Case-Study: Protocol Operationalization and Site Engagement Strategies for Cooperative International Neuromuscular Research Group Studies

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(or)

How to Start Your Own Academic CRO / MicroPharma Group with 7 Researchers, an Idea, a Little Experience, and a Chrysler Minivan
Disclosures

– CINRG Executive Committee
– Consulting for Genzyme, PTC Therapeutics, Prosensa Inc.

Overview

3500 Years of DMD
Why we started the CINRG network
Developing the Infrastructure
Logistical Issues & Funding
Site Selection
Study Protocols
Site Support & Communication
Challenges (A few fun examples)
Leveraging Your Data for Clinical Trials
Lessons Learned
Duchenne Muscular Dystrophy

- Neuromuscular
  - Affects proximal muscles more severely
- Progressive
  - Loss of ambulation by early teens
- Most common NMD of childhood
  - 30 per 100,000 liveborn males
- Treatment: glucocorticoids
- X-linked
- Due to changes in the dystrophin gene and complete loss of the dystrophin protein.

Descriptions of DMD:

- Illustrations in temple of Beni Hasan, Egypt (2500BC) (according to Emery...)
- Case descriptions by Charles Bell (1830) and Gaetano Conti (1836), WJ Little (1847)
- Edward Meryon first to systematically describe “Granular degeneration of voluntary muscles” AKA Meryon’s Disease (1851) in 4 families.

Duchenne (1862)


100 years pass...
The Dystrophin Gene/Protein (Discovered 1989)


Sets the stage for steroids to alter the natural history of DMD.
The Problem

– Lots of patients ~15,000 in U.S. alone
– No significant clinical trials since the 1980s
– Lack of clinical trials infrastructure
– Lack of funding
– No pharmaceutical interest or research in muscle diseases.
– Funding mostly via advocacy organizations – MDA
  ~$2M nationwide in research funding in 2000, all basic research
– Federal Funding $17M/year, no NIH-funded multicenter clinical trials (about $.01 for every NIH $1 spent in oncology, and >90% to basic work)
The Idea (1999)

Build a collaborative multidisciplinary international network to advance the clinical study of new interventions for children with neuromuscular diseases

The Resources

- Small lab (7 people) and Institutional Support for a Muscle Genetics Lab (2 Neurologists, 4 Geneticist and a Public Health Specialist)
- New Advances in Genetics and Technologies – Lots of new toys
- Growing Body of Basic Science Data on Potential Interventions from Established Collaborating Labs
- Multiple drug candidates with identified pathways
- Many interested expert clinicians around the world with established pediatric neuromuscular clinics
- GCRC (for biostatistics, pharmacy)
- Outreach partners and advocacy groups
- Patient Advocacy Groups with Seed Funding and High Profile “Connections”
- Chrysler Minivan (with Evita C.D.)
The German Response
Association Francaise Contre les Myopathies (AFM)
Nice, France, 2000

Developing the Necessary Organizational Structure (2000-2005)
The Cooperative International Neuromuscular Research Group

CNMC Microarray Center
- Affymetrix gene expression profiling
- cDNA spotted array
- Oracle database support
- Data mining tools
- Temporal and cross-sectional expression profiling of therapeutic interventions

Animal Research Facilities
- High-throughput multidisciplinary drug screening with whole-body strength testing (Buffalo, NY, Bari IT)
- In Vivo mouse muscle pathophysiology and multiparametric pharmacology (Lausanne, CH)
- Golden retriever dog drug toxicity testing and screening for efficacy in severely vs. mildly affected muscle groups (Columbia, MO)

CINRG Study Sites
- CINRG Investigators
- Established DMD clinic populations
- Study Coordinators
- Certified Clinical Evaluators
- Investigational drug pharmacies
- Institutional Review / Ethics Review Boards

CINRG Coordinating Center
- Central Medical Director
- Central Program Coordinator
- DMD/CINRG Translational Research
- Fellows Program
- Data and Safety Monitoring Board
- Web-based data management
- Central pharmacy
- Coordination of regulatory review
- CINRG Pediatric Clinical Research Center
- Biostatistical services
- Bioanalytical services

CINRG Executive Committee (EC)
- Scientific Advisory Board (SAC)
- Patient Support Organizations
- Data Safety Monitoring Board (DSMB)

CINRG Clinical Study Sites
And you wanted to be a scientist.....

If you are running a multicenter network, doing the hands-on research is 10% of the work

– If you’re thinking of running a one-off multicenter clinical trial, ask yourself whether it’s worth it!
– (The answer might be yes)
– Infrastructure and “coordinating center” activities for 1 study vs. multiple studies are nearly the same, so think about the long-term.
– Are you going to 1) be an administrator; or 2) hire one?
– You will also need to 1) be a Study Designer, Study Coordinator, Personnel Coordinator, Regulatory Affairs Coordinator, Legislative Affairs Coordinator, Grant Writer, Finance Coordinator, Contract Coordinator, Data Manager, Web Developer, Outcome Measure Developer, Publication Author, Meeting Planner, Travel Coordinator, Cab Driver, Caterer; or 2) hire them.
– So - Make sure you have TIME to do those jobs, or FUNDING to hire the people.

