation
Experience
Getting started is about seizing or making the opportunity.