ACTIVE: Utilizing video game technology to quantify function and measure change across the lifespan

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Learning Objectives:

Upon completion of the course, the learner will:

- Provide at least one example of a feasible application of this type of outcome technology to PT practice in a clinical or research setting.
- Correctly explain how integrating technology into physical therapy practice advances the field and fosters interdisciplinary collaboration.
- Accurately summarize the process of relating ACTIVE scores to clinically meaningful functional outcomes.
- Describe the steps associated with the FDA Clinical Outcome Assessment Qualification Program.

About Us

- Our Team: Neuromuscular Physical Therapists, Center for Gene Therapy at Nationwide Children’s Hospital

- Typical Week:
  - 25% Clinical:
    - Evaluate patients in multidisciplinary MDA, SMA, and Neuromuscular Clinics
  - 75% Research:
    - Outcome measure development
    - Perform functional assessments for children enrolled in clinical trials
    - Grant and manuscript writing
    - Training other PTs to perform specialized outcome measures
Quick Overview:

Neuromuscular Disease: a broad term that encompasses a group of conditions which affect any part of the nerve or muscle

Duchenne Muscular Dystrophy (DMD)

- Dystrophin works to strengthen muscle fibers
- Protect from injury
- Serves as anchor between cellular cytoskeleton and extracellular matrix
- Cells without dystrophin are damaged over time with repeated cycles of contract/relax
- Progressive muscle weakness
DMD cont.

<table>
<thead>
<tr>
<th>Duchenne</th>
<th>Becker</th>
</tr>
</thead>
<tbody>
<tr>
<td>No dystrophin</td>
<td>Some dystrophin</td>
</tr>
<tr>
<td>• Progressive muscle weakness diagnosed early</td>
<td>• Loss of ambulation after 15 yr</td>
</tr>
<tr>
<td>• Decline in function ~7yr</td>
<td>• Diagnosis can occur as late as the 8th decade</td>
</tr>
<tr>
<td>• Loss of ambulation ~12yr</td>
<td>• Milder phenotype due to partially-functional dystrophin</td>
</tr>
<tr>
<td>• Severe cardiomyopathy &amp; respiratory decline</td>
<td>• Death in 20-30s</td>
</tr>
<tr>
<td>• Death in 20-30s</td>
<td>• Loss of ambulation after 15 yr</td>
</tr>
</tbody>
</table>

DMD Clinical Presentation

- Increased proximal v. distal weakness
- Gower’s maneuver
- Frequent falls
- Gait impairments
- Calf pseudohypertrophy; DF ROM limitation
- Increase in skills up to age 7
- Loss of ambulation around 12 years
- High risk for scoliosis once nonambulatory
- Progressive cardiomyopathy & respiratory decline

Photos courtesy of Wendy King, PT
DMD Clinical Care

Current care guidelines:
  - Part 1: Diagnosis, and neuromuscular, rehabilitation, endocrine, and gastrointestinal and nutritional management
  - Part 2: Respiratory, cardiac, bone health, and orthopaedic management
  - Part 3: Primary care, emergency management, psychosocial care, and transitions of care across the lifespan

DMD Treatment and Research

- No Cure
- Timeline of DMD
The Truth About Clinical Trials

- Required for advancements in treatments
- May not help the participant
- Initial trials are small and have strict inclusion criteria
- Many years before FDA approval—only 9.6% of drugs are approved (Nature).

2011 at Nationwide Children's Hospital

- Recruiting for a groundbreaking clinical trial studying Eteplirsen (Exondys 51) in ambulant boys with DMD
  - 12 participants 7-13 years old, must walk within 200 and 400 meters on the 6MWT
- Local family had 2 sons with DMD
  - Younger son qualified for the study
  - Older son was no longer able to walk far enough in the 6MWT

Identifying the Need

Linda Lowes, PT, PhD  Lindsay Alfano, PT, DPT, PCS
ACTIVE: Ability Captured Through Interactive Video Evaluation

ACTIVE development

- Need for a valid & reliable measure of upper extremity function in DMD for use in both clinical and research environments
  - Continuous scale variables
    - Minimal training required
    - Consistent motivation
    - Reduce variability
    - Utility across the disease spectrum

