Outline

- Setting the stage for successful trials
  - Natural history data
  - Outcome measures
  - Trial recruitment registries
  - Partnership in protocol development
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  - Information on specific trial opportunities

- Implementing trials
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  - Entry criteria
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  - Retention
  - Dissemination of findings
Natural History

- High quality natural history data are needed for trial planning
  - Inform choice of sample
    - Subgroups along the phenotypic spectrum
    - Disease stages
  - Inform the choice of endpoint
    - Measurement feasibility, reproducibility
    - Clinical relevance
    - Variance
Natural History Data

• Prospective (pre-trial)
• High quality chart review
• Focus on variables relevant for trial planning
• Harmonize data collection across clinical sites
• Plan for data sharing (ICF)
• Include biospecimen repository (ICF, SOPs)
• Recent data needed – moving target
The changing natural history of spinal muscular atrophy type 1
M Oskoui, G Levy, CJ Garland, JM Gray, J O’Hagen, DC De Vivo, P Kaufmann

<table>
<thead>
<tr>
<th>Variables</th>
<th>HR (95% CI)</th>
<th>p-value</th>
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<tr>
<td>Ventilation &gt;16 hours/day†</td>
<td>0.3 (0.2-0.7)</td>
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<td>MI-E device</td>
<td>0.2 (0.1-0.5)</td>
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<tr>
<td>Gastrostomy</td>
<td>0.5 (0.2-0.9)</td>
<td>0.02</td>
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SMA 1 Natural History
Indiana Registry
n=150
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Clinical Outcome Measures

- Feasible in population (e.g. children)
- Acceptable burden to research participants
- Applicable to a wide range of the population
- Meaningful
- Sensitive to change
Considerations in rare diseases

- Multiple clinical sites, likely international
  - simple, “low-tech” measure are preferable
  - Avoid measures that require frequently and highly trained staff
  - Central data processing or reading?
  - Telemedicine?
  - In-community/in-home measurements
Biomarker of Biological Activity

- Does the treatment move the target?
- Example: SMN mRNA or protein for drugs targeting SMN
- Early readout of drug activity
- Pharmacodynamic marker
  - Allows decisions mechanistically not only on single drug, but class of drugs
Background:
Biomarkers of Disease Progression

- Predictive of downstream disease progression
- Biological signal that can provide early read-out of treatment effect
- Has to be closely associated with clinical outcome
- Ideal biomarker can be obtained without invasive procedures
- Can accelerate drug evaluation
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Trial Design considerations

• Designs for small trials and adaptive trials
• Adequate controls
  ▪ Consider alternatives to placebo controls
  ▪ Caution with historic controls: moving target
  ▪ When placebo controls needed to answer the question
    • Communication with patients
    • Consider open label extension when adequate
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The problem: slow recruitment of trial participants

• Many trials cannot recruit participants as planned, resulting in
  ▪ Delays in obtaining important answers
  ▪ increased cost
  ▪ Time effect as possible confounder
  ▪ Delayed answers
  ▪ Dampened enthusiasm of academic and industry investigators to conduct trials
Trial Readiness – Registries
Example: SMA

- The International SMA Patient Registry at Indiana University
  - founded in 1986
  - Enrollment: n=2383 (1566 in USA)
  - Funded by advocacy groups (FSMA, FightSMA, SMAF, MDA and others) - ICC
  - Has helped recruit participants into clinical trials
  - Joined International TREAT NMD registry in 2008

- TREAT-NMD Database —
  Research in Europe for the Assessment and Treatment of Neuromuscular Diseases
  - 18 countries
  - genetically confirmed SMA diagnosis, 3-25 years of age
  - SMA Type 2 (~62%), SMA Type 3 (~38%, of those currently ambulant 47%, non-ambulant 40%, and unknown 13%)
  - Inquiry France: Trial planning – no. of patients with SMA Type 2 and 3 aged 3-25, plus trial site details, trial recruitment via registry
Trial Readiness – Recruitment Registries

- Patients volunteer information so that they can be contacted for opportunities
- Information may include clinical, genetic and contact information
- Broad informed consent as applicable
- Can respond to pre-trial inquiries from academic or industry investigators
- Provide information on trial opportunities
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Partnership for trial success

- Patient participation in trial conception
  - Does the question matter to the community
  - May need compromise between ideal scientific method and reality of patient needs

- Patient participation in protocol development
  - Feasibility
  - Burden

- Patient input in recruitment plan
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Partnership for trial recruitment: Information and Communication

• Provide high-quality information on new treatments that helps patients balance what they read online

• Information on the role of controlled clinical trials
  ▪ Examples: NIH website- clinicalresearch.gov, www.ciscrp.org (Center for Information and Study on Clinical Research Participation)

• Information on specific trial opportunities
  ▪ Survey showed that main reasons for not participating in a trial are lack of awareness, concern over cost, confusion over goals and procedures (Bedlack at al, ALS)
Avoiding therapeutic misconceptions

- High quality information
- Set realistic expectations
- Education
- Thoughtful communication
Trial Readiness – Partnership with Patients

