



Translation of Promising Therapeutic Compounds to Clinical Trials in Duchenne Muscular Dystrophy

Andrew Skalsky, MD

Neuromuscular Medicine Clinical Fellow
Department of Physical Medicine & Rehabilitation
University of California, Davis



Key Players

- **FDA**: Food & Drug Administration
- **Industry**: pharmaceutical companies
- **Funding Agencies**: NIH, MDA
- **Academic Centers**: Major university medical centers
- **Patients & Families**



FDA Defined Steps in Drug Development

- Pre-clinical studies
- Phase 1 clinical trials
- Phase 2 clinical trials
- Phase 3 clinical trials



FDA Defined Steps in Drug Development

- **Pre-clinical studies**

- Toxicology studies use agent at 10X dose for clinical trial
- Route of administration, regimen and duration must mimic clinical trial



FDA Defined Steps in Drug Development

- **Phase 1**: *Safety and Biologic Activity*
(how does the compound work and is it safe?)
- **Phase 2**: *Activity, Dosing, Efficacy*
(effect on outcomes, optimal dose)
- **Phase 3**: *Unequivocal efficacy* (large sample size, consistent outcomes across groups)



FDA Defined Outcomes

Testing must display clinically meaningful outcomes

- “Clinically Meaningful” = Does the patient or family consider it life altering?



Clinically Meaningful Outcomes

- Depends on:
 - Disease
 - Severity / stage of the disease
 - 5 year old boy vs. 18 year old man with DMD
 - Personal factors
 - Patient or family member?



Clinically Meaningful Outcomes for DMD

- Clinically Meaningful Outcomes:
 - Ambulatory or Walking Function
 - Functional Status (dressing, feeding, transfers)
 - Pulmonary / Cardiac Complications
 - Patient Reported Quality of Life



Accelerated (Fast Track) FDA Approval

- Validated **surrogate** measures facilitate bringing compounds to market for serious or life-threatening diseases
- Therapeutic benefit must be greater than existing treatments
- Approval includes on-going commitment to further document true clinical benefit



Surrogate Measures or Outcomes in DMD

- **Surrogate Outcomes:**
 - Amount of Dystrophin in muscle biopsy
 - Creatine Kinase levels
 - Lean Tissue Mass
 - Quantitative Strength
 - Timed Functional Testing
 - Lung Forced Vital Capacity (FVC)



Clinical Trials in DMD

- Primary Endpoints or Outcomes
- Secondary Endpoints or Outcomes



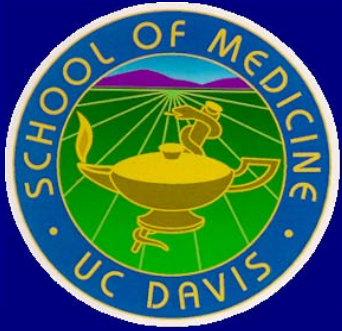
Clinical Trials: Primary endpoints

- Primary Endpoints:
 - Sensitive and specific to treatment effect
 - Sufficient preliminary data to power a study
 - Examples
 - Quantitative Strength
 - Timed Functional Testing
 - FVC
 - **ALL SURROGATE OUTCOMES**



Quantitative Strength Testing in DMD

Testing of the strength of various muscles, such as measurement of knee extension torque, is one of the measures used as a primary end point in clinical studies of DMD.



How clinically meaningful is quantitative strength?

- e.g. is a 20% increase in peak knee extension torque clinically meaningful?



Timed Functional Testing

- Time to run 10 meters or 30 feet
- Time to climb 4 steps
- Time to stand from supine position
- Advantages:
 - Measure changes in disease progression over short time intervals
 - Highly Reliable
 - Easily Obtained
- Problem: Are changes *clinically meaningful* to patients?



Predicting Transition to Wheelchair in DMD

- **Time to walk/run 30 feet**
 - **< 6 sec → > 2 years to chair (100%)**
 - **6-12 sec → 1-2 years to chair**
 - **> 12 sec → < 1 year to chair (100%)**



Clinical Trials: Secondary Endpoints

- Secondary Endpoints:
 - Unknown Sensitivity and specificity in relation to treatment
 - Insufficient preliminary data to power a study
 - **BUT Clinically Meaningful**
 - 6 minute walk test
 - Step Activity Monitoring
 - Patient-reported Quality of Life
 - Complications / secondary conditions



Development of new Clinical Outcomes

- 50 meter Walk/Run
 - Real World Distance
- 6 minute Walk Test
 - Previously used for other diseases
- Community Gait testing
 - StepWatch Activity Monitor (SAM)



StepWatch Activity Monitor (SAM)

(Cyma, Seattle, WA)

- i.e. Super Pedometer
- Accuracy exceeds 99.5% at variable cadences
- Quantify Levels of Ambulatory Activity
- Community based measure
(real-world mobility)





StepWatch Activity Monitor (SAM)

- **Next Step:**
- Collect longitudinal natural history data
- Assess day to day variability
- Assess seasonal influences
- Use the measure as a secondary outcome measure for a pharmacologic intervention



Quantitative Assessment of “Real-world” Ambulatory Activity:

- 1) When during a day subject is active/sedentary
- 2) Magnitude of peak activity
- 3) Avg. total daily physical activity over extended sampling time
- 4) Unobtrusive monitoring in community
- 5) Clinically Meaningful



Other Important Outcome Measures

- Neuropsych testing / Cognitive Functioning
- Affective disorders / Psychological problems
- Health-related Quality of life Surveys
 - General measures (SF-36, Peds QL, POSNA)
 - Disease-specific quality of life **measures**



What is next?

- We need to establish data for *clinically meaningful outcomes* before any therapeutic trials can go through FDA drug approval process.



What can YOU do?

- We need *volunteer patients* to establish the data for clinically meaningful outcomes. Then these outcomes are available for therapeutic intervention trials such as pharmacologic compounds.



Industry-Academics- Patients Partnership

- Role for academic centers in drug development:
 - 1) *Building Natural history database*

Identify surrogate markers that predict outcome, including the co-morbidity profile and burden of disease
 - 2) *Build the Tools to establish clinically meaningful results*

Quantitative, relevant and logistically feasible adaptable to multi-clinic, multi-country settings



Industry-Academics-Patients Partnership

- Role for academic centers in drug development (cont.):

3) *Centralized database for molecular diagnoses*

Facilitates planning and implementation of clinical trials

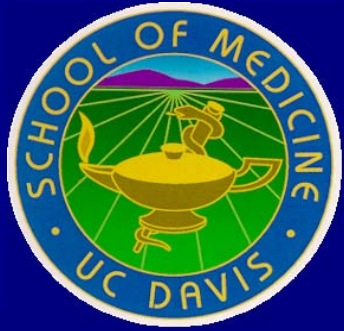
4) ***Clinical networks to conduct therapeutic trials***

Access to Patients and Families



Challenges in Clinical Trials

- Authorities agree that we need to:
 - *Develop natural history database*
 - *Develop better tools for clinical trials*
 - *Establish networks for clinical trials*



University of California, Davis

Thank You