Workspace Volume

- Quantifies the accessible area surrounding a patient
- Relevant in ambulatory & non-ambulatory patients
- Expected to relate to function as functional tasks require a discrete amount of space
  - Typing
  - Eating
  - Dressing
Phase I: Proof of Concept

Partnership with Vectorform
Software development company

• Lessons learned:
  – Our idea could work!
  – Communication across disciplines is challenging
  – Measuring velocity/fatigue consistently is difficult

Phase II: ACTIVE

Partnership with colleagues at The Ohio State University
Students working on software development as part of their curriculum

• Lessons learned
  – Boys with DMD need to be motivated to reach
  – Pros/cons of working with students
Phase III: ACTIVE

Partnership with Multivarious Games
Software development company familiar with working in the healthcare space

• Lessons learned
  – Company invested in the work
  – Patients during development is key

Phase IV: ACTIVE

Partnership with thePlan
Software development company familiar with working in the healthcare space

• Lessons learned
  – Technology is constantly evolving, need software that can be easily transferred to other platforms

ACTIVE Trial
ACTIVE score

Raw Score is reported as cubic meters of volume
ACTIVE score is scaled for age and size based on a subject’s height:

\[
\text{ACTIVE score} = \left( \frac{\text{raw score} (\text{m}^3)}{\text{predicted score based on height}} \right) \times 100
\]

Generally: If the subject can lean while reaching he will score over 100
Poor trunk control/limited antigravity movement gives score <100

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ACTIVE Completion Report

Subject ID: SMA28
Visit Date: 23-Aug-2017
Ulna Length (cm): 18
Brooke Level: 2
Diagnosis: SMA2

Age (yr): 7
Last Successful Calibration: 23-Aug-2017T04:12:38

<table>
<thead>
<tr>
<th>Trial Time (s)</th>
<th>Total Volume (m³)</th>
<th>Scaled Score</th>
<th>Trunk Left (m)</th>
<th>Trunk Center (m)</th>
<th>Trunk Right (m)</th>
</tr>
</thead>
<tbody>
<tr>
<td>70</td>
<td>0.321</td>
<td>91.74</td>
<td>0.065</td>
<td>0.173</td>
<td>0.102</td>
</tr>
</tbody>
</table>

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Evaluating the Reliability and Validity of ACTIVE
Validity

1. **Concurrent validity** measures the test against a gold standard and high correlation indicates that the test has strong criterion validity.
2. **Criterion Validity** assesses whether a test reflects a certain set of abilities.
3. **Content validity** is the estimate of how much a measure represents every single element of a construct.

1. **Concurrent Validity**: ACTIVE v. VICON

- ACTIVE uses sternum and wrist joints only
- Shoulder position is different between systems

<table>
<thead>
<tr>
<th>Brooke Level</th>
<th>ACTIVE v.SWSV</th>
<th>Median</th>
<th>IQR</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>362</td>
<td>154.64</td>
<td>(137.11, 176.15)</td>
</tr>
<tr>
<td>1</td>
<td>14</td>
<td>99.43</td>
<td>(96.14, 114.95)</td>
</tr>
<tr>
<td>2</td>
<td>15</td>
<td>75.19</td>
<td>(65.56, 99.85)</td>
</tr>
<tr>
<td>3</td>
<td>17</td>
<td>26.67</td>
<td>(21.69, 35.09)</td>
</tr>
<tr>
<td>4</td>
<td>10</td>
<td>20.87</td>
<td>(17.85, 28.25)</td>
</tr>
<tr>
<td>5</td>
<td>6</td>
<td>9.86</td>
<td>(6.20, 12.01)</td>
</tr>
</tbody>
</table>

p-value <0.001 using Jonckheere-Terpstra test for trend

2. Criterion Validity: ACTIVE measures upper extremity ability

PROMIS: Person centered measure that evaluates the respondents ability to do functional activities with hands and arms

3. Content Validity: how much a measure represents every single element of a construct

<table>
<thead>
<tr>
<th>Test Description</th>
<th>Correlation ACTIVE</th>
<th>Correlation Trunk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Revised Upper Limb Module</td>
<td>Rₛ = 0.92</td>
<td>P&lt;0.001 N=22</td>
</tr>
<tr>
<td>Expanded Hammersmith Functional Motor Scale</td>
<td>Rₛ = 0.85</td>
<td>P&lt;0.001 N=23</td>
</tr>
</tbody>
</table>
**ACTIVE: Function**

