Creating, Maintaining, and Growing Clinical Research Networks in Rare Diseases

Conference on Clinical Research in Rare Diseases
September 22, 2010

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- European League Against Rheumatism
- National Institutes of Health (NIAMS • NIAID • NCRR • ORD)
- US Food and Drug Administration
- The Vasculitis Foundation

This is an excellent time to engage in clinical trials of innovative therapies in rare diseases

Multi-center research collaborations are extremely helpful for conducting high-quality, high-impact clinical research in rare diseases
Barriers to the Study of Novel Therapies for Rare Diseases

- Numbers – Market
- Lack of recognition of importance
- Overlap of mechanisms with other diseases:
  - good: helps
  - bad: new drugs usually tested in other diseases first!
- Need expert centers to ensure quality of evaluation
- Start-up costs similar for $N=100$ vs. $N=1000$
  - Regulatory requirements
  - Site initiation costs
  - CRFs
  - IND
  - Contractual issues (sponsor/NIH/other)

Ramifications of studying a rare disease for developing new therapies

- Some diseases are too rare to conduct RCTs
- Sample sizes of trials must be smaller
- Must consider novel study designs
- Need for careful study center selection
- Extended timelines for trial completion
  - Can take many years to complete RCT or cohort study

Ramifications of Longer Timelines for Studies of Rare Diseases

- Higher costs
- Staff retention and retraining (turnover)
- Danger of lost interest/momentum
- Must choose more carefully among promising agents
- Can only do 1-2 studies and thus block others
- Fewer companies interested
  - especially companies with short time horizons
    (e.g. some private, VC-funded)
- Funding agencies lose patience
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Solutions/Responses to Longer Timelines for Studies of Rare Diseases

- More centers → delicate balance
  - Expertise vs. Trial expertise
    - Additive cost vs. Practicality
- Aggressive/better recruitment (more effort)
- Establish research network(s)

Research Networks for Rare Diseases

- **Pros:**
  - Reduce start-up time/costs-leverage resources
    - Centers, personnel, systems already in place
    - Forms/data entry/CRFs, training, communications
  - Established cohorts and recruitment streams
  - Share workload & credit → trust
  - Combine expertise
  - Recycle experience
  - Look good to funding agencies/sponsors

- **Cons:**
  - Must maintain infrastructure
  - Need to avoid stagnation → add flexibility
  - Require work to maintain cohesiveness
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Creating a Clinical Research Network for a Rare Disease

Types of Research Networks

• **Loose associations with common interests**
  - Collaboration but no major infrastructure
  - E.g. Scleroderma Clinical Trials Consortium

• **NIH-chosen networks with specific task**
  - In response to RFA
  - E.g. Dialysis Access Consortium

• **Specialty-driven but not disease-specific**
  - E.g. CARRA (Pediatric Rheumatology group)

• **Disease-specific, investigator-driven, NIH-supported infrastructures**
  - E.g. ECOG, ACTG, RDCRN Consortia
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Creating Rare Disease Research Network

• Start with a core group of passionate clinical investigators
• Planning the grant and organization takes much more time than you possibly realize (to do it right)
• Talk to patients early and often (PAGs)
• Start talking to NIH/funders yesterday
• Seek home institution support (good luck)
• Must have initial set of hypotheses, studies, projects and not just vague idea for network

Creating Rare Disease Research Network

• Consider needs for data coordinating center
  – Forms development, data entry, management
  – Data analysis
  – Study coordination, AE reporting, etc.
  – Can be same as PI center but usually not
• Will need DSMB
• Consider need for specimen repository

Being PI of a Rare Disease Network

• Everyone loves you
• Everyone hates you
• Everyone (shockingly) listens to you
• Everyone (annoyingly) ignores you
• However, if it is all about you \(\rightarrow\) recipe for failure
• You must share
  Credit • Roles • Funds
• GET HELP
  – Administrative/clinical
  – Project Manager
• This must be your no. 1 research priority/time commitment
• Work is hard and not everyone does it equally (or at all)
Prime Needs: Patients and Patience

- No patients, no research
  - There’s a reason they’re called “rare” diseases!
- Everything takes forever (and then some)
  - Anticipate delays and mitigate where possible
  - Parallel processing not sequential steps

Selecting Sites/Collaborators for a Rare Disease Network

- Size of patient cohort/catchment area
- Reputation/importance/sensitivity of local PI
- Enthusiasm of site investigators
- Site and investigator experience in clinical research and trials
- Geographic distribution
- Personalities
- Site co-investigators (junior faculty, etc.)
- Grantsmanship is good but not paramount

Pros/Cons of Foreign (non-US) Sites for Rare Disease Clinical Research Networks

- Pros:
  - Often larger/centralized centers
  - Often less costly than US sites
  - Expands the possibilities
  - NIH allows foreign sites and will fund them
- Cons:
  - Legal/administrative approvals can be difficult
  - Drug and sample shipments more complex
  - Communication more difficult (time zones/language)
  - Industry varies in approach to foreign sites
Personality Issues Affect Creation of Rare Disease Networks

- Best if some history of working together
  - Must avoid ego clashes (especially senior PIs)
  - Must have and/or build trust
- May need to bring in “competitors”
- Don’t squash junior investigators
- Club vs. Chaos

Patients and Advocacy Groups are CRUCIAL Partners in Developing Rare Disease Research Networks

- Talk to them before you plan or form network
- PAGs provide support in many ways
  - Political/lobbying support to funders
  - Logistic and scientific insight from different prospective
  - Recruitment, recruitment, recruitment
  - Volunteer assistance
  - Funding (especially for trainees, pilot studies)
- Important to educate PAGs on processes and help them have realistic expectations
- Important to listen to PAGs—they know stuff!
  They listen to, and represent, many patients
- Mutual respect and joint goals are essential

