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

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OPTA Annual Conference
April 13, 2018

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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.

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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

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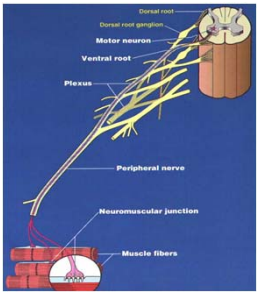
Quick Overview:

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



Gregory T C, Rehabilitation Management of Neuromuscular Disease, http://emedicine.medscape.com/article/321397-overview
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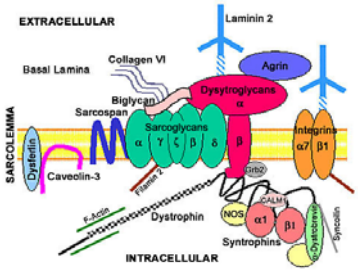
Neuromuscular Disease Umbrella

Metabolic Disorders	Myopathy	Neuromuscular Junction Disorders	Neuropathy	CNS/Spinal Cord Disorders

• Barth syndrome
• Leigh disease
	• Muscular dystrophy
	  • DMD
	  • BMD
	  • LGMD
	• Inflamm. myopathies
	  • DM
	  • PM
	  • IBM
		• Myasthenia Gravis
		• Congenital Myasthenia syndromes
		• Lambert-Eaton syndrome
			• Charcot Marie Tooth
			• Guillain Barré
			• Chronic Immune Demyelinating neuropathy
				• Spinal muscular atrophy
				• Hereditary spastic paraparesis
				• Friedreich ataxia

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

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DMD cont.

Duchenne — Becker

No dystrophin ⟷ Some dystrophin

- Progressive muscle weakness diagnosed early
- Decline in function ~7yr
- Loss of ambulation ~12yr
- Severe cardiomyopathy & respiratory decline
- Death in 20-30s

- Loss of ambulation after 15 yr
- Diagnosis can occur as late as the 8th decade
- Milder phenotype due to partially-functional dystrophin

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DMD Clinical Presentation

- Increased proximal v. distal weakness
- Gower's manuever
- 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

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DMD Clinical Care

Current care guidelines:

- Birnkrant DJ, et al. Diagnosis and management of Duchenne muscular dystrophy, Lancet Neurol. 2018.
  - 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

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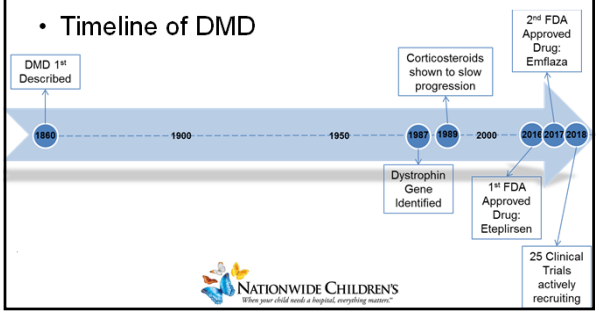
DMD Treatment and Research

- No Cure
- Timeline of DMD



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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).

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2011 at Nationwide Children's Hospital

- Recruiting for a ground-breaking 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

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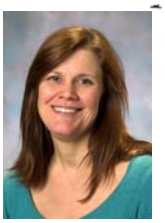
Identifying the Need



Linda Lowes, PT, PhD

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ACTIVE:

Ability Captured Through Interactive Video Evaluation

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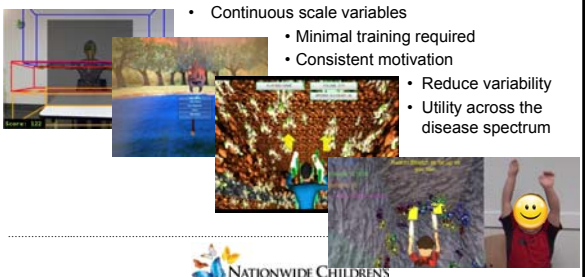
ACTIVE development

- 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



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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

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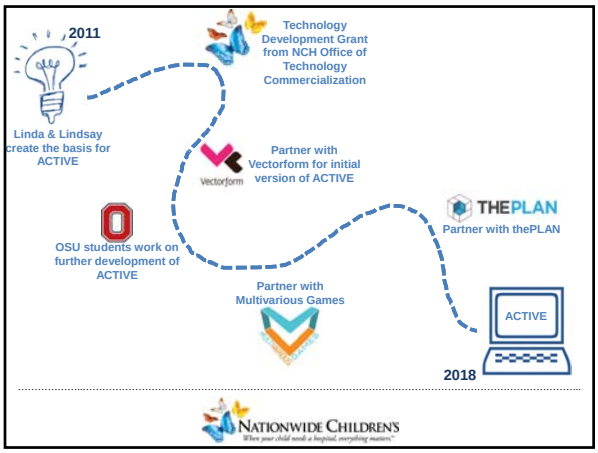