<table>
<thead>
<tr>
<th>Function</th>
<th>Correlation ($r_e$)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-minute walk test</td>
<td>0.36</td>
<td>0.02</td>
</tr>
<tr>
<td>100 meter timed test</td>
<td>-0.54</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>10 meter walk/run</td>
<td>-0.52</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Rise from floor</td>
<td>-0.35</td>
<td>0.006</td>
</tr>
<tr>
<td>NSAA</td>
<td>0.54</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PUL</td>
<td>0.86</td>
<td>0.04</td>
</tr>
</tbody>
</table>

**ACTIVE in DMD Longitudinal**

Discrete quantities of WSV are required for individual functional activities. These graphs show the minimal workspace volume required for select functional activities. Increased WSV should directly improve function.

**ACTIVE Scores Are Meaningful to Patients, Regulators, and Payors**
ACTIVE: Trunk strength influences performance

- Ambulant boys have better trunk strength therefore they can lean and reach further.
- Non ambulant boys with the same Brooke level score lower due to decreased trunk strength and lesser ability to lean.

Responsiveness to Change

Natural history suggests a decline in function over time.
Treated group shows increased WSV and therefore improved function.

DMD Cohort Compared to healthy age-matched peers

<table>
<thead>
<tr>
<th>Age</th>
<th>Control WSV</th>
<th>DMD WSV</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>121.4 ± 35.9</td>
<td>64.0 ± 1</td>
</tr>
<tr>
<td>5</td>
<td>130.3 ± 30.0</td>
<td>108.5 ± 32.5</td>
</tr>
<tr>
<td>6</td>
<td>136.5 ± 33.3</td>
<td>140.9 ± 48.1</td>
</tr>
<tr>
<td>7</td>
<td>150.3 ± 37.4</td>
<td>120.8 ± 31.2</td>
</tr>
<tr>
<td>8</td>
<td>147.6 ± 24.4</td>
<td>130.1 ± 32.7</td>
</tr>
<tr>
<td>9</td>
<td>146.9 ± 29.8</td>
<td>95.5 ± 42.1</td>
</tr>
<tr>
<td>10</td>
<td>145.7 ± 28.7</td>
<td>93.7 ± 35.9</td>
</tr>
<tr>
<td>11</td>
<td>160.4 ± 32.3</td>
<td>98.7 ± 37.3</td>
</tr>
<tr>
<td>12</td>
<td>160.3 ± 31.1</td>
<td>97.3 ± 28.1</td>
</tr>
<tr>
<td>13</td>
<td>157.0 ± 25.4</td>
<td>69.1 ± 35.1</td>
</tr>
<tr>
<td>14</td>
<td>159.3 ± 19.7</td>
<td>81.5 ± 48.9</td>
</tr>
<tr>
<td>15</td>
<td>164.4 ± 37.1</td>
<td>72.2 ± 48.1</td>
</tr>
<tr>
<td>16</td>
<td>154.6 ± 15.2</td>
<td>19.4 ± 17.0</td>
</tr>
<tr>
<td>17</td>
<td>185.2 ± 15.8</td>
<td>18.8 ± 21.8</td>
</tr>
</tbody>
</table>

- Only a small number of boys with DMD met or exceeded the average scaled WSV of our control group.
- Identify deficit in higher functioning individuals.
- Reduce ceiling effect seen with other measures.
Broader Neuromuscular Cohort

ACTIVE scaled WSV declines with increasing Brooke level and compared to controls (p<0.001)
- In a larger cohort, the Jonckheere-Terpstra test for trend goes beyond identifying differences between groups and supports a stronger hypothesis that scaled WSV follows a downward trend with increasing Brooke level

