Organization of Multicenter Trials

Are Oncopolitics different than other Clinical Research Politics?

Robert M. Califf, MD
Vice Chancellor for Clinical Research
Duke University
Multicenter Clinical Trials

- A complex social interaction among multiple parties
- A constant series of compromises to reach consensus on a protocol
- Millions of individual transactions among human beings (subjects, coordinators, investigators, data managers, regulators, statisticians)
- The costs are driven by the cost of valuable professional time
- It's amazing that anything gets done
- Trials are too slow, too expensive and often don’t answer the questions posed

- We have to do it better!
Key Questions

★ What staff, infrastructure and or/financial resources are allocated for Phase III clinical trials research?

★ How are quality and ethical integrity of research ensured in multicenter trials?

★ What are the issues influencing timeliness, cost-effectiveness, and impact of multi-center trials?

★ What are the lessons (short term, intermediate term, long term)?
Organization of Multicenter Clinical Trials—Key issues

- Sponsorship
- General Structure
- Site organization
- Coordinating Centers
- Decision making
- Results Reporting
Sponsorship

★ NIH

Slow, bureaucratic, doesn’t pay full expenses of doing the work
Questions determined by complex set of compromises

★ Industry

Pressure for speed, pays the bills, inefficient, often gamed to make products look good
Questions addressed by trials determined by NPV calculations (trials aren’t done if the expected result is not financially positive for the sponsor)

★ Mixed NIH and Industry

Sometimes best of both worlds, sometimes worst of both worlds
General Structure
Large Trial Organizational Structure

Executive Center
  Study Chair

Coordinating Center
  Study Co-Chair

International Data Centers
  International Co-Chair

Steering Committee
  Chairms + NCs + RDs + experts in clinical studies

DSMB

Events Review Committee

Sponsor
General Trial Structure

★ Balance of power

Sponsor, Executive Committee, Steering Committee, Site PI’s (representing subjects), DMC, ? Subjects

★ Efficiency/Ethics tradeoffs not simple

★ Behavioral rules for decision making require judgment

Fundamental issue is dealing with uncertainty on a continuous scale in the context of a requirement for binary decision making that affects many people
Critical Importance of Focusing on the Clinical Research Site (the “Cinderella” of clinical trials) as an Entity
Growth in Numbers of Active FDA-Regulated Investigators
(estimated 14% drop in US at the same time)

<table>
<thead>
<tr>
<th>Country</th>
<th>2001</th>
<th>2003</th>
<th>2006</th>
<th>5-yr Growth Rate</th>
<th>Most Recent 3-yr Growth Rate</th>
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<tbody>
<tr>
<td>Russia</td>
<td>176</td>
<td>317</td>
<td>623</td>
<td>28.8%</td>
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<tr>
<td>Poland</td>
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<td>322</td>
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<td>.8%</td>
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<tr>
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<td>145</td>
<td>464</td>
<td>48.6%</td>
<td>47.4%</td>
</tr>
</tbody>
</table>

Sources: Tufts CSDD
Investigative Site Operating Profit
(With and Without Hidden Cost Adjustments)

Reported Profit: 9%
After Adjustment*: 2%

Percent of Annual Revenue

Source: CenterWatch and Rapidtrials, July 2003. Assumes total average hidden costs per trial of $7,753
PI Turning and Experience

U.S. 'Drop-out' Investigators
- Novice: 42%
- Experienced: 58%

N = 5,356

Non-U.S. 'Drop-out' Investigators
- Novice: 75%
- Experienced: 25%

N = 3,768

Sources: Tufts CSDD
Why do we do Clinical Research?

- Research itself is a **core mission** (education, care)
- Clinical Research allows for the potential of delivery of **innovative therapies** to our patients
- Clinical Research can facilitate **service improvement**
  - Evolves the application of therapies towards best practices
- Clinical Research provides potential advantages to our patients via extra care and reduced cost care

- We do not do clinical research to generate additional income
History of Clinical Research at Duke

• As with all AMC’s, clinical research was historically more a “mom and pop” undertaking
  – Performed by each incremental faculty member
  – Uncertain cost tracking and inconsistent management
  – Back room deals- ….I’ll waive the professional fee….

• Slow centralization of some support function offices, though most were not service-oriented
  – Contracts
  – IRB
Duke’s Recent View of Clinical Research

• As a result of:
  – Risk mapping: Increased regulatory requirements
  – Growing budget constraints in School of Medicine
  – Uncertain academic output
  – Compliance concerns

• Close examination by leadership and formation of an empowered taskforce to fundamentally change the construct- including realignment of clinical research with the clinical mission.
Define the Core Principles

• Clinical research on our patients is a professional activity
  – Common standards, policy and procedure
  – Training, budgeting, trial performance and review
  – Appropriate scientific and economic impact review
  – Creation of a (supportive and educated) community

• Efficiency is an important component
  – Goal: cover expenses, easy for our patients and their caregivers, competitive in the market

