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TITLE: Validation of Functional Reaching Volume as an Outcome Measure across the Spectrum of Abilities in Muscular Dystrophy

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14. ABSTRACT

ACTIVE measures functional reaching volume using the Microsoft Kinect camera while the participant plays an interactive video game regardless of ambulatory status. The objective of this project was to produce a trial ready outcome measure enabling clinical trials to recruit subjects with a wider range of physical abilities and ages and address the limitation in current Duchenne muscular dystrophy outcomes. The specific aims were designed to improve the current ACTIVE system, determine the utility of integrating wireless motion sensors called Solitons into ACTIVE, and quantify the natural rate of change in FRV and determine the minimal clinically important difference (MCID). A comparison of ACTIVE and Solitons to the gold standard Vicon motion capture system showed the current ACTIVE system is more valid and reliable at the present time. A reliable and valid set of Solitons were not able to be produced during the length of this grant. We moved forward improving aspects of our original system and collected data to establish the reliability and validity of this assessment tool. We now have a trial ready version of ACTIVE.

15. SUBJECT TERMS

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1. INTRODUCTION:

Enrollment in clinical trials for individuals with Duchenne muscular dystrophy (DMD) is often dependent on the ability to walk independently since this is the primary efficacy outcome. These enrollment criteria exclude a large proportion of the population who no longer walk but may be willing to participate. Additionally, if a subject loses the ability to walk during a clinical trial, this subject's future data is lost. An outcome measure that measures a change in function on a continuous scale would improve access to clinical trials and minimize data loss. ACTIVE, a custom-designed video game using the Microsoft Kinect camera, measures functional reaching volume (FRV) across the spectrum of the disease in DMD regardless of ambulatory status. Our preliminary data support our hypothesis that FRV is a sensitive and functionally relevant outcome for DMD. In a study comparing participants with muscular dystrophy to a cohort of healthy control, ACTIVE was able to discriminately rank FRV across Brooke levels and from controls ($P < 0.001$). ACTIVE scaled volume was found to correlate highly with parental reports of daily activities ($r=0.454$; $P<0.05$) and mobility sections ($r=0.756$; $P<0.01$) of the Pediatric Evaluation of Disability Inventory (PEDI) indicating that FRV would be a meaningful outcome to the patient. Initial test-retest reliability of ACTIVE was also excellent (ICC=0.97; $P<0.0001$). In order to improve our current ACTIVE system and allow for implementation of ACTIVE across the lifespan in DMD in clinical trials, three areas were identified that could be further refined including 1) ensuring all individuals can be recorded, 2) improving the quantification of small movements, and 3) improving measurement accuracy. To this end, we collaborated with Dr. Furrukh Khan and Jessie Zhao, who developed miniature wireless motion capture sensors, known as Solitons to pair with the ACTIVE system. The following specific aims were developed to further enhance ACTIVE. The first is to expand the context of use of ACTIVE by utilizing the Soliton system. The second is to establish the natural rate of change and quantify the minimal clinically important difference (MCID) in FRV in males with DMD.

Specific Aim 1	Timeline	Site 1	Consultant	Status
Major Task 1 **Expand the context of use of ACTIVE by utilizing the Soliton system.**	Months			
Local IRB Approval for Soliton use with ACTIVE: study protocol, recruitment plan	1-3	Dr. Lowes		Completed/ Approved 2/25/16
Local IRB Approval for verbal consent with information sheet with ACTIVE-Soliton functional reaching volume game	1-3	Dr. Lowes		Completed/ Approved 4/20/16
Development of 6 Soliton System	1-3		Dr. Khan/ Ms. Zhao	Partially completed (90%)
Development of ACTIVE-Soliton functional reaching volume game	1-3	Jeremy Patterson/ Steve Rust		Completed
Major Task 2 **Clinical testing and Refinement**				
Testing on 15 subjects with DMD and 15 healthy controls using Solitons	4-6	Dr. Lowes	Dr. Khan/ Ms. Zhao	Partially completed (20%) Discontinued

Specific Aim 2				
Major Task 1 **Establish the natural rate of change in FRV in boys with DMD.**				
Collect longitudinal data with ACTIVE	6-24	Dr. Lowes		Completed
Major Task 2 **Quantify the Minimal Clinically Important Difference (MCID) in FRV in boys with DMD.**				
Collect functional data and patient reported outcomes	6-24	Dr. Lowes		Completed

2. KEYWORDS: Provide a brief list of keywords (limit to 20 words).

Outcome measure, Duchenne muscular dystrophy, wireless sensors, Kinect, video game, clinical trial readiness, neuromuscular disease, Soliton, functional reaching volume, workspace volume, function, ACTIVE

3. ACCOMPLISHMENTS:

What were the major goals of the project?

