Clinical Trials in Neuromuscular Disease: Lessons Learned and Steps Forward

Course Description:
Over 7,000 rare diseases affect an estimated ~30 million Americans. Many of these conditions involve movement systems and cause disability or early mortality. Due to these serious consequences, several initiatives have been implemented to catalyze interest in curative therapies. The National Institutes of Health defines a clinical trial as “a research study in which one or more human subjects are prospectively assigned to one or more interventions to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes.” The purposes of this educational session are to help participants understand clinical trial structure and regulations, identify roles of PT in rare disease research, recognize interactions between study outcomes and PT practice, and explore the changing natural history of rare diseases as new therapies are approved.

This session will outline clinical trial development in rare disease, initiatives to facilitate clinical trials, and general regulatory standards. We will then use case studies to highlight interactions between clinical trials and PT practice, emphasizing how study biomarkers have led to new understanding of movement dysfunction, influences of exercise and PT on clinical trial endpoints, and on changing disease phenotypes, as products achieve commercial approval. Speakers will reserve time for discussion and question-answer with the audience.

Introduction: Current State of Clinical Trials in Rare Neuromuscular Diseases (20 min plus 5 min Q&A), A. Pariser

- Outline the mission and major programs of the Office of Rare Diseases Research.
- Relate the general regulatory process for achieving approval of new investigational products for the treatment of rare diseases.

1. Summarize historical initiatives to promote clinical trials in rare disease

**Rare Disease**: a disease or condition that affects <200,000 individuals in the US. Collectively, there are an estimated 7,000 rare diseases affecting more than 30 million people in the US.

Research challenges in rare disease:
- Many diseases are still poorly understood
- Most rare diseases are serious or life-threatening
- Around one-half to two-thirds of rare diseases present in childhood
- Each individual rare disease affects a small number of patients who are often geographically dispersed
- There are a limited number of clinical and scientist experts by disease
- Around 80% of rare diseases are Mendelian genetic, and there is often diversity in clinical presentation within a disease
- Less than 5% of rare diseases have FDA-approved treatments, and there is limited precedent for clinical trial development for most rare diseases

Historical Initiatives to promote clinical trials in rare disease
The Orphan Drug Act (ODA) of 1983 established a pathway whereby a new product with data supporting its “promise” for treating a rare disease or condition can receive orphan status designation (Orphan Drug Act, 1983). The Rare Disease Act of 2002 (RDA) was enacted to establish increased investment in the development of diagnostics and treatments in rare diseases and disorders, and to promote a national research agenda for rare diseases.

2. **Outline the mission and major programs of the Office of Rare Diseases Research.**

Office of Rare Diseases Research (ORDR), at the National Center for Advancing Translational Science (NCATS), NIH

**Mission of the Office of Rare Diseases Research (ORDR):**
Accelerating rare diseases research to benefit patients. This mission is accomplished by facilitating coordination between scientists, clinicians, patients, and advocacy groups in the rare disease community.

ORDR’s major goals include:
- Coordinate rare diseases research nationally and international to meet the needs of patients with rare diseases. Foster collaboration and information sharing within the rare diseases community
- Catalyze the development of innovative solutions to address the unique challenges posed by rare diseases
- Provide reliable information related to rare diseases to the public
- Develop and share tools and resources to support rare diseases research and therapeutics development
- Support training of the next generation of rare diseases researchers and educational activities

**Key Programs of the ORDR include:**

**Genetic and Rare Diseases Information Center (GARD)**
- An online publicly accessible information source that provides plain-language information on more than 6,500 rare diseases.
- Designed for patients and families, clinical professionals, researchers, and the general public.
- A contact center with information specialists to answer questions and direct patients, caregivers and others to helpful resources. Online and phone assistance is available for English- and Spanish-speaking individuals
- GARD is a joint collaboration between NCATS and the National Human Genome Research Institute (NHGRI)

**Rare Diseases Registry Program (RaDaR)**
- Initiated in 2010, originally as the Global Rare Diseases Registry Data Repository (GRDR) program intended to facilitate registry building for rare diseases.
- The registries program was re-envisioned as RaDaR in 2017, which is intended to provide step-by-step directions for patient groups that seek to create high quality registries to support clinical trials and therapy development.
• RaDaR is currently under construction, but aims to provide easy to use templates and tools to incorporate best practices and standards for registries, and strategies for maintaining, promoting, using and expanding patient registries