• Full and informed compliance
Structure

• Basic research unit is the SBR (site based research unit)
• SBR Functions:
  – Economic approval of each planned and ongoing study
  – Scientific review of each planned and ongoing study
  – Human resources for all non-faculty research staff
  – Orientation/oversight- general and protocol specific
  – Trial execution
• Includes
  – Physician/Nurse faculty, CRA’s, assistants
• Leaders (3)
  – Faculty Lead, lead CRA, Administrator
• Maximum/minimum Size
How it Works

• CRSO- Clinical Research Support Office
  – Rules and Tools
  – IT (Velos) deployment
  – Management reports, revenue cycle reports

• SBR’s
  – Budget, ongoing review, management

• Core Support Functions
  – Contracts (Federal and non-federal), IRB, CRSO,

• Duke Medicine: Operational Oversight
  – (New) Vice Dean for Clinical Research
  – VP Medical Affairs (representing DUHS, the clinical enterprise)
SBR Key Principles Document

• **Guiding Principles**
  – • Scientifically aligned with the interests of the faculty and the mission of the Depts and the SOM.
  – • Compliant with applicable regulatory requirements and standards for site-based research.
  – • Financially transparent and accountable with balanced budgets that include all the costs and supports for the research.
  – • Conducted by individuals with the appropriate qualifications, training, and certification.

• **Structure and Organization of Site-Based Research Groups**
  – Site-Based Research (SBR) groups will be the organizing structure for the faculty and staff who conduct clinical research in which a Duke Medicine entity is the investigative site for the research or a Duke faculty member is responsible for a research activity that directly touches patients or tissues from patients.
  – The SBR will serve as the organizational home for site-based research in a particular therapeutic area. The SBR will be the operating and business unit responsible for the integrity, financial accountability, regulatory compliance, quality and academic productivity of research involving human subjects. Study selection decisions will be made within the SBRs, study coordinators and other clinical research staff will be hired and supervised within the SBRs, and the flow of funds associated with individual studies will occur within the SBRs.

• **Each SBR will consist of the following Components/positions**
  – • Group of faculty members in a particular therapeutic area who are involved in the enrollment of Duke patients in clinical research studies
  – • Group of study coordinators and research staff (i.e., regulatory staff, clinical trial assistants, etc.) who are specifically aligned with a group of faculty
  – • Faculty Advisory Board
  – • Director/Faculty Leader
  – • Lead Study Coordinator
  – • Financial Manager
The Essence of an SBR Group

• Provides intellectual focus for a group of investigators interested in similar medical issues
• Provides economy of scale in infrastructure
  – Regulatory compliance
  – Study coordinator efficiency and career ladder
  – Scalable investments in IT
  – Influence with health system/hospital
  – Sponsor relationships
• Provides nexus for balancing portfolio
  – Government and industry
  – Academic interest and financial solvency
  – Variable mixes of time and commitment of practitioners
Coordinating Centers

★ Academic Medical Centers
Tend to be inefficient with limited operational capabilities

★ CRO’s
Essentially work as extensions of the sponsor
“Arms and legs” – begs the question: “where’s the head?”

★ Non-profit corporations/Academic Research Organizations (AROs)
Focus on efficiency of CRO with mission of AMC (public good)
In a trend that has received surprisingly little attention, contract research organizations (CROs) have gradually taken over much of academia’s traditional role in drug development over the past decade. They’ve been able to do $500 million each (see Fig. 1). In 2005, a Bloomberg News report revealed the inadequate conditions and minimal oversight at a phase 1 and 2 clinical trials unit housed in a converted...
Core Elements of the ARO

Providing INTELLECTUAL Leadership
- Trial design expertise—epidemiology, pathophysiological interactions, scientific input into protocol
- Statistical expertise—sample size, data analysis design
- Outcomes research
- Communications, manuscripts, dissemination into practice, education

Infrastructure/Support Functions
- Finance
- Human Resources
- Information Technology
- Business Development
- Quality Assurance
- Contracts

Harnessing DATA
- Gathering data
- Transmitting data
- Storing and managing data
- Maintaining data integrity
- Analyzing data

Coordination/Planning
- At the enterprise level—COO
- At the project level—project leaders

Selecting, Delivering, and Maintaining SITES
- Site identification and recruitment
- Site management
- Clinical monitoring
- Patient enrollment
- Site training & development
Decision Making

- Key role of PI(s) and Executive Committee
- Many industry trials have no independent PI or Executive Committee
- Even in “ideal architecture” decision making involves a complex social interaction
- In the end the sponsor (entity funding the research) holds the trump card of discontinuing funding
Contracts—The Bottom Line of Societal Expectations

⭐ Takes much longer than IRB

⭐ The “Big 4” are always the issue
   Confidentiality, indemnification, intellectual property, publication

⭐ Our most prestigious academic centers
   Do not require that the results of a trial are published in their contracts!
   Routinely sign agreements to keep plans for human experiments secret!
   Do not require trial architecture that ensures protection from suppression of negative results!
Turmoil in Clinical Research: Research Agreements between AMCs and Industry

Do research agreements between medical schools and industry sponsors adhere to the standards embodied in the new ICMJE guidelines?