The ***objective*** of this proposal was to produce a distributable, clinical trial-ready outcome measure to improve the reliability and validity of functional assessments and increase the potential enrollment pool for clinical trials in Duchenne muscular dystrophy (DMD).

What was accomplished under these goals?

One hundred seventy-six unique individuals with DMD, and 102 age-matched controls were tested with the ACTIVE system.

ACTIVE Quarterly Enrollment Tables

Soliton System: Did not meet enrollment target due to soliton development obstacles

		Year 1				**Year 2**			
Enrollment of Subjects (per quarter)		**Q1**	**Q2**	**Q3**	**Q4**	**Q1**	**Q2**	**Q3**	**Q4**
Cross sectional subjects	Projected	---	15 control 15 DMD	25 DMD	25 DMD	25 DMD	25 DMD	10 DMD	---
	Actual	---	2 control 5 DMD	0	0	2 control	3 control 2 DMD	1 control 5 DMD	5 control 2 DMD
Longitudinal 6 Month Follow up	Projected	---	---	---	12 DMD	18 DMD	17 DMD	17 DMD	17 DMD

	Actual				0	0	0	0	0
Longitudinal 12 Month Follow Up	Projected	---	---	---	---	---	12 DMD	48 DMD	---
	Actual						0	0	
Cumulative Target Enrollment of <u>Unique</u> Subjects	Projected		**30**	**55**	**80**	**105**	**130**	**140**	**140**
	Actual		7	0	0	9	14	20	27

<u>ACTIVE System- Exceeded projected enrollment</u>

		Year 1				**Year 2**			
Enrollment of Subjects (per quarter)		**Q1**	**Q2**	**Q3**	**Q4**	**Q1**	**Q2**	**Q3**	**Q4**
Cross sectional subjects	Projected	---	15 control 15 DMD	25 DMD	25 DMD	25 DMD	25 DMD	10 DMD	---
	Actual	25 control 38 DMD	18 control 29 DMD	23 control 17 DMD	36 control 23 DMD	21 DMD	22 DMD	18 DMD	8 DMD
Longitudinal 6 Month Follow up	Projected	---	---	---	12 DMD	23 DMD	23 DMD	23 DMD	---
	Actual				33 DMD	28 DMD	35 DMD	37 DMD	26 DMD
Longitudinal 12 Month Follow Up	Projected	---	---	---	---	---	12 DMD	48 DMD	---
	Actual						32 DMD	34 DMD	29
Cumulative Target Enrollment of <u>Unique</u> Subjects	Projected	**---**	**30**	**55**	**80**	**105**	**130**	**140**	**140**
	Actual	**63**	**110**	**150**	**209**	**230**	**252**	**270**	**278**

Specific Aim 1 Accomplishments: Expand the context of use of ACTIVE by utilizing the Soliton system.

1) Gain approval from the local IRB to use Solitons in conjunction with ACTIVE.
   i. *Gain local IRB approval for soliton use with ACTIVE*
   The IRB at Nationwide Children's Hospital granted approval to allow the use of Solitons in conjunction with the ACTIVE system on 25 February 2016.

   ii. *Gain local IRB approval for verbal consent after reviewing an information sheet with ACTIVE-Soliton functional reaching volume game*
   The IRB at Nationwide Children's Hospital gave approval to use verbal consent to play the ACTIVE-Soliton functional reaching game after the subject and/or guardian has reviewed an information sheet detailing the study on 20 April 2016.

2) Integrate the Solitons into the ACTIVE system: *Develop Soliton System*
   Dr. Khan and Ms. Zhao delivered 6 Solitons to Dr. Lowes on 03 November 2016 for initial validation testing. After early testing, it was determined that a calibration system, development of a standardization skeleton, and improvements to the Soliton software to account for varying degrees of metal on subject wheelchairs would need to be corrected before they were useable in the clinic. Iterative Soliton development occurred across the timeline of the grant, however the developed system of Solitons did not capture a full skeletal dataset with each subject trial after 18 months of development so further use was discontinued. It was determined that use of these devices in a clinical trial setting was not feasible due to the inconsistency of data capture and time-consuming setup. This prevented us from completing our aim of capturing reliable and valid data from the Solitons and ACTIVE systems in both individuals with DMD and control subjects for analysis.