Phase I: Proof of Concept

Partnership with Vectorform

Software development company

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

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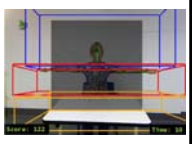
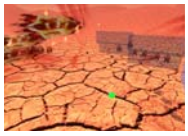
Phase II: ACTIVE

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



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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

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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

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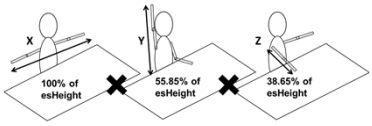
ACTIVE Trial

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:



$$ACTIVE\ score = \left(\frac{raw\ score\ (m^3)}{predicted\ score\ based\ on\ height}\right) x\ 100$$

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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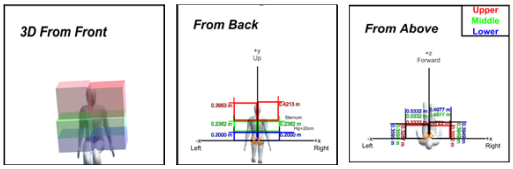
ACTIVE Completion Report

Subject ID: SMALB	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

Trial Time (s)	Total Volume (m^3)	Scaled Score	Trunk Left (m)	Trunk Center (m)	Trunk Right (m)
70	0.321	91.74	0.065	0.173	0.102
Expected [This Trial = 0.321, Expected = 0.42]					
70	0.379	72.76	0.093	0.173	0.101



Evaluating the Reliability and Validity of ACTIVE

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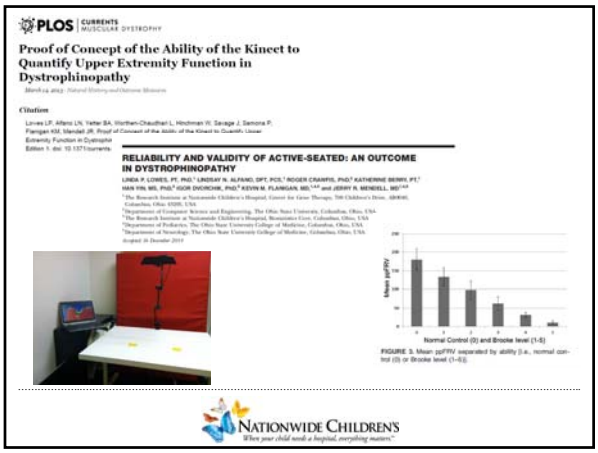
PLOS | CURRENTS MUSCULAR DYSTROPHY

Proof of Concept of the Ability of the Kinect to Quantify Upper Extremity Function in Dystrophinopathy

Citation

RELIABILITY AND VALIDITY OF ACTIVE-SEATED: AN OUTCOME IN DYSTROPHINOPATHY

FIGURE 3. Mean ppFRV separated by ability (i.e., normal control (0) or Brooke level (1–5)).

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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.

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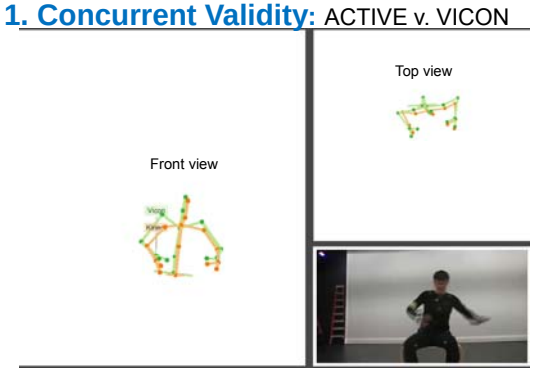
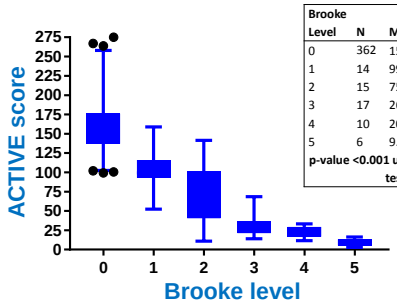
1. Concurrent Validity: ACTIVE v. VICON