“We encourage investigators to use the revised ICMJE requirements…to guide the negotiation of research contracts.”

JAMA. 2001;286:1232-1234.
--Schulman KA, et al. NEJM 2002;347:1335
### Conflict of Interest in Clinical Research: Research Agreements between AMCs and Industry

Schulman KA, et al. NEJM 2002;347:1335

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<td>(Interquartile Range)</td>
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<td>Agreement requires an independent data and safety monitoring board</td>
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## COI Disclosure in Stent Trials

Weinfurt KP; PLOS 1, May 7th, 2008

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*Data are expressed as n (%). The number of author instances is the sum of the number of authors from all articles in the database.
†p = 0.04 from χ² tests for comparisons between research articles and other articles.

doi:10.1371/journal.pone.0002128.t002
Fractured Decision Making and Poor System Alignment Leads to Massively Excessive Costs
Sensible approaches for reducing clinical trial costs

Eric L Eisenstein\textsuperscript{a}, Rory Collins\textsuperscript{b}, Beena S Cracknell\textsuperscript{c}, Oscar Podesta\textsuperscript{d}, Elizabeth D Reid\textsuperscript{a}, Peter Sandercock\textsuperscript{g}, Yuriy Shakhov\textsuperscript{f}, Michael L Terrin\textsuperscript{b}, Mary Ann Sellers\textsuperscript{a}, Robert M Califf\textsuperscript{h}, Christopher B Granger\textsuperscript{a} and Rafael Diaz\textsuperscript{j}
Sensible Approaches to Reducing Trial Costs

- Took a clinical outcomes trial protocol
- In a committee with industry, government, and academic representation examined the key drivers of cost
- Used 3 structural designs to achieve the same primary outcomes measure
- Compared the costs
Sources of Research Funds

US Biomedical Research Funding

- 1994: $37.1
- 2003: $94.3

Phase 1-4 Clinical Trial Funding by Industry

- 1994: 33%
- 2003: 52%

Moses III H, JAMA, 2005
Clinical Trial Costs - Massively Different Cost Estimates to Get the Same Primary Answer

<table>
<thead>
<tr>
<th>$ In US 2007 Millions</th>
<th>Full Cost Industry</th>
<th>Streamlined Industry</th>
<th>More Streamlined</th>
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<tr>
<td></td>
<td>Total</td>
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<tr>
<td>More Streamlined</td>
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</tbody>
</table>
Major Milestones – Operational Metrics

- Final Protocol
- Study Materials Sent
- Last Patient
- Last Patient Clean
- Protocol Sent
- First Patient
- Last Visit
- Lock/Reveal Data

DTMI
Transforming Medicine
21 Separate Trials Coordinated by DCRI Were Evaluated

- ACROSS
- ACHIEVE 1
- APPLE
- CABANA
- CAPTN
- COSTAR II
- DILIN PRO
- DILIN RET
- EARLY ACS
- HAP0019
- HF ACTION
- IMPROVE IT
- OSIRIS 603
- PAERS
- PPCOS
- REVEAL
- ROCKET
- STICH
- TACT
- VALGAN
- VX950104

🌟 Time from IRB submission to approval
- Average: 136 days
- Range: 17-360 days

🌟 Time for contract execution
- Average: 137 days
- Range: 7-272 days

🌟 Problems were present in both industry and government sponsored trials and across all specialties
Results Reporting

★ Current contracting at the site level does not assure reporting of trial results

★ Clinicaltrials.gov and WHO registry are important steps in the right direction

★ Best approach would be to assure proper architecture in all trials

  Should include adequate site contracts

  Should include independent executive/steering committee and statistical group
Lessons and Suggestions—Short Term

- Public reporting of start up metrics could make a big difference in start up times

- Focus on understanding the business practices necessary to conduct research at the site level
  - Structural alignment
  - Financial accountability
  - Appropriate institutional support
  - Institutional economies of scale
  - Appropriate rewards for site based investigators

- Develop more effective mechanisms for PPP

- AAHRPP accreditation
Clinical Trials Transformation Initiative (CTTI):

We Need to Reengineer the Clinical Trials System!
CTTI

Mission:

To identify practices that through broad adoption will increase the quality and efficiency of clinical trials

www.trialstransformation.org
Lessons and Suggestions—Mid-Term

- Do “research on research” to develop evidence to support improved Federal and global guidelines

- Build capacity through reengineering clinical research enterprise (CTSA as key driver in US)

- Move accreditation to the level of the clinical research site
Each CTSA academic health center is a home for clinical and translational science.
Building a National CTSA Consortium

Participating Institutions

- New members 2008
- Members 2006 & 2007
Lessons and Suggestions—Long Term

- Develop a national learning system
- Continuous recording of clinical practice data in electronic health records and disease registries
- RCTs conducted by inserting randomization into the data already being collected
Clinical Research Vision—the Learning Health System

- Concept, Core labs, Translation
- Local Translation
- Clinical Trials
- Registries
- Professional Society & Guidelines Leadership
- Regulatory, Policy Leadership
- Clinical Learning Networks