Figure 1: Comparison of recordings from control subject using ACTIVE (above) and Vicon, the gold standard (below) recording software

Unexpected Challenges and Solutions Implemented: Real World Accuracy

1) Impact of Magnet Fields

One major limitation is the necessity of a uniform magnetic field for IMU based motion tracking. We did not foresee that this would not be readily available in a hospital environment. After determining that the results we were obtaining were not valid we did unidimensional movements to see where the errors were occurring. We saw that the visualization of the movement generated by the Soliton would occasionally deviate at a non-physiologic angle. After using a compass to assess the changes in the magnetic field in 4 different testing rooms, only 2 of the rooms gave accurate results. The other 2 rooms had significant changes in the magnetic field depending on the height of the Soliton. This change was about 5-6 degrees (measured by a compass) within a height variation of only about 0.5m. This would invalidate the calculated workspace

volumes. This technological barrier has no clear solution and was one reason for discontinued use of the Solitons in the context of clinical trials.

Comparison to the gold standard was completed on the Solitons version 2. The Solitons version 2 (v2) were compared to the current Kinect-based ACTIVE system and the gold-standard 12 camera Vicon motion capture system on 13 April 2017. A control subject performed reaching activities seated in an armless chair while the Soliton, ACTIVE, and Vicon systems simultaneously recorded data (Figure 1). Multiple trials were recorded and the subject was instructed to perform reaching motions in multiple directions, amplitudes, and speeds to mimic varying levels of function. Jeremy Patterson and his team developed an interface to convert the data from all three systems and interpose the three recordings over time to analyze the results. The Kinect system had a smaller measure of error compared to the Soliton system. The Soliton system frequently overestimated excursion compared to the Vicon system. In the figure on the right the Vicon recorded maximum right arm excursion as 49.03 cm compared to 54.36 cm and 57.42 cm by the ACTIVE and Soliton systems, respectively. Dr. Khan and Ms. Zhao used the results of this analysis to improve the algorithms employed by Solitons to increase the accuracy.

Additionally, it was determined that the Soliton version 2 system was not ready for use. During the Vicon testing session only 2 of the anticipated 6 Solitons were working. The lengthy calibration process of the Solitons resulted in only 10 useable 60 second collections. Dr. Khan and Ms. Zhao delivered Soliton version 3 (v3) on Oct 5, 2017. Due to continued challenges in consistency of data collection, we were unable to justify a return trip to the gait lab until the Solitons were more reliable.

2) Fragility of Solitons

Solitons were hand crafted custom designed wearable sensors specific chosen for their measurement accuracy and light weight (>25 grams). Light weight sensors were targeted for eventual use in use in very weak infants with neuromuscular disorders. Despite receiving 3 different Soliton prototypes, the Solitons continued to fail from unknown causes. Replacement Solitons were provided but we were unable to keep a working system to collect data over any period of time. The current development state of the Soliton system is not stable enough for use outside of the engineering laboratory. In the last quarter of the project we were notified that the key component for Soliton, the IMU sensor, has been marked as obsolete by its manufacturer and has been replaced by a new IMU which will require a complete software redesign.

Successful Soliton development work:

1) Problem: Daily calibration was time consuming.
   Solution: Improved calibration process. We were able to completely remove the need for user on-the-spot calibration.

2) Problem: An additional inaccuracy was identified when the Soliton was spun in 360 as when on rotating stool.
   Solution: The technical team implemented an algorithmic correction to address this issue.

3) Problem: Ulna length estimation.
Solution: Obtaining accurate ulna length is problematic but necessary to scale the raw volume based on the size of the person. Solitons use angles and therefore can be imposed onto a standard sized skeleton and eliminate the need for scaling. This eliminate one source of error.

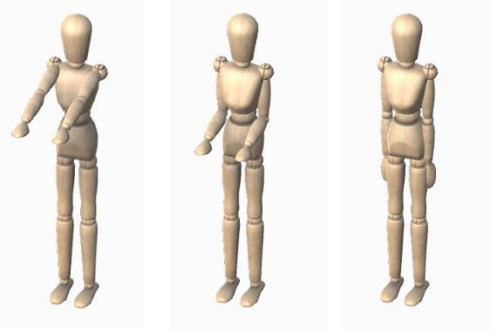


Figure 2: Alignment pose options to accommodate weakness and limitations in subjects' range of motion

4) Problem: Soliton alignment. Initially it was difficult to initialize the soliton set in the appropriate alignment. Each device needed to be placed directly in line.
Solution: A new automatic alignment program self-corrects sensor misplacements on limbs by having patients pose in a standard posture and hitting a key on the keyboard; the system automatically performs a correction in real time. This feature, which is unique in the industry, corrects for small misplacements and system setup errors. Weak boys and men with DMD frequently develop contractures which made it impossible for some participants to assume the original "standard posture". We have experimented with providing a variety of poses for the clinicians to select from to accommodate individual abilities. Several possible standard alignment postures are highlighted in Figure 2.