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

Green is Vicon
Orange is Kinect

1. Concurrent Validity: ACTIVE v. Brooke



Brooke Level	N	ACTIVE sWSV Median	IQR
0	362	154.64	(137.11, 176.15)
1	14	99.43	(96.14, 114.95)
2	15	75.19	(45.56, 99.85)
3	17	26.67	(21.69, 35.09)
4	10	20.87	(17.33, 28.25)
5	6	9.86	(6.20, 12.01)

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

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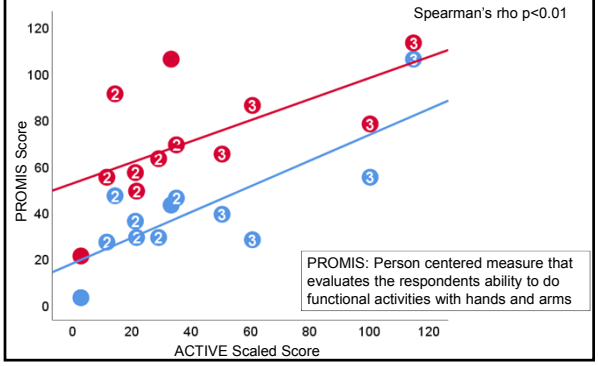
2. Criterion Validity:

ACTIVE measures upper extremity ability

PROMIS parent	0.70
PROMIS self	0.63

Spearman's rho p<0.01



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

	Test Description	Correlation ACTIVE	Correlation Trunk
Revised Upper Limb Module	20 items: placing hands on table, picking up small items, pushing buttons, and lifting weights	R_s= 0.92 P<0.001 N=22	R_s= 0.85 P<0.001 N=22
Expanded Hammersmith Functional Motor Scale	33 items: sitting, rolling, standing, walking and climbing stairs	R_s= 0.85 P<0.001 N=23	R_s= 0.73 P<0.001 N=23

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ACTIVE:
Function

	Correlation (R_s)	*P* value
6-minute walk test	0.36	0.02
100 meter timed test	-0.54	<0.001
10 meter walk/run	-0.52	<0.001
Rise from floor	-0.35	0.006
NSAA	0.54	<0.001
PUL	0.86	0.04

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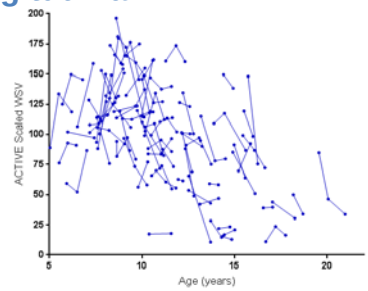
ACTIVE in DMD Longitudinal



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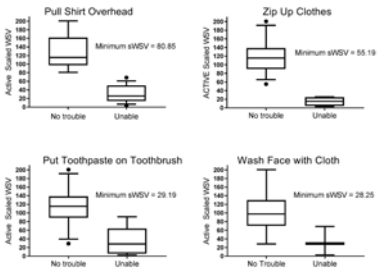
ACTIVE Scores Are Meaningful to Patients, Regulators, and Payors

Discrete quantities of WSV are required for individual functional actives

These graphs show the minimal workspace volume required for select functional activities

Increased WSV should directly improve function



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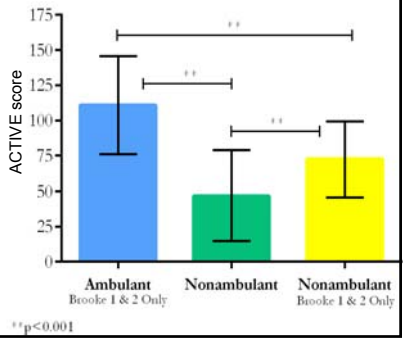
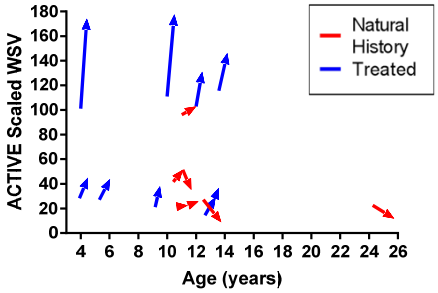
ACTIVE:
Trunk strength influences performance

- 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



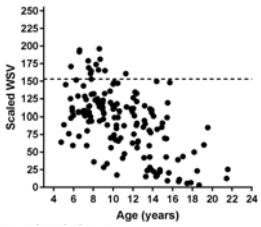
Natural history suggests a decline in function over time
Treated group shows increased WSV and therefore improved function