**NCATS Tool for Patient-Focused Therapy Development**

• Also new in 2017, the Toolkit was launched to help patient organizations play a role in advancing research.
• The Toolkit is a resource hub for processes and best practices needed for patient organization to develop and advance their research programs
• Includes the information on starting a patient registry, promoting patient-focused research and development, working with the FDA and NIH resources, and the post-market evaluation process, and more
• The Toolkit was developed in collaboration with patient organization leaders

**Rare Diseases Clinical Research Network (RDCRN)**

• The RDCRN advances medical research on rare diseases by facilitating collaboration, study enrollment and data sharing
• NCATS and 9 other NIH institutes and centers support research consortia composed of researchers, clinicians, trainees and patient groups that work together to investigate and share knowledge on groups of 3 or more related rare diseases
• By supporting infrastructure, facilitating collaboration, recruiting subjects for trials, and data sharing, the RDCRN aims to advance research of rare diseases. Through this collaborative research structure, there are currently more than 200 rare diseases that are part of a RDCRN.

**NCATS Conferences and Meetings Grants Program**

• NCATS supports conferences and scientific meetings through small research grants
• Topics of interest include rare diseases and proposals to improve the research process through innovation in cross-cutting approaches to basic, translational or clinical scientific research

**Rare Disease Day at NIH**

• This yearly event facilitates scientific exchange related to recent breakthroughs or new research endeavors among researchers, clinicians and patients
• Features presentations, posters, exhibits, an art show and tours of the NIH Clinical Center
• Rare Disease Day at NIH is held on or around the last day of February at the NIH campus in Bethesda MD or the event may be viewed by webcast. Registration and attendance are free to the public.

3. **Relate the general regulatory process for achieving approval of new investigational products for the treatment of rare diseases**

Generally, drug development follows the following basic principles (although there may be substantial variability across the wide variety of diseases and candidate therapeutics):

**Step 1 – Discovery and Development** – understanding mechanisms of potential new drugs and biologic compounds intended to halt or reverse the effects of a disease.
Step 2 – Pre/non-clinical research – in vitro, in vivo and in silico studies designed to identify whether a product has potential for toxicity and identify potential dosing levels that could be tolerated.

Step 3 – Clinical Research – identifies how a product interacts with the human body. In the US, investigators must initiate the Investigational New Drug (IND) process prior to starting any trials in human subjects. Based on discovery and non-clinical work, the study sample, design, protocol, and primary outcome measures should be determined prior to human administration and are refined as new information is collected and analyzed along the clinical development process. Generally, clinical research has been divided into phases, although there is substantial flexibility in this process for rare diseases:

- Phase 1 – evaluate the safety and dose-finding of a device, drug, or product
- Phase 2 – evaluate initial efficacy ("proof of concept") and potential side effects of a device, drug, or product
- Phase 3 – Phase 3 clinical trials are designed to provide substantial evidence of efficacy and risk-benefit for intended use in the target population that will use the product after approval.

In most cases, an IND application must be reviewed for compliance with federal regulations and overseen by the FDA, prior to initiating human clinical trials of devices, drugs, and other biological products.

Step 4 – Marketing applications and FDA Review – The totality of evidence from product development, including chemistry, manufacturing and controls (CMC), non-clinical and clinical information from the IND phases of development are collected and integrated into a marketing application in order to provide the evidence of the safety and efficacy of the proposed product for its intended use. This evidence is submitted to FDA (or in other countries and regions, to other regulatory authorities) and is filed as a marketing application. A New Drug Application (NDA) (or a Biologics License Application (BLA) for biological products) is a comprehensive summary of the information known about the proposed drug, including data and reports from all studies. If the NDA application is determined to be complete and reviewable, the FDA will file the application and it will undergo review by a multi-disciplinary review team that evaluates whether to approve the drug (a 6-10-month process). Various standard and “expedited” pathways (e.g., Fast Track, Priority review) may be used during the marketing application review period. More information may also be requested by the review team prior to approval. If the product is found to be effective for the intended use and has a favorable benefit-to-risk profile, the prescribing information (“labeling”) is defined.

Step 5 – FDA Post-Market Safety Monitoring – active monitoring of longer-term safety, to further refine the usage information. Includes recent initiatives to incorporate existing electronic health databases and registries to evaluate safety and sentinel events.

- Phase IV Clinical Trials – in some circumstances after approval of a drug, longer-term safety or additional evidence may be requested or required by FDA to further monitor and study the drug after approval.
Lesson Learned: Mechanisms Beyond the Study Endpoint (20 min plus 5 min Q&A), C. Senesac

1. Define the criteria for an FDA-approved clinical trial endpoint, surrogate endpoint, and biomarker.
2. Identify relationships between a mechanistic biomarker and function.
3. Cite examples of how imaging study biomarkers have informed our understanding of gait dysfunction in Duchenne muscular dystrophy and altered clinical physical therapy practice.