5) Problem: Adhering Solitons. Originally we used a roll of medical paper tape to directly secure the sensors onto the limbs. Much to our surprise the pressure from the bandage itself affected the readings of the sensors by a few degrees.
Solution: We created a lightweight casing for the Solitons using 3-D printing. This allows us to use medical paper tape without the interference (Figure 3).

Figure 3: Depiction of a lightweight, 3-D printed Soliton case designed to eliminate interference of the direct pressure from tape on subject's arms

6) Problem: Laborious set up and implementation.
Solution: A new user interface was developed to provide step by step system-setup, data-recording and data-playback (Figure 4). The data being recorded conforms to three different formats: box volume report, Raw Soliton recording in quaternion, and in binary file (with file extension .sltn) used for data playback. Figure 5 shows data output using the new interface.

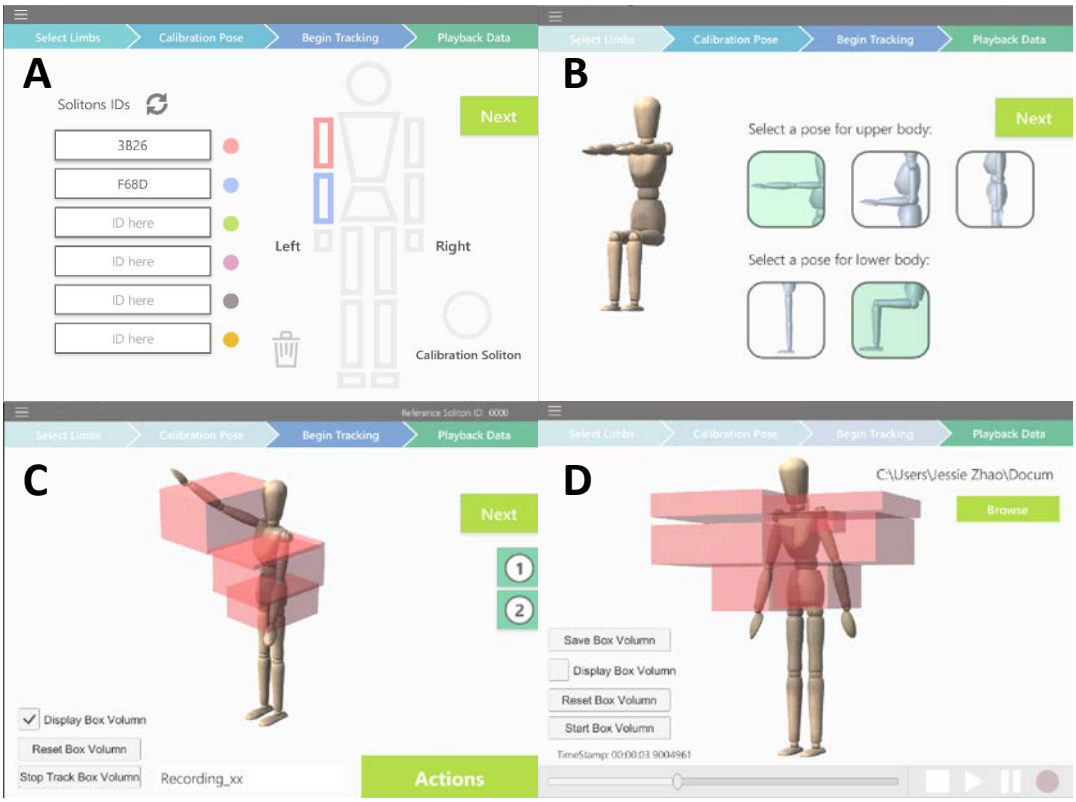


Figure 4: Sequential steps of utilizing the new user interface for the Soliton system.

A) System detects and lists Solitons in the network and assigns Solitons to limbs.
B) User selects appropriate pose for the ensuing capture.
C) System initiates self-correction and begins recording.
D) File of recording can be played back for analysis and detection of any errors during recording.