LEVERAGE

- You need to leverage existing
  - Alliances/networks/working groups
  - Professional relationships
  - Research infrastructure
    - CTSA-clinical research units
    - Trial units
    - Scientific cores
  - Ongoing trials
  - Data management capabilities
  - Data and specimen repositories
  - Other Funding
  - PAGs
  - Anything and everything (as appropriate)
Funding Rare Disease Clinical Research Networks

- Funding is good and everyone wants it
  - Must spend more time on budgets than you think
  - Don’t forget the science
- There is never enough funding & everyone wants more
- Consider combining funding sources
  - Federal: NIH, FDA
  - Industry
  - Patient Advocacy Groups
  - Academic Institutions
  - Other
- The costs add up rapidly
- Ask for what you really need (you need more)

NIH Numerology, Alphabet Soup, and Nomenclature

- K08
- K12
- K23
- K24
- K30
- T32
- NRSA
- R01
- R21
- U01
- U54

- Grants
- Contracts
- Cooperative agreements
- Networks
- SBIRs
- ISTs
- RFAs
- RFPs
- Explores them all

NIH Support for Clinical Trials in Rare Diseases

- The NIH is increasingly engaged in supporting clinical trials in rare diseases
  - Especially for innovative treatments
  - Multiple institutes may overlap and be interested in disease under study
  - (e.g. in Rheumatology: NIAMS, NIAID, NHLBI, others)
- Mechanisms
  - RFAs and RFPs via Contracts and Cooperative agreements (U awards)
  - Large R01 grants
  - NIH-Academic-Industry Partnerships
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NIH, FDA, and Industry for Rare Diseases

- NIH and FDA encourage and understand the need for collaboration with industry
- Many examples of successful partnerships
- Caveats
  - Priorities may differ
  - Data sharing
  - IP issues
  - Conflicts of interest
  - All of these are resolvable

Investigator-Sponsored Studies in Rare Diseases
Partnered with Industry
(some funds/drug from industry: IST, IIT, IIP)

- Advantages
  - Control
  - Operations
  - Data
  - Everything
  - Academic credit
  - Often unlikely to be done otherwise
  - Flexibility
  - Less industry involvement

- Drawbacks
  - Less funding
  - Do it all yourself
  - Regulatory tasks
    - IND
    - Monitoring
    - AE reporting
    - DSMB
  - Site supervision
  - Budgets
  - Takes longer
  - Less industry involvement

Non-Federal, Non-Industry Funding

- Professional organizations
  - Often have pilot funding grants

- Private foundations
  - Disease-specific
  - Fellowships available
  - Possibly funds for pilot data
  - With few exceptions (e.g. CFF), no way they can support major trials
Maintaining and Growing a Clinical Research Network for a Rare Disease

Nurturing Rare Disease Networks
- Keep everyone engaged
- Feed the kitty
- Feed the egos
- Complete some projects
- Introduce fresh studies
- Involve trainees and let them grow and flourish
- Cut the failing/sloppy centers, poor partners (not easy to do in a close community)

Maintaining Rare Disease Networks
- Publish
- Spread credit
- Branding
- Write more grants
- Add more sites
- Make it irreplaceable (though it always is)
- Failure is not an option!
Keeping A Research Network Happy

- Buy-in is Critical
  - Good: Everyone should at least have a chance to review everything and make comments/changes
  - Better: People contribute early in the process
  - Best: Different leaders on different projects and tasks
- Keep information flowing to avoid major surprises
  - Scientifically
  - Logistically
  - Financially
- Make decisions and make progress
  - Success in recruitment, funding, data, and papers makes everyone happy

Example of a Clinical Research Network for a Rare Disease

VASCUITIS CLINICAL RESEARCH CONSORTIUM

www.RareDiseasesNetwork.org/VCRC
A Member of the NIH Rare Diseases Clinical Research Network

www.RareDiseasesNetwork.org
The VCRC Diseases

- Takayasu’s Arteritis
- Giant Cell Arteritis/PMR
- Polyarteritis Nodosa
- Wegener’s Granulomatosis
- Microscopic Polyangiitis
- Churg-Strauss Syndrome

Addition of other diseases under consideration

Vasculitis Clinical Research Consortium

- Consortium Center
- Primary Clinical Site
- Other Sites
- Affiliated Partners/Sites
- Affiliated Patient Group
- DMCC
- Biomarker Lab Site

Randomized Trials

Pilot Studies

Longitudinal Study of Giant Cell Arteritis

Longitudinal Study of Takayasu’s Arteritis

Longitudinal Study of Polyarteritis Nodosa

GWAS: Genome-wide Association Studies
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VCRC Steering Committee

VCRC Coordinating Center

VCRC Data and Specimen Repository

VCRC Patient Registry

VCRC Website

VCRC Clinical Sites

VCRC Biostatistical Unit

VCRC Data and Specimen Repository

VCRC Patient Advocacy Groups

VCRC Fellowship

NIH Program and Science Officers

VCRC-NIH DSMB

RDCRN Data Management Coordinating Center

RDCRN Steering Committee

VCRC Clinical Collaborators

Industry Partners

VCRC Laboratory Collaborators

VCRC Core BU Group

VCRC PI-NIH Science Officer

VCRC PI & DMCC PI

DMCC Liaison & Project Manager

Radiologists (imaging study)

OMERACT (outcomes measures group)

Project-specific calls

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IT CAN BE DONE!