FDA approved clinical trial endpoints: surrogate/ biomarker vs. clinical endpoints

1. The FDA has strict guidelines for clinical trial endpoints
   • Clinical outcome assessments (COAs) provide a measure function, symptoms, and QOL. They can be used to measure benefit of a particular treatment or intervention. “measurable changes”
   • [https://www.fda.gov/drugs/developmentapprovalprocess/drugdevelopmenttools/surrogateendpointqualificationprogram/ucm284077.htm](https://www.fda.gov/drugs/developmentapprovalprocess/drugdevelopmenttools/surrogateendpointqualificationprogram/ucm284077.htm)
     o “COA qualification is based on a review of the evidence to support the conclusion that the COA is a well-defined and reliable assessment of a specified concept of interest for use in adequate and well-controlled (A&WC) studies in a specified context of use.”
   • Examples of COA’s related to DMD clinical trials and longitudinal studies
     o 6-minute walk test *Gold Standard
       ▪ PTC 124
     o 10 m walk/run
     o Timed functional tests
     o NorthStar Ambulatory Assessment
     o Other
   • What have these COA’s told us about DMD?

2. The FDA has strict guidelines for surrogate endpoints (SE)
   • SE can be seen as a substitute for clinical outcomes. A SE does not directly measure clinical benefit but once established to be reliable can predict clinical value. The FDA requires extensive evidence that an SE demonstrate effects that correlate with or predict clinical benefit.
     o Three levels of validation
       ▪ Validated- can reliably predict
       ▪ Clinically reasonable- reasonably likely to predict
       ▪ Candidate- still under evaluation
     o Examples of SE’s
       ▪ Urine markers, blood/serum markers, survival/disease free, FEV₁ (forced expiratory volume), BP, hormone levels, etc…
     o Examples of mechanistic biomarkers
       ▪ “Mechanistic” biomarkers”, are considered by some to be a subtype of surrogate endpoints that are rooted in disease pathogenesis and regarded by some as a superior biomarker providing more information about the disease progression.
     o According to section 507(e)(9) of the FD&C Act “[t]he term ‘surrogate endpoint’ means a marker, such as a laboratory measurement, radiographic
image, physical sign, or other measure, that is not itself a direct measurement of clinical benefit, and—
  o “(A) is known to predict clinical benefit and could be used to support traditional approval of a drug or biological product; or
  o “(B) is reasonably likely to predict clinical benefit and could be used to support the accelerated approval of a drug or biological product in accordance with section 506(c).”

- Examples of SE’s related to DMD clinical trials and longitudinal studies
  o Magnetic Resonance Imaging (MRI)
  o Magnetic Spectroscopy (MRS)

- What have these SE’s told us about DMD?

3. What we know now about the progression of DMD by combining our understanding of COA’s and SE’s from longitudinal and clinical trials in DMD
  - Prediction of function
  - Predication of loss of ambulation
  - Predication of progressive weakness in the UE’s

4. Confirming our observations of the natural history of DMD
  - Toe walking- why does it happen, what is the status of muscles of the LE’s?
  - Common deformities- what are some of the drivers of these deformities?
  - Compensations of movement- understanding what we see, how can we interpret these movements?

5. The changing landscape in DMD and what it means to clinicians in the field and the relationship to current Care Guidelines
  - Stretching- does it make a difference?
    i. Positive aspects and what we don’t know
  - Exercise- is it beneficial?
    i. What we know and what we don’t
  - Other

6. The role of PT with this population
  - Education about the disease progression-caution when speaking with parents
  - Support
  - QOL- most important
1. **Distinguish study required tests and procedures at clinical trial sites from treatments and goals measured in clinical care.**

**Research Tools Available to Identify Clinical Trial Endpoints:**

**ClinicalTrials.gov** – database maintained by the US National Library of Medicine.
- Includes nearly 300,000 privately and publicly funded clinical studies conducted in all 50 states and 207 countries.
- Many local IRB’s require registration on ClinicalTrials.gov as a condition for approval.
- Many publications (including PTJ) require prospective registration on ClinicalTrials.gov as a condition for publication.
- Primary study outcomes are announced in advance.
- Requires updates at least every 6 months and reporting of outcomes and adverse events within 1 year of completion.