Limb	extention X	extension Y	extension Z
Upper Right	0.901	0.687	0.973
Middle Right	0.929	0.295	1.022
Lower Right	0.834	0.293	1.019
Upper Left	0.895	0.68	0.998
Middle Left	0.896	0.296	1.04
Lower Left	0.727	0.31	1.011
Torso Right	0.186	0.233	0.406
Torso Left	0.251	0.233	0.406

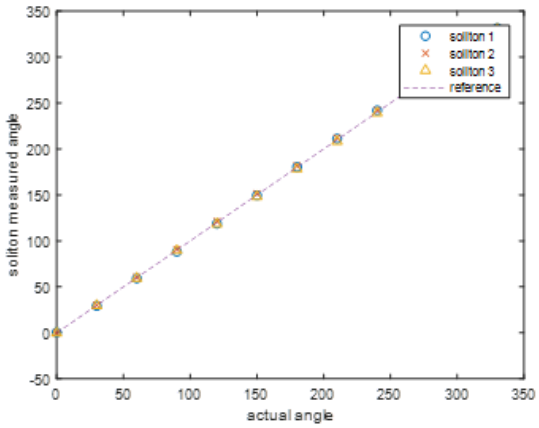
Figure 5: Example of a real box volume report from the application utilizing the adjusted interface in Figure 4

To evaluate the accuracy of the Solitons after the new technical changes were made (i.e. removal of the need for on-the-spot calibration), we designed and 3-D printed a Gimble device (Figure 6) to evaluate the accuracy of the new Soliton. This Gimble device allows us to accurately measure the static reading of the new Solitons at various angles.

	0	30	60	90	120	150	+/-180	-150	-120	-90	-60	-30
Soliton 1	0.5	29.3	59.2	88.2	118.8	149.6	-179.6	-148.8	-118.1	88.2	-58.6	-28.6
Soliton 2	-0.3	30.3	60.4	90.6	121.2	151.3	-178.4	-148	-117.9	-88.6	-58.9	-29.3
Soliton 3	0.3	29.8	59.4	89.5	118.6	148.4	178.3	-151.7	-120.8	-90.8	-59.8	-29.7

Figure 6: Design of the 3-D Printed Gimble

Figure 7: Relative readings from the three Solitons compared to the actual angle of measurement while using the Gimble device



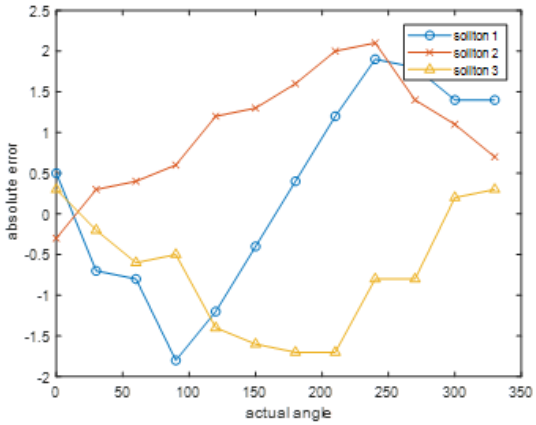


Figure 8: Relative readings from 3 Solitons compared with actual angles

Figure 9: Absolute Error from 3 Solitons tested at different angles

Develop ACTIVE-Soliton functional reaching volume game- Game completed.

Due to the continued issues with the Solitons, this game was never interfaced with the Solitons. A full description of the game created by Jeremy Patterson and his team was described in previous reports. In summary, the team created an interactive functional reaching volume game that is compatible for both the ACTIVE-Soliton system and the Kinect-based ACTIVE system (Figure 10). The subject is able to select a character and then guides the character through a fantasy course by moving his/her arms and trunk. Maximal leaning and reaching is encouraged by having the character collect coins and avoid robot-like characters that appear throughout the course. Upon completion of the mission, a screen appears that states the mission was accomplished and shows the score (calculated by the number of coins collected) to the subject. The functional reaching volume is recorded along with the trunk excursion in both lateral and forward directions. Due to the continued issues with the Solitons, this game has not been tested using the Solitons.

Figure 10: Screenshot of the reaching volume game designed by Jeremy Patterson

Perform clinical testing and refinement with ACTIVE-Soliton – Discontinued

Testing on 15 subjects with DMD and 15 controls
Dr. Khan and Ms. Zhao delivered 6 Solitons to Dr. Lowes on 03 November 2016. Two control subjects and five subjects with DMD played ACTIVE using both the Kinect and Soliton motion tracking sensors. The Solitons were attached to the subject's sternum and upper extremities. The subject played the current Kinect-based ACTIVE game while the Solitons simultaneously recorded data in order to compare the two systems for initial validity. In this trial, some technical issues with the Solitons were discovered including difficulty with calibration and battery life that made clinical integration difficult. Dr. Khan and Ms. Zhao used this information to continue to refine the Solitons.