No resources? No problem! (Well, maybe a problem). Partnering with Advocacy Groups
(The Flaming Phone Call and Decimal Dust)

– The magazine interview that went wrong and how it created a longstanding partnership with advocacy groups (MDA, PPMD, FED).
– Frustrations with Family Involvement
– Frustrations with Funding Agencies
– How our partnership helped lead to the MD-CARE Act
The MD CARE Act: A Game-Changer

- Legislative Advocacy – 2000 Muscular Dystrophy Community Assistance, Research and Education (MD CARE) Act
- Congressionally-mandated NIH Muscular Dystrophy Coordinating Committee established goals
- MD CARE Act authorized every year since 2001, today $75M annually in federal grants, over $300M since 2000
- Now funding multiple cooperative groups (CINRG, Muscle Study Group, TreatNMD, etc.), pharma industry projects.

CINRG: Where We Are Today

- CINRG with 25 sites worldwide
- Multiple investigator-initiated CINRG clinical trials and mechanistic/observational studies completed and published
Choosing Sites:

Just because everyone wants to join the network today, does not necessarily mean it’s a good idea!

- If you build it, they will come. Often without invitation.
- Big networks look awesome on paper. Don’t let your eyes get bigger than your stomach (or staff).
  - Once you have X sites on board, you have to support them. Do you want 30 (variable) sites, or 15 high-quality ones?
  - Be very selective and set a high bar for entry. Less productive sites provide the smallest fraction of scientific data (the whole point), but take the most time to supervise and support.
  - Starting a site is a LOT of work and can be expensive, you don’t want it to be wasted.
- Carefully evaluate each investigator and evaluate their resources.
- If you lack funding, say so up front. Sites and investigators who are willing to invest in an effort make great partners.
- Use a formal site application to set expectations and ensure standardized resources.
Writing Your Study Protocol:
Know who will read it (and where they are!)

– Review all of the regulatory guidance
– Fit your study protocol format to meet all of the requirements (See example TOC)
– Get some local peer review ahead of time from sites to identify weak areas
– Organize your central and site files and make sure they are complete (See example Key Document Checklist)

Site Support: Annual Meetings as a Forum for Science, Education and Testing

– Annual meetings include:
  • All investigators, coordinators, evaluators
  • Coordinating Center leadership and staff
  • Outside committee and advisory group members
  • Advocacy organizations
  • Pharma Industry Collaborators
– Public day – Scientific Forum
– Private day – Training and Reliability Testing
– Dinner Party for All (Hosted/Catered by Scientific Director)!
Site Support Activities

- Regular “Leadership Team”/study chair teleconferences (Monthly or greater)
- Regular investigator/site staff teleconferences (Quarterly)
- Regular (and active) site regulatory and data monitoring
- Coordinator “Hotline”
- IRB Preparation Assistance
  - Assistance with IRB package and consent preparation (Incl. translations)
  - Review of final documents prior to submission
  - Central tracking for “future use of data” provisions
- Enrollment Assistance
  - ClinicalTrials.gov
  - Advocacy Foundations
- Enrollment Tracking
  - Setting enrollment goals
  - Regular communication of actual vs. planned enrollment
  - Working with PIs and coordinators to craft site-specific enrollment assistance plans if lagging behind

Other Ideas for Site Support Materials

- Group or Study Specific Website
- **Example Study Document CD**
- Standardized Fax Coversheets for Coordinating Center (and any other required regular contacts)
- Central Contact Information Sheet
- Visit Calculators
- Study Materials Checklists and Order Form
- Central Pharmacy Medication Request Form
- Sample Prescriptions
- Sample Outside Consult Requests (if used)
Challenge: New Toy on the Block: Partnering with Big Pharma to Invent, Build, Validate and Distribute Pediatric Strength Testing Equipment

- Ask investigators to find local funding assistance
- Source materials locally where possible.
- Plan and budget for import taxes
- Know the customs regulations for host nations
- Sometimes small-batch electronics look like bombs – you will answer lots of questions

Challenge: DNA is everywhere but you can’t always get it (directly, that is)

- Case of India:
  - lack of molecular diagnostics
  - can’t get DNA out of the country
- DNA can’t transport. Data can!
  - Training a new fellow with the Stichting-Porticus Foundation
  - Setting up a new MLPA lab (First in India)
Leveraging Our Data for Clinical Trials

- 15 trial, biomarker and natural history publications
- Advisory board and data sharing with multiple novel drug development programs
- 1 EU marketing approval (U.S. pending)
- 3 “spinoff” startup pharma companies

Lessons Learned

- This is very expensive. Coordinating Center ~$1.5M/year on a “shoestring” budget. Leverage all the resources you can (CTSC, etc.)
  - Data management / Biostatistics
  - Project managers / CRAs / Monitors
  - Annual meetings (~$75-100K) and face to face ++ important.
  - Evaluator training (ongoing and necessary)
- Specific funding required for C.C. “infrastructure”. This is NOT feasible on a project-by-project basis.
- There is always a site that needs staff trained. Reliability needs to be checked regularly. Plan your finances accordingly.
- Investment is worth it, with enough sites.
  - 5 sites? Probably not.
  - 15-25 sites? Yes, some sites more prolific than others, some will drop out. A small central staff will be very busy, select sites carefully.
  - >25 sites? Bigger infrastructure grant.
- Streamline administrative processes early to avoid becoming the stereotypic bureaucracy.
- You will be a great resource for Pharma, they can contribute $.
- BUT, no matter how good your infrastructure is, Pharma will build and run their own trials - don’t count on being a CRO.
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Parent Project: Muscular Dystrophy

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