**Common Data Elements (CDEs)** – National Institute of Neurological Disorders and Stroke (NINDS) sponsored project designed to develop, distribute, and standardize collection of research data, in order to compare research findings more effectively across studies.
- General CDEs have been developed, which are common to many neurological disorders. In addition, 24 disease-specific CDE’s have been established by teams of experts in each area.
- Distinguishes between Core, Recommended, and Exploratory CDEs
  - Core – applicable to any study (ex: demographic information) or to a specific disease state (ex: Ranchos scale in TBI)
  - Supplemental/Highly Recommended – essential, based on certain disease states or study designs
  - Exploratory – some promising information is available, but additional validation is required before more widespread use can be recommended
- Standardize case report forms are freely available for researchers to download and record clinical study data

**Health Measures** – a free, publicly available battery of measurement systems, developed as a collaboration between 12 NIH Institutes and dozens of scientists from multiple external academic institutions.
- Addresses physical, mental, and social well-being, as well as physical, social, sensory and cognitive function.
- Suitable for healthy individuals and patients – individual scores are provided, as well as population-based normative scores. Able to provide an individual score as well as a standardized score against a reference healthy population.
- Most measurement batteries are available in multiple languages and as a paper test, mobile app, or web-based format.

**Health Measures includes the following:**

**PROMIS** – reliable patient-reported measures of physical, mental, and social health. A wide range of measures have been validated for children and adults, published in over 40 languages, available in paper and electronic formats, and can evaluate pain, fatigue, depression, anxiety, sleep, social function, and sexual function among others.
Quality of Life in Neurological Disorders (NeuroQOL) – designed to track mental, physical, and social ramifications of living with a neurological disorder. Suitable for ages 8-90: contains 17 adult content areas and 11 pediatric content areas. Diagnoses include: multiple sclerosis, Parkinson’s disease, epilepsy, amyotrophic lateral sclerosis, and muscular dystrophies. Ex: Physical health subset includes lower extremity function and mobility, upper extremity function and fine motor control, fatigue, and sleep problems.

Adult Sickle Cell Quality of Life Measurement System (ASCQ-Me) – patient reported outcome measurement system for individuals aged 19-90 diagnosed with sickle cell disease.

NIH Toolbox: diverse set of physical, sensory, emotional, and cognitive functional outcome measures. Appropriate for ages 3-85 years, as well as a multitude of chronic diseases. Over 100 outcome measures can be used alone, or as a 30-minute battery addressing one of the four measurement domains. Includes both performance-based and self-report measures. Example: early childhood motor battery: evaluates dexterity, grip strength, standing balance, and endurance.

PROsetta Stone – a research tool designed to provide a standardized metric for comparing PROMIS-developed instruments to other instruments (ex: SF-36).

Clinical Tools Available to Guide Outcome Measure Selection:

Evaluation Database to Guide Effectiveness (EDGE) – taskforce initiate by the Section on Research in 2006, with objective to identify most relevant tests and measures in a practice area. Provides recommendations for acute care, inpatient/outpatient settings, entry-level education in a variety of neurological conditions, cancer rehabilitation.

Physical Therapy Outcomes Registry – a qualified clinical data registry (QCDR) approved by the Center for Medicare and Medicaid Services (CMS) to report outcomes required by the CMS Merit-based Incentive Payment System.

PTNow – APTA-sponsored initiative to provide member clinicians with evidence-based resources to facilitate evidence-informed practice and optimize clinical decision making. Resources include: clinical summaries, detailed instructions for tests and measures, clinical practice guidelines, Cochrane reviews, and article search/access. In addition, members may access the Rehabilitation Reference Center, a resource provided by EBSCOhost that includes information on diagnoses, medications and supplements, patient education, images of exercises, and other practice resources.

Similarities in Research and Clinical Approaches to Patient Assessment
- Measures selected in advance and validated for patient population
- Standardized testing approach: equipment, tester, time of day, instructions
- Outcomes are used to justify an intervention

Differences Between Clinical and Research Assessments
- Length/complexity of outcomes can be much greater in clinical trials (multi-day visits)
Clinical trials may include new (exploratory) outcome measures.
Clinical trials may also include composite outcome measures, which measures an effect based on multiple endpoints. Useful when the experimental product may benefit participants in multiple ways.
Objectives: detection of statistically-significant vs clinically-meaningful differences
Time-points to track outcomes over time – precise window required in clinical trials
Trial participants meet an established (typically narrow) set of entry criteria, and the study design provides precise, deliberate control of potential confounding variables, including comorbidities and effects of learning.

