

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

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**Peter A. Merkel, M.D., M.P.H.**  
Professor of Medicine  
Section of Rheumatology and  
The Clinical Epidemiology Unit  
Director, Vasculitis Center  
Boston University School of Medicine  
Boston Medical Center  
[pmerkel@bu.edu](mailto:pmerkel@bu.edu)

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**Peter A. Merkel, M.D., M.P.H.**  
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- Actelion
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- Genzyme
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- Regeneron
- American College of Rheumatology
- European League Against Rheumatism
- National Institutes of Health  
(NIAMS • NIAID • NCRR • ORD)
- US Food and Drug Administration
- The Vasculitis Foundation

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**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**

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**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)

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**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*

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**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
  - vs.
  - Additive cost
  - vs.
  - Practicality
- Aggressive/better recruitment (more effort)
- Establish research network(s)

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**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

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• 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**

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**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

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**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

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**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 → recipe for failure
- You must share
  - Credit • Roles • Funds
- GET HELP
  - Administrative/clerical
  - Project Manager
- This must be your no. 1 research priority/time commitment
- Work is hard and not everyone does it equally (or at all)



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**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

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**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

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**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

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**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

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**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

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**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)

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**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)

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**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

Explore them all!

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**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

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

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|---|--|
| <ul style="list-style-type: none"><li>• <u>Advantages</u></li><li>– Control<ul style="list-style-type: none"><li>• Operations</li><li>• Data</li><li>• Everything</li></ul></li><li>– Academic credit</li><li>– Often unlikely to be done otherwise</li><li>– Flexibility</li><li>– Less industry involvement</li></ul> | <ul style="list-style-type: none"><li>• <u>Drawbacks</u></li><li>– Less funding</li><li>– Do it all yourself<ul style="list-style-type: none"><li>• Regulatory tasks<ul style="list-style-type: none"><li>– IND</li><li>– Monitoring</li><li>– AE reporting</li><li>– DSMB</li></ul></li><li>• Site supervision</li><li>• Budgets</li></ul></li><li>– Takes longer</li><li>– Less industry involvement</li></ul> |
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**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

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**Maintaining and Growing a Clinical  
Research Network for a Rare Disease**

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**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)



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**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!

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**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

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**Example of a Clinical Research Network  
for a Rare Disease**

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**VASCULITIS  
CLINICAL  
RESEARCH  
CONSORTIUM**

[www.RareDiseasesNetwork.org/VCRC](http://www.RareDiseasesNetwork.org/VCRC)

**A Member of the NIH Rare Diseases Clinical  
Research Network**



[www.RareDiseasesNetwork.org](http://www.RareDiseasesNetwork.org)

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### 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*

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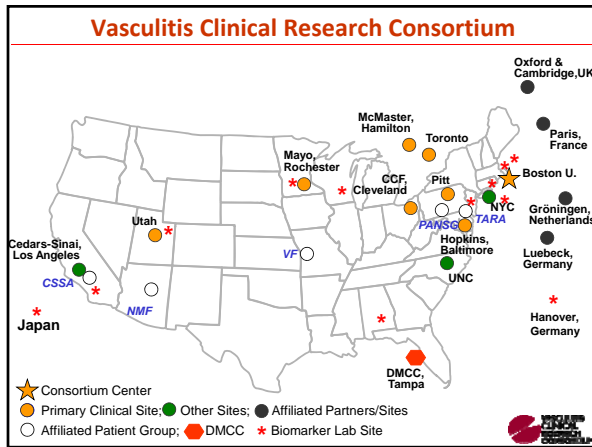
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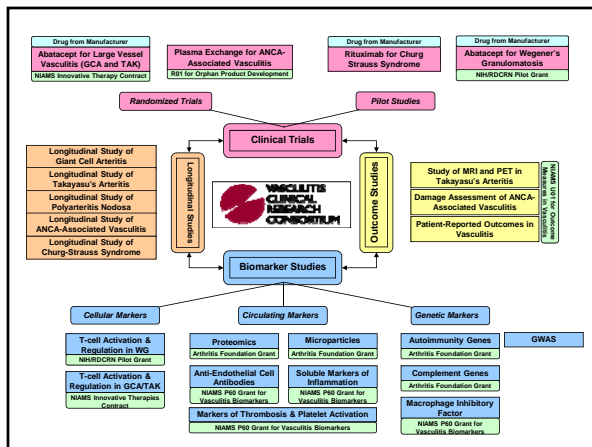
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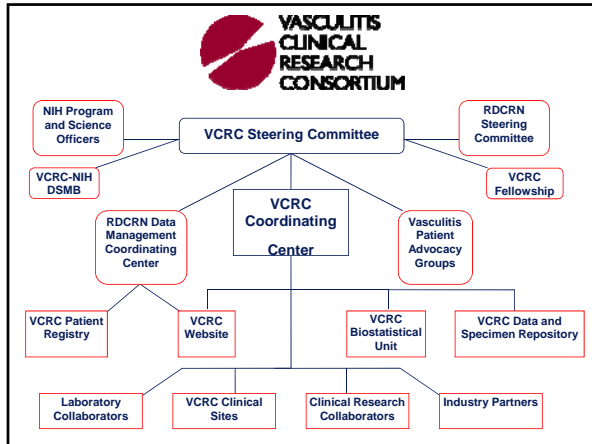
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- VCRC Communication**
- Steering Committee: twice/month
  - Study Coordinators: once/month
  - Patient Advocacy Groups: once/month
  - DMCC Liaison & Project Manager: once/week
  - VCRC PI & DMCC PI: Regularly
  - VCRC: one-two in-person meetings/year
  - PI & Project Manager: daily-weekly
  - VCRC core BU group: once/week
  - Radiologists (imaging study): PRN
  - OMERACT (outcomes measures group): PRN
  - Project-specific calls: PRN
  - VCRC PI-NIH Science Officer: Quarterly

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

**IT CAN BE DONE!**

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