<table>
<thead>
<tr>
<th>Group</th>
<th>Group #</th>
<th>Mean Age (SD)</th>
<th>Age Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>488</td>
<td>16.68 (13.31)</td>
<td>3.27 – 64.53</td>
</tr>
<tr>
<td>DMD</td>
<td>119</td>
<td>11.04 (3.85)</td>
<td>5.21 – 21.56</td>
</tr>
<tr>
<td>BMD</td>
<td>41</td>
<td>14.70 (4.70)</td>
<td>7.08 – 25.87</td>
</tr>
<tr>
<td>LGMD 2A</td>
<td>46</td>
<td>24.80 (13.23)</td>
<td>4.98 – 64.72</td>
</tr>
<tr>
<td>LGMD 2B</td>
<td>28</td>
<td>22.75 (11.71)</td>
<td>9.87 – 61.15</td>
</tr>
<tr>
<td>LGMD 2E</td>
<td>29</td>
<td>25.73 (11.73)</td>
<td>5.61 – 51.22</td>
</tr>
<tr>
<td>LGMD 2I</td>
<td>27</td>
<td>33.75 (16.02)</td>
<td>8.75 – 73.64</td>
</tr>
<tr>
<td>SMA Type 2</td>
<td>52</td>
<td>9.42 (5.89)</td>
<td>2.83 – 24.00</td>
</tr>
<tr>
<td>SMA Type 3</td>
<td>10</td>
<td>12.01 (3.55)</td>
<td>8.58 – 20.42</td>
</tr>
</tbody>
</table>

Characteristic of Good Outcome Measures

- Span a large range of ages and abilities
  - No functional ceiling or floor effects
  - Size/Age – Successful down to 4ish years
- Standardized Instructions
  - In-game tutorial DDT
- Reliable
  - ICC = 0.96, P<0.001
- Valid
- Affordable and Easy to Implement
  - Tutorial for Set up and Administration

FDA Clinical Outcome Assessment Drug Development Tool Qualification Program
What is a DDT-Qualified COA?

- The FDA certifies that the COA is a well-defined and reliable assessment of a specified concept of interest for use in adequate and well-controlled studies

Qualification Process:

1. Letter of Intent
2. Qualification Plan
3. Full Qualification Package

DDT Certified

FDA Feedback

Expected feedback:
- Cross-sectional & longitudinal data
- Relationship to function/meaningfulness

Other useful feedback:
- Objectivity/motivation – standardize instructions
- Consistency; comparison to visual field tests
- Focus on one diagnosis at a time
- Evidence that patients understand the assessment

ACTIVE-mini Overview
ACTIVE-mini uses color tracking to quantify the x, y, and z coordinates of the extremities at up to 30 Hz.

ACTIVE mini vs. Traditional Outcome Measure

- Actual CHOP Score
- Predicted Score

Actual v Estimated Score

- ICC: 0.945, p < 0.001
- Wilcoxon p=0.729

Mean = 6.4 ± 5.1
Median = 5.0 (0 – 24)
Mode = 3
Translation of ACTIVE into the Clinical Setting

Clinical Applications of ACTIVE

Pre & Post Core/UE Strengthening Program
Pre & Post rehab in Patient with Asymmetrical UE Abilities (CVA, CP, RTC)

Justify Equipment to Payors using Minimum WSSV Values needed for ADL Tasks

Demonstrate Functional Improvement with Initiation of Medical Treatment

ACTIVE Setup & Instructions

Equipment Needed
- Camera and Adapter
- TV or Projector
- Laptop or PC
- ACTIVE Software
- Segmometer

Space Requirements
- Minimum of 2.5 m x 2.5 m space
- Room for maximal reaching
ACTIVE Setup & Instructions

**Positioning**
- Patient sits comfortably in an armless chair or wheelchair
- Feet well-supported
- Remove lateral supports on wheelchair, if safe

**ACTIVE Setup & Instructions**

**Measuring Ulnar Length**
- Patient sits with right arm positioned on a table
- Elbow in 90 degrees of flexion
- Measure from posterior aspect of the olecranon process to the styloid process of the ulna
- Measure 3 times

**ACTIVE Setup & Instructions**

**Determining Brooke Level**

1. **Score = 1:** Starting with arms at the sides, the patient can abduct the arms in a full circle without shoulder or elbow flexion until hands reach overhead.
2. **Score = 2:** Can raise hands above head only by flexing the elbow (i.e. shortening the circumference of the movement) or using accessory muscles.
3. **Score = 3:** Cannot raise hands above the head but can raise a cup with 200g weight in the mouth using both hands if necessary.
4. **Score = 4:** Can raise hands to mouth but cannot raise a cup with 200g weight in the mouth.
5. **Score = 5:** Cannot raise hand to mouth but can use hands to hold pen or pick up pennies or a checker from table.
Let’s Practice!

Questions?

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