Measuring Outcomes in the Face of Variability

Parent Project Muscular Dystrophy
JOIN THE FIGHT. END DUCHENNE.

Clifford Bechtold
June 27, 2019

The Challenge

- Find a means to demonstrate an improvement (disease modifying) or stabilization of disease (symptomatic)
- Measurement must be:
  - Accurate
  - Easy to perform with acceptable patient burden
  - Reliable and accessible equipment
  - Cost-effective
- Define the contribution of investigational agent

Evolution of Endpoints in HIV

Omari, M (2019)

#PPMDConference
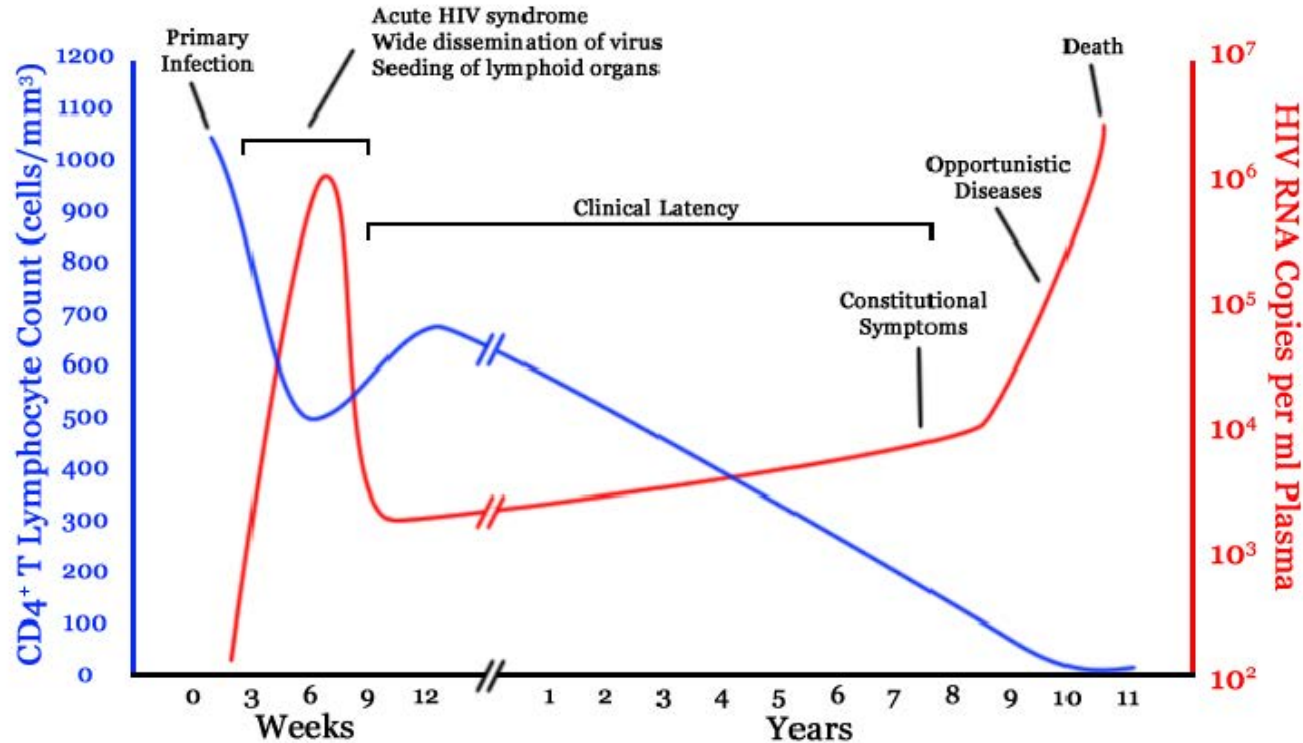
Outcomes should:

- Correlate with disease progression
- Represent how a patient "feels and functions"
- Be reliable, repeatable
- Be objective, not subjective
- Be validated

