An Academic Perspective on the Design of Studies of Rare Diseases

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Financial Disclosure

• Pharmaceutical Company Support
  • Novartis
  • Amgen
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• Collaborative Clinical Research
• Public Resources and Education
• Centralized Data Coordination and Technology Development
• Training
About the RDCRN
Data as of September 24, 2012

• 17 Consortia
• 167 distinct institutions around the world
• 2,290 consortium members
• 90+ patient advocacy groups
• 174 trainees
• 77 actively accruing studies
• 22,542,917 data points, photographs, CT scans, PET scans, x-ray images and videos
RDCRN2 Achievements
2nd grant cycle August 1, 2009 – September 24, 2012

- 67 activated studies
- 11,624 participants enrolled
- 130 trainees
- 293 journal articles
- 61 conference presentations
- 50 books and book chapters
- 19 posters
- 175 audit site visits
- 65 monitoring visits
RDCRN: Common infrastructure that is scalable and generalizable.

http://rarediseasesnetwork.org

- Portal to websites for each Consortium
- Portal to members’ website
- Portal for patient advocacy groups
- RDCRN Contact Registry
- RDCRN Media Center
Common Characteristics

• Defined eligibility criteria
• Specific aims
• Uniform clinical assessments within the context of usual care
• Uniform follow up frequency
• Employ data standards
• Incorporate analysis plans
A contact registry enriched for patients willing to participate in studies.

Data as of September 1, 2012

- Over 200 Diseases
- 9,871 Total Registrations*
- 89 countries

Goals:
To inform registrants about RDCRN studies available;
To disseminate information about RDCRN activities

*Excluding former consortia registrations (BMF, CINCH, CLIIC, CRC-SCA, GSD, RLD, RTD)
## Contact Registry Protocols

<table>
<thead>
<tr>
<th>RDCRN #</th>
<th>Title</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>VCRC 5531</td>
<td>Reproductive Health of Men and Women with Vasculitis*</td>
<td>Closed to Accrual (N = 467) Accrual goal met in 2 mos.</td>
</tr>
<tr>
<td>VCRC 5533</td>
<td>Illness Perceptions, Fatigue, and Function in Systemic Vasculitis† (The VCRC Vasculitis Perception (VIP) Study)</td>
<td>Closed to Accrual (N = 707) Accrual goal met in 2 mos.</td>
</tr>
<tr>
<td>INC 6604</td>
<td>Development and Validation of a Disability Severity Index for Charcot-Marie-Tooth Disease (CMT)</td>
<td>Closed to Accrual (N = 249) Accrual goal met in 4 mos.</td>
</tr>
<tr>
<td>VCRC 5534</td>
<td>Educational Needs of Patients with Systemic Vasculitis - An International Study</td>
<td>Closed to Accrual (N = 386) Accrual goal met in 2 mos.</td>
</tr>
<tr>
<td>INC 6606</td>
<td>An Analysis of the Symptomatic Domains Most Relevant to Charcot Marie Tooth Neuropathy (CMT) Patients</td>
<td>Recruiting (opened 07/17/12) N = 239 as of 09/20/12</td>
</tr>
<tr>
<td>NEPTUNE 6802</td>
<td>Assessment of Educational Experience for Patients with Newly Diagnosed Nephrotic Syndrome</td>
<td>Pending IRB approval</td>
</tr>
</tbody>
</table>

### Abstracts:


The Issue

- Few patients.
- Few patients.
- Few patients.
- Few patients.

The Implication

- Multi-site Studies.
- Difficulty getting drugs for limited indications.
- Longer studies.
- Possible design options for clinical trials.
Multi-site Studies

- Recruiting collaborators.
- Expanding Co-authors.
- Multiple IRBs.
- Central IRB.
- Complex funding arrangements.
- Subcontracts, multiple IDCs.
- Complexity of adverse event reporting.
- Need to standardize assessments across sites.
Multi-site Studies

Vasculitis Clinical Research Consortium Sites

Vasculitis Patients

[Maps showing the distribution of sites and patient counts across the United States]
Difficulty getting drugs for limited indications.

- Market may be limited and company not willing to invest in a study for a rare disease.
  - IND issues.
  - Drug distribution and supply.
  - Need for a placebo.
- Unwilling to be a part of studies of combination therapies.
Possible Design Options

- Parallel group design
- Cross-over design
- Factorial design
- Historical controls design
- Randomized withdrawal design
- Early escape design
- n-of-1 design
- Group sequential design
- Case-Control design
- Prospective cohort design
- Decision analysis-based design
- Ranking and selection design
- Adaptive design
- Risk-based allocation design
- Bayesian designs
- Enhanced designs

Reduce the number of study subjects needed by using enrolled subjects more than once.
Longer Studies

- Meta-analyses of “good quality” RCT’s
- Individual RCT’s
- Meta-analyses of observational studies
- Individual observational studies
- Published case reports
- Anecdotal case reports
- Opinion of experts
Observation

- Many rare diseases are stable over long periods of time and
- When treatment is withdrawn, subject condition reverts to baseline.

... not necessary to limit enrollment to newly diagnosed patients.
... can re-treat after suitable wash out period.
Issues to be considered

• Patient refusals and dropouts.
• Carryover or interaction effects.
• Lack of knowledge of suitable washout or optimal treatment durations.
• Duration of study.
• Untestable assumptions.
Novel Methods for the Conduct of Clinical Trials

- Aim 1: To test whether direct recruitment of potentially eligible study participants is a more effective and efficient strategy to achieve target enrollment in a clinical trial compared to the standard method of recruitment through physicians at centers of excellence.

Direct Recruitment is Patient Centric;
Standard Method is Center of Excellence (CoE) Centric
Novel Methods for the Conduct of Clinical Trials

- **Aim 2:** To test whether protocol performance (i.e., eligibility, compliance, completeness, subject safety, retention, and other measures of protocol adherence) is affected by focusing on the patient-participant as compared to an investigator located in a center of excellence.

- **Aim 3:** To identify weaknesses and strengths in areas of data collection and quality, depending on the data source (physician vs. study participant) and treatment setting (no center vs. center of excellence).
Novel Methods for the Conduct of Clinical Trials

- Aim 4: To determine whether novel on-line approaches to obtaining research subjects’ informed consent are as effective as traditional in-person approaches by determining to what extent subjects are truly informed about their participation and how satisfied participants and physicians are with the process.

Novel On-line Approach is Patient Centric; Traditional In-person is Center of Excellence (CoE) Centric
Thank You