Example: Clinical Research Learning Institute (CRLI)

- Launched in July 2008 by the Parkinson’s Disease Foundation (PDF)
- prepare people with PD to engage as patient advocates within the clinical research enterprise
- multi-day training taught by national experts
  - PD therapies and future research
  - the clinical research process
  - participant protections
  - Bioethics
  - study evaluation and analysis
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Information on specific trial opportunities

- web-based resources (clinicaltrials.gov)
- Social media
- Support groups
- Written material
- Clinicians
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Recruitment feasibility analysis and plan

- Collect detailed information on number of patients meeting entry criteria
- Review geographic distribution
- Prospective inquiry
- Registry inquiries
- “pre-enrolled” trial
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Recruitment – Entry criteria

• Balance between scientifically ideal entry criteria and feasibility
• Allow for wide safety margin
• If insufficient margin, consider modifying entry criteria
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Trial infrastructure and logistics

- Few centers – patients travel
  - Requires adequate support for travel
  - Consider local safety evaluations
  - Local or remote efficacy evaluations?

- Multiple sites
  - Training
  - Language and cultural differences
  - Communication
Trial Infrastructure

- Preparatory research can help set up infrastructure
  - Natural history studies
  - Clinical outcome/biomarker studies
- Consider features for trial network
  - Shared SOPs and tools
  - Governance
  - Conflict of interest and publication policies
  - Incentives
  - Training
  - Outreach and partnerships
NEXT – Network Excellence in Neuroscience Clinical Research

• Clinical Coordinating Center, Data Management Center, and up to 25 US clinical sites

• Goals are to
  ▪ Support the translation of neuroscience discoveries into better treatments
  ▪ Test the most promising treatments in exploratory trials
  ▪ Encourage partnerships between industry, foundations, and academic investigators
  ▪ Increase the efficiency of clinical research

Standard of Care

• Clinical care can have a measurable effect on outcomes
• Need to promote uniform standard of care
  ▪ Develop and disseminate guidelines
• Consider blocked randomization by site
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Retention

• As important as recruitment

• Missing outcomes data can invalidate data
  ▪ Can lead to false positive and false negative conclusions

• Maximize retention
  ▪ Multiple contact information
  ▪ Frequent contact (calls, newsletter etc.)
  ▪ Acceptable visit burden (frequency, lengths, effort)
  ▪ Provide support and user-friendly visits (reminders, travel support, scheduling, comfort etc.)

• Track and intervene
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Dissemination of results

• Inform trial participants and public
• Expectation management
• Negative trial can be successful because it answered a question important to the community
• Positive trial can have greater impact on patient care when results are disseminated effectively
Plan for broad use of data

• Data in rare diseases are very valuable
• Maximize benefit of data collection through broader data access
  ▪ Meta-analyses, sub-group analyses, trial planning
• Make sure patient intentions are known
• Consider investigator needs and incentives
• Consider institutional barriers
• Plan for exchange of data or samples across borders
Accelerate clinical research through broad data access

Goals

- To increase the efficiency of the research enterprise
  - reduce start-up time
  - Reduce cost to develop data collection tools
  - Help avoid that money is spend on similar databases being created over and over
  - Help new investigators and researchers in developing countries to get started
Goals (continued)

- To improve data quality
  - Promote data collection in a consistent manner
  - Facilitate research in rare diseases/international efforts

- To facilitate data sharing
  - Improve opportunities for meta-analysis
  - Increase the availability of data for the planning and design of new trials
  - Help avoid that data are collected and never analyzed to their full potential
Process

• CDEs are identified, vetted, and developed by experts in the scientific community
• The process is transparent and inclusive
• NINDS provides continuous review, oversight, and updates, but has a hands off approach in the development (except support and guidance).
Finding common ground

• identify data elements that transcend studies and disease areas and are found in most if not all studies – these are referred to as the “General” CDEs
  ▪ Demographics
  ▪ Adverse event reporting
  ▪ Medical history

• Include elements for their relevance across neurological studies

• Identify common data element projects at the NIH and in the greater clinical research community
Data elements for a particular disease can be classified as:

1. “General” Core Common Data Elements (CDEs)
   Relevant across diseases

2. Disease-specific Core CDEs
   should be used in all studies for this disease

3. Supplemental Disease-specific CDEs
   extended set that are “common”, but supplemental, i.e. not required - choose from a “menu”

4. Exploratory Disease-specific Data Elements
   Developing of novel outcomes, not yet validated

Coriell Forms or links to other repositories
Rare Disease Registries

NIH Office of Rare Diseases Research (ORDR)

THE LANCET
August 2010

The case for a global rare-diseases registry

Christopher B Forrest, Ronald J Bartek,
Yaffa Rubinstein, Stephen C Groft
CONCLUSIONS

• Partnership for trial readiness in rare diseases
  ▪ Education
  ▪ Registries
  ▪ Standard of Care
  ▪ Natural History and outcomes data
  ▪ Investigator collaborations
  ▪ Recruitment/retention
  ▪ Data harmonization
  ▪ Data access

COORDINATION AND SYNERGY