Ease of Testing

- Straight forward technique
  - Easy to teach
  - Easy to perform well
- Quality control
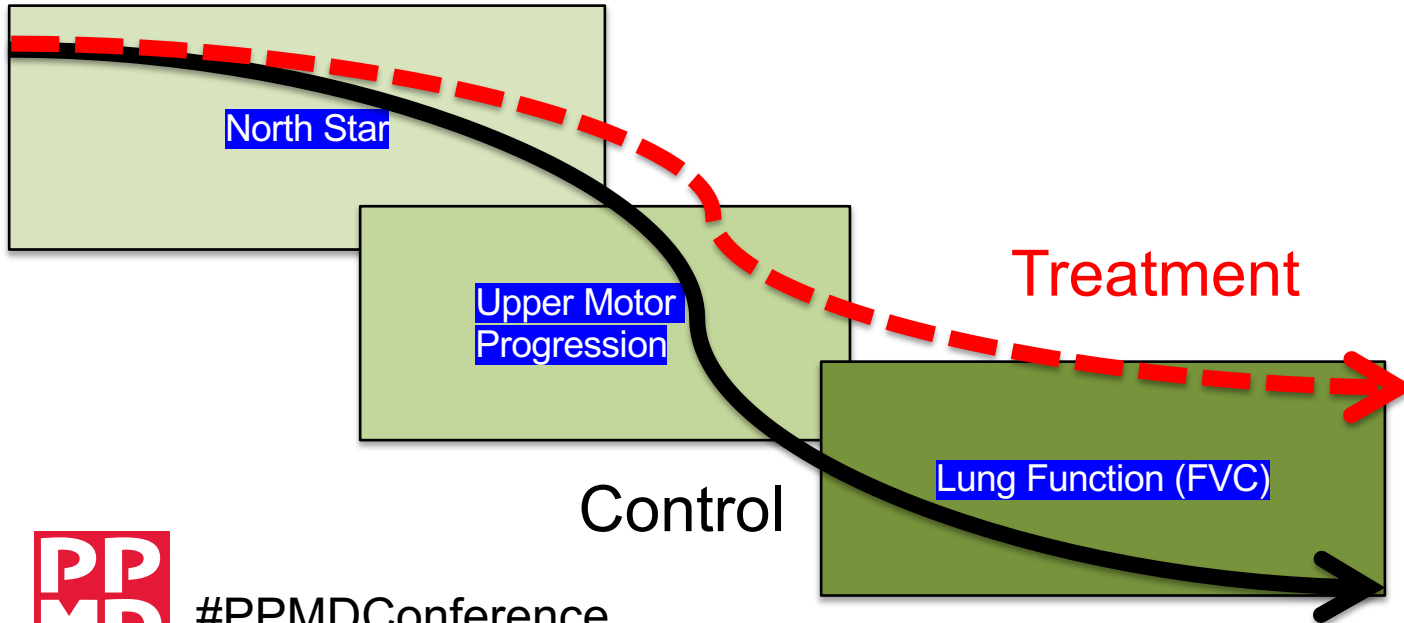 - Over-reading
  - Standardized Execution

Outcome Measures

- Functional Test or Timed Function Testing (North Star, 4SC)
- Biomarker
  - Ideally direct link (imaging)
  - Correlation vs Coincidence (CK)
- Patient Reported Outcome (PRO)
- Activities of Daily Living (ADL)
- Rating Scales – (PODCI)

PP MD

#PPMDConference

DMD Endpoint Evolution

North Star

Upper Motor Progression

Treatment

Control

Lung Function (FVC)

#PPMDConference

Additional Biomarkers

Examples of biomarkers are included in this study to further assess pharmacodynamic activity

Biomarker	What it Measures/Reflects
Dystrophin Level	Measure of protein expression
Muscle Proteins (CK, ALT)	Protein measures of muscle health
DXA Imaging	Lean body mass, fat mass, BMD
Serum Micro RNAs	Associated with muscle atrophy
Urine Titin	Associated with muscle atrophy
MRI and cMRI	Muscle Volume, Fat Fraction, Ejection fraction, volume of fibrosis
Accelerometry - Wearable	Activity level, objective measure of falls

Typical Study Data Collection to Ensure Signal Detection

- ***Primary Objective***
  - Compare the change from baseline in Four Stair Climb (4SC)
- ***Secondary Objectives***
  - Compare the change from baseline at Wk 48:
    - NSAA total score – 17 different data points / visit
      - Stand from supine velocity
      - 10 m walk/run velocity
    - Pediatric Outcomes Data Collection Instrument (PODCI) total sub score
    - Proximal lower extremity flexor strength measured using manual myometry
    - 6 Minute Walk Distance
- ***Exploratory Endpoints - Change from baseline in:***
  - Performance of Upper Limb (PUL) total score
  - Pulmonary Function Tests (FVC, % predicted FVC, FEV1, MEP, MIP, CPF, PFR)
  - Pediatric Outcomes Data Collection Instrument (PODCI) total score
  - cMRI measures of EF, fractional strain, fibrosis
  - Strength of should abductors, elbow flexors & extensors, hip abductors, grip & pinch
  - Health Utilities Index III & Peds QL Family Impact Module scores
  - DXA measures of lean body mass, fat mass, BMD

**PP
MD**

#PPMDConference

Our Challenges in Duchenne

- High variability in disease progression and performance
- Patients are growing as disease progresses
- Many interventions are symptomatic vs disease modifying
- Endpoints may not reflect direct improvement
- Measurement errors with manual data collection
- Treatment effect depends on the baseline
- Limit the measure to avoid fatigue or patient risk
- Rare diseases limit number of patients
- Impact of other non-standardized interventions (steroids, PT)

PP MD

#PPMDConference

How accurate can we be?