Kinect ACTIVE system development- completed

Based on the likelihood that Solitons would not be ready in sufficient time to collect longitudinal data for this grant, we pursued a simultaneous development plan to address comments from the review committee evaluating our system as an approved drug development tool. This included the development of a standardized tutorial that provides standardized instructions to every subject that plays the game and therefore minimizes any bias that may occur if a different clinical evaluator across visits. Initially text was used to convey directions. We quickly determined that players were too busy or young to read the instructions during the game. Voice-overs to read the tutorial at the beginning of the trial and provide standardized encouragement throughout the trial were then implemented. We have pilot-tested the instructions by having novice users play the game based only the information provided by the tutorial. Small iterative changes were made based on player feedback. We are now in the process of

adding other language options. Currently we have French, German, Russian and Arabic. We have plans to include Spanish and Dutch. This will make the game available in the native languages of many of the current clinical trial locations.

Specific Aim 2 Accomplishments: Establish the natural rate of change in FRV in boys with DMD and quantify the Minimal Clinically Important Difference (MCID) in FRV in boys with DMD.

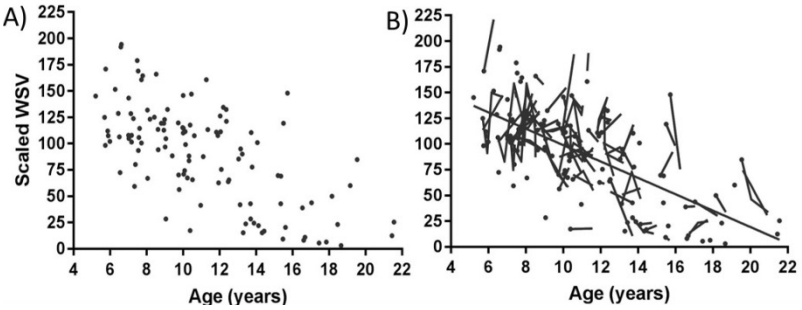


Figure 11: Workspace Volume by Age in boys with DMD
A) Cross-Sectional B) Longitudinal

1) <u>Longitudinal data with ACTIVE</u>
Due to the unforeseen technical issues with the Solitons, no longitudinal ACTIVE-Soliton data has been collected. However, current results show that we exceeded our estimated data collection with our original ACTIVE system (Figure 11).

2) <u>Collect functional data and patient-reported outcomes in boys with DMD.</u>
In order to determine the minimal clinically important difference (MCID) in ACTIVE, the change in FRV over time was compared to results on other functional assessments and patient-reported outcomes that are administered as a standard of care in our clinic. One hundred seventy-six boys and men with DMD and 102 controls played ACTIVE. The physical therapist determined which functional assessments were appropriate for each patient based on age and abilities. Both ACTIVE scaled WSV and total volume scores were strongly positively correlated with PROMIS Upper Extremity (UE) scores. Scaled WSV was moderately associated with the 6-minute walk test (6MWT), 100-meter timed test (100m), 10-meter walk/run (10m), and the North Star Ambulatory Assessment (NSAA), and was only weakly associated with time to rise (Rise), time to ascend 4 stairs (Ascend), and time to descend 4 stairs (Descend). Total volume scores were weakly correlated with all functional measures except PROMIS (Figure 12).

		Scaled WSV	Total Volume
6MWT (n=65)		0.326	0.052
	p-value	0.008	0.67
100m (n=70)		-0.490	0.049
	p-value	<.001	0.690
10m (n=113)		-0.44	0.004
	p-value	<.0001	0.965
NSAA (n=106)		0.467	0.152
	p-value	<.001	0.120
Rise (n=101)		-0.192	0.131
	p-value	0.054	0.192
Ascend (n=80)		-0.151	0.055
	p-value	0.182	0.627
Descend (n=55)		-0.261	-0.249
	p-value	0.054	0.067
PROMIS UE Ped (n=41)		0.794	0.755
	p-value	<.001	<.001
PROMIS UE Parent (n=51)		0.656	0.656
	p-value	<.001	<.001

Figure 12: ACTIVE Correlation with other functional measures

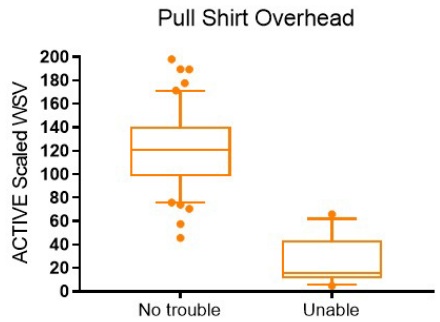


Figure 13: An example of differences seen between Workspace Volume and Ability to "Pull Shirt Overhead" as seen in the PROMIS Reporting

Using the PROMIS parent report upper extremity function data we are able to identify cut-off guidelines for being able to complete a variety of common activities of daily living. We compared the workspace volume of individuals whose caregivers rated their 5 ability to complete a task as "with no

difficulty" to those reported as being "unable". This difference is highlighted visually in the figure to the left (Figure 13).