DMD Cohort
Compared to healthy age-matched peers

Age	Control	DMD
4	121.4 ± 35.9	64.0 ± 1
5	130.3 ± 30.0	108.5 ± 32.5
6	136.5 ± 33.3	140.9 ± 48.1
7	150.3 ± 37.4	120.8 ± 31.2
8	147.6 ± 24.4	130.1 ± 32.7
9	146.9 ± 29.8	95.5 ± 42.1
10	145.7 ± 28.7	93.7 ± 35.9
11	160.4 ± 32.3	98.7 ± 37.3
12	160.3 ± 31.1	97.3 ± 28.1
13	157.0 ± 25.4	69.1 ± 35.1
14	150.2 ± 19.7	61.0 ± 46.9
15	164.4 ± 37.1	72.2 ± 48.1
16	154.6 ± 15.2	19.4 ± 17.0
17	185.2 ± 15.8	18.6 ± 21.8

Only a small number of boys with DMD met or exceeded the average scaled WSV of our control group

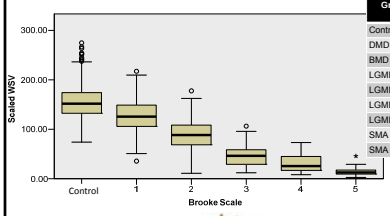
- Identify deficit in higher functioning individuals
- Reduce ceiling effect seen with other measures



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



Group	N	Mean Age (SD)	Age Range
Control	488	16.68 (13.31)	3.27 – 64.53
DMD	119	11.04 (3.85)	5.21 – 21.56
BMD	41	14.70 (4.70)	7.08 – 25.87
LGMD 2A	46	24.80 (13.23)	4.98 – 64.72
LGMD 2D	11	11.91 (3.50)	7.52 – 18.19
LGMD 2E	29	25.73 (11.12)	5.61 – 51.22
LGMD 2I	27	33.75 (16.02)	8.75 – 73.64
SMA Type 2	52	9.42 5.89)	2.83 – 24.00
SMA Type 3	10	12.01(3.55)	8.58 – 20.42

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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

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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:

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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

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ACTIVE-mini Overview

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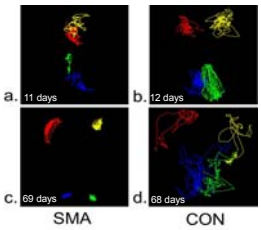
ACTIVE-mini uses color tracking to quantify the x, y, and z coordinates of the extremities at up to 30 Hz



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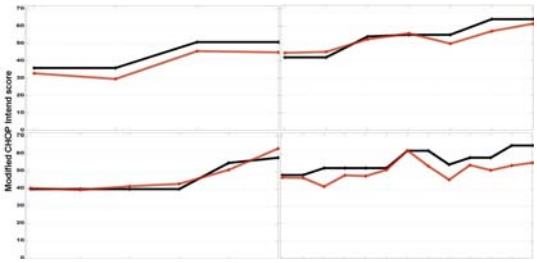
ACTIVE mini vs. Traditional Outcome Measure



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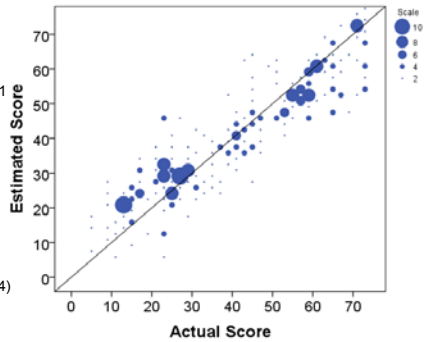
Actual v Estimated Score

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

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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 sWSV Values needed for ADL Tasks
- Demonstrate Functional Improvement with Initiation of Medical Treatment

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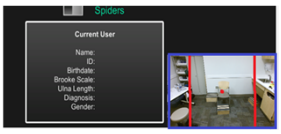
ACTIVE Setup & Instructions

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



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ACTIVE Setup & Instructions

Positioning

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

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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

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ACTIVE Setup & Instructions

Determining Brooke Level

1.


2.


3.


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.

Score =2: Can raise arms above head only by flexing the elbow (i.e. shortening the circumference of the movement) or using accessory muscles.

Score = 3: Cannot raise hands above the head but can raise a cup with 200g weight in it to mouth using both hands if necessary.

Score = 4: Can raise hands to mouth but cannot raise a cup with 200g weight in it to mouth.

Additional Brooke 4 Requirements:

- Shoulder flexion ≤ 45degrees
- Neck/Cervical Flexion ≤30 degrees – watch for excess protraction
- Minimal trunk forward and/or lateral flexion (≤30 degrees)

Fingers must reach bottom lip with or without elbow support

Score = 5: Cannot raise hand to mouth but can use hands to hold pen or pick up pennies or a checker from table.

4.


5.


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Let's Practice!

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Questions?

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