Pediatric Outcomes Data Collection Instrument (PODCI)

- PODCI can document functional status changes in children and adolescents
- PODCI sub-constructs or domains measure –
  - upper extremity function, transfers and mobility, physical function and sports, comfort (lack of pain), happiness, satisfaction, and expectations
- The scale has established psychometric properties – reliability, internal consistency, and discriminant validity
- Pediatric trials in various therapeutic areas have shown PODCI to be responsive to changes in patient's underlying disease condition

PPMD

#PPMDConference

PODCI domains show good correlations with clinical trial endpoints

Correlations between DMD clinical endpoints and PODCI domains

◇ Sports/Physical   □ Transfers   △ Happiness
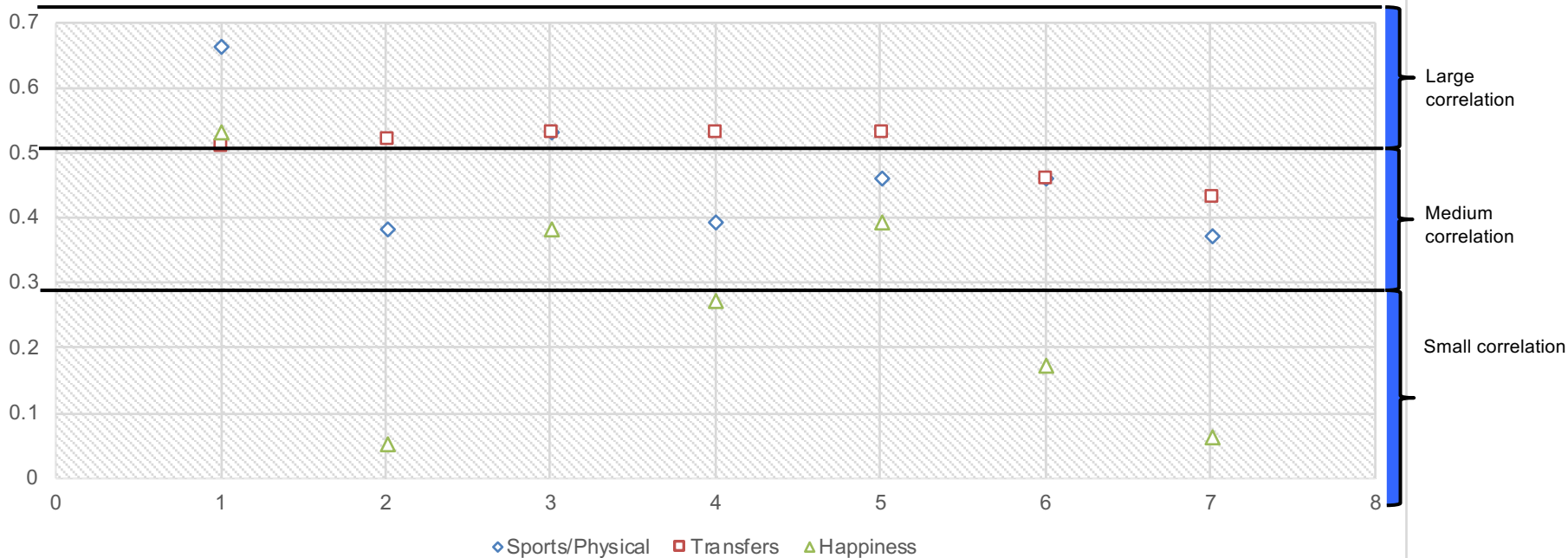
1 = age; 2= Vignos lower extremity; 3=Time to stand from Supine; 4=Time to climb 4 stairs; 5=Time to walk/run 10 meters; 6=Isometric knee ext per Kg; 7=Walking velocity

Takeaways

What are we doing to optimize our outcomes data

- Improve the standardization of endpoint selection and training
  - Discussion with Health Authority on preferred endpoints (ie Platform Trial)
  - Reduce risk of coaching and training by how we define the endpoint
- Improved use of Technology: (Wearables and Video Measurements)
  - Better test measurement
  - Ability to confirm training and quality of the implementation
  - Determine quality of performance
  - Ability to measure activity in out-patient settings
- Collection of prospective patient natural history data

What are we doing to optimize our outcomes data

- Developing disease models to predict performance
  - CINRG, C-TAP, D-RSC (Critical Path Institute)
- Better characterize the complete life-span of disease
  - Need to consider the patient's development and disease
  - Generating appropriate non-ambulatory endpoints
  - Develop a single endpoint that can measure disease progression and treatment effect (composite?)
- Advancing the science to understanding disease factors
  - Implications of gene mutations on disease progression
  - Characterizing co-factors that correlate with different rates of progression
- Openly sharing our learnings, data and modeling

PP
MD

#PPMDConference

Thank you!