What opportunities for training and professional development has the project provided?

John Luna, a graduate student at The Ohio State University's Advance Computing Center for the Arts and Design, interned in virtual environment design/ development at Nationwide Children's Hospital under the guidance of Jeremy Patterson, lead of User Experience Technology Research and Development, to develop the ACTIVE-Soliton functional reaching volume game. John was able to gain professional experience and was a vital contributor to the development of the ACTIVE-Soliton functional reaching game. He conceptualized the graphics for the game and developed the game under the direction of Jeremy Patterson. Due to his contribution to this project and others, he was offered a full-time position after graduation as a Full-Stack Application Developer in the Research and Development department at Nationwide Children's Hospital.

The process of data collection and analysis provided 1 undergraduate pre-physical therapy student and 2 high school students with the opportunity to complete projects as a part of their standard curriculum. They learned about the muscular dystrophy community, outcome measures, and clinical trials. They contributed to several abstracts related to this project.

How were the results disseminated to communities of interest?

ACTIVE was presented at several scientific and family meetings during the grant period. Specific conference details are below.

- 2017 Parent Project Muscular Dystrophy Annual Connect Conference
  Chicago, IL
  Tina Duong, MPT presented "Outcomes- Current and Forthcoming Outcome Measures" in the Our New Duchenne Basics- Care, Data, Trials, and Outcomes session. She described ACTIVE and its potential for use in clinical trials in DMD regardless of ambulatory status.

- 21st Annual Cure SMA International Researcher Meeting
  Orlando, FL
  Linda Lowes, PhD presented "Utility of ACTIVE Workspace Volume as a Clinically Meaningful Measure of Upper Extremity Function." She outlined the ACTIVE development process, its use in DMD, and also discussed its potential for use in the spinal muscular atrophy (SMA) population.

- 2017 Myotubular Myopathy- Centronuclear Myopathy Family Conference; Nashville, TN
  Lindsay Alfano, DPT presented "Motion assessments in individuals with XLMTM." She discussed ACTIVE's potential use in this population and the ongoing research in DMD.

In addition to the scientific and family meetings listed above, ACTIVE was also presented at the Sixth and Seventh Annual Nationwide Children's Hospital/ OSU/ Wellstone Myology Course in Columbus, Ohio. This course is oriented toward MD and PhD trainees to provide specialized training of neuromuscular disease. Linda Lowes, PhD lectured the trainees about the importance of outcome

measure development and selection and discussed ACTIVE's ongoing refinement, development, and utility as an outcome assessment in clinical trials.

Dr. Lowes and her team visited a local elementary school to teach the students about careers in science/ research and ACTIVE. The students were able to play ACTIVE during their physical education class and ask the team any questions they had.

Ongoing plans

The current ACTIVE system was found to be more valid and reliable than the Solitons' current level of development when compared to the gold standard Vicon motion capture system. Therefore, we will move forward with the current ACTIVE system and determine the MCID and natural rate of change in patient with DMD. We plan to use these results to submit a finalized Drug Development Tool Qualification Program for ACTIVE.

4. **IMPACT:** Describe distinctive contributions, major accomplishments, innovations, successes, or any change in practice or behavior that has come about as a result of the project relative to:

What was the impact on the development of the principal discipline(s) of the project?

Research in the field of neuromuscular disease, particularly in Duchenne muscular dystrophy is increasing at an astonishing pace. In order to determine if a potential treatment is efficacious, change has to be detected by the designated outcome assessment. Most of the current clinical trials in DMD use the Six Minute Walk Test (6MWT) as the outcome assessment, which excludes individuals in the late-ambulatory or non-ambulatory phase. In addition, if a subject loses ambulation during the clinical trial period, that data is lost as he can no longer complete the primary outcome measure. An outcome measure that is able to detect change on a continuous scale across the spectrum of disease would increase the recruitment pool for clinical trials as well as allow researchers to better understand the potential treatments' impact on later stages of DMD.