2. Discuss potential influences of clinical care on function, measured as study endpoints, using a case example.

Case Example: Effects of Respiratory Exercise and AAV-Mediated Gene Therapy in Children with Pompe Disease

Respiratory Management of Neuromuscular Disease
Widespread, historical basis for need: respiratory problems account for largest proportion of morbidity and mortality in most neuromuscular diseases.
Pulmonary function, hypoventilation, respiratory failure
Retention of secretions, airway clearance dysfunction
Sleep-disordered breathing
Related issues: nutritional problems, scoliosis

Major advancements in past 10-20 years:

Clinical Care Guidelines:
- Both diagnosis-specific (DMD, BMD, SMA, Pompe disease) and general (children with NMD) guidelines have been published and/or updated within the past 5-10 years. Guidelines include primary care neurological, orthopedic, nutritional, pulmonary, and rehabilitation evaluation and treatment recommendations.
- Routine use of pulmonary hygiene, ventilatory support, and/or exercise may result in gains in clinical lung function tests that can confound clinical trial findings.
- Record detailed use and/or changes in any of the following:
  o Mechanical insufflation – exsufflation (Cough Assist)
  o BiPAP or Non-Invasive Ventilation
  o Lung Volume Recruitment Therapy
  o Respiratory Muscle Training

3. Specific strategies to improve communication between clinical providers, study participants, and investigators.

Communication Tips for Clinicians:
- Ask for permission to contact the study team – establish whether there are
- Identify study outcome measures and timeframes for testing
- Inquire regarding requirements and restrictions on physical activities
- Sign up for automatic updates from clinicaltrials.gov and PubMed
Communication Tips for Researchers:

- Ask your subjects whether they participate in rehabilitation. Identify the frequency, type, and focus of each individual therapy.
- Establish other clinical supportive therapies and devices used at baseline. Update this information at each study encounter.
- When possible, educate patients on the meaning of their standardized test results.
- When possible, standardize the clinical rehabilitation intervention, if the outcome measures are performance based and susceptible to influence from clinical care.
Looking Ahead: The Diagnosis You Knew Yesterday Is Not the Disorder You Treat Today (20 min plus 5 min Q&A), K. Krosschell

1. Review the history of pivotal trials for spinal muscular atrophy drug approvals.
   - Tackling a rare disease: working toward a treatment
   - SMA as an ideal candidate for rational drug discovery: Unique back-up gene lays the stage for ongoing work
   - From mice to men, past to present: How did we get where we are today?

![Timeline diagram showing key events in SMA research and drug development.](Image)

- Targets in drug development and treatment strategies

![Diagram showing various treatment options for SMA patients.](Image)

- The drug pipeline

![Drug pipeline image.](Image)

- Standard of care: development, updates and education
  - How standard of care may shape or influence new studies
• The clinical outcome vs biomarker in pivotal trials:
  o Selecting, developing and modifying fit for purpose clinical outcome measures in a rare disease requires understanding of:
    ▪ Disease etiology and natural history, rate and variability of symptoms, onset, etc
    ▪ Phenotypic heterogeneity/subsets and evolving changes in phenotypic spectrum
    ▪ Patient age ranges
    ▪ Attempt to understand and target manifestations of disease most meaningful to patients
  o Critical role of the PT in the process
    ▪ Functional outcomes
    ▪ Patient reported outcome measures (PROMs)
    ▪ Reliability, validation, sensitivity, standardization
    • Modification and new development with changing phenotypic spectrum

2. Contrast the natural history of untreated infantile spinal muscular atrophy with results from clinical trials of emerging and approved treatments.
• The changing landscape:
  o Evolution of a rare disease over time (SMA as a prime example)
  o Changes and impacts over time: What you need to know
    ▪ No treatment (natural history) → standard of care (new natural history) → pharmacologic clinical trials → early access programs → commercial pharmacological treatment and availability (timeline)
  o No treatment → pre-symptomatic treatment → later treatment
    ▪ What we now know, what we don’t know
  o Case studies/videos for SMA (type 1, type 2, type 2)

3. Project future directions for expanded testing and approvals in SMA.
• Ramping up:
  o Education and advocacy (physicians, families, caregivers and patients)
  o Patient registries
  o Clinical trial readiness
  o Newborn screening
  o Clinical centers of excellence
  o The patient voice
    ▪ Ethics
    ▪ Identity
    ▪ Meaningful change

Panel Discussion (20 min), Krosschell, Pariser, Senesac, Smith
• Methods for PTs to learn about clinical trials available to their patients
• Communication strategies between study investigators and clinicians
• Approaches for PTs to stay up to date