ACTIVE has the potential to serve as this outcome measure using the Kinect camera to quantify functional reaching volume while the subject plays an interactive video game. A preliminary data show ACTIVE is a valid and reliable assessment of function (Lowes, 2015). Three areas of improvement were identified in order to implement ACTIVE across the spectrum of abilities in DMD. The first is to ensure all individuals can be recorded. The second is to eliminate the floor effect by improving quantification of small movements. The third is to improve measurement accuracy. Although Dr. Furrukh Khan and Jessie Zhao were unable to deliver a "clinic-ready" set of Solitons we were able to address the 3 areas of improvement listed above by making improvements to the current ACTIVE system.

1) Ability to record a larger variety of individuals. The addition of an auditory component to the tutorial will allow younger children to understand the directions. Translation into several languages will also increase the target population. 2) Eliminate floor effect. We were able to change the visual perspective for those individuals with limited function which allowed them to see their movements amplified on the screen. This was more motivating and encouraged them to continue playing the game. To truly solve this problem, we will need to adopt a wearable sensor in the future when they are at a commercially ready stage of development. 3) Based on comparing out data to the gold standard

VICON system, we learned that our data capture system is very accurate. We believe our changes to the tutorial and game graphics will encourage more consistent performance by ensuring that the player is clear on the goal.

What was the impact on other disciplines?

ACTIVE, originally developed for use in Duchenne muscular dystrophy, has the potential to be utilized in other patient populations as well. Dr. Lowes is currently collecting data to determine the utility of ACTIVE in other neuromuscular disorders including spinal muscular atrophy (SMA), limb girdle muscular dystrophy (LGMD), facioscapularhumeral dystrophy (FSHD), myotubular myopathy (MTM), and DMD carriers. Preliminary data has supported ACTIVE's reliability and validity in the above listed populations. Submission of the SMA ACTIVE data for publication is planned for 2018.

ACTIVE may also be useful in other patient populations outside of neuromuscular disorders. For example, ACTIVE may be able to be used in rehabilitation settings post-cerebral vascular accident and/or spinal cord injury to quantify reaching abilities and compare to the non-affected side. These areas will be explored after development of ACTIVE in DMD is complete.

What was the impact on technology transfer?

Upon completion of the project goals including quantifying the natural rate of change and determining the minimal clinically important difference (MCID) of functional reaching volume in DMD, ACTIVE will be available to other institutions for use in clinical and research settings. The Muscular Dystrophy Association (MDA) Clinic at Nationwide Children's Hospital currently uses ACTIVE as a standard of care functional assessment. There are ongoing initiatives to standardize care in DMD, including physical therapy functional testing, across MDA Clinics. ACTIVE may be a useful addition to the standardized battery of assessments that would fill a void of a functional assessment that spans the entire disease process and is able to quantify change on a continuous scale.

What was the impact on society beyond science and technology?

Implementation of ACTIVE as a clinical outcome assessment in clinical trials will improve access to experimental treatments to individuals with DMD who have previously often been excluded due to the inability to complete the Six Minute Walk Test (6MWT). Allowing access to clinical trials to those who are no longer ambulatory may increase hope and improve interest in research, which will in turn continue to advance the field of DMD research.

The non-ambulatory cohort of individuals with DMD is a historically underserved population in terms of research. Increased understanding of disease processes in the late stage of disease may lead to improved policies and decision making practices in terms of clinical care for these individuals.

5. **CHANGES/PROBLEMS:** The Project Director/Principal Investigator (PD/PI) is reminded that the recipient organization is required to obtain prior written approval from the awarding agency Grants Officer whenever there are significant changes in the project or its direction. If not previously reported in writing, provide the following additional information or state, "Nothing to Report," if applicable:

Changes in approach and reasons for change

Implementation of Solitons into the current ACTIVE system: Dr. Khan and Ms. Zhao were unable to deliver a stable and reliable set of Solitons during the grant period. As outlined in the grant as an alternate strategy the work was completed using ACTIVE.

Actual or anticipated problems or delays and actions or plans to resolve them

Dr.Khan and Ms. Zhao were unable to deliver trial ready solitons so were unable to complete data collection with this system. We determined that optimizing our current system was the best strategy and completed the project using ACTIVE

Changes that had a significant impact on expenditures

Nothing to report

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Significant changes in use or care of human subjects
Nothing to Report

Significant changes in use or care of vertebrate animals.
Nothing to Report/ Not Applicable

Significant changes in use of biohazards and/or select agents
Nothing to Report/ Not Applicable

6. PRODUCTS:

- **Publications, conference papers, and presentations**

Oral Presentations:

Alfano, L.N. (2018, April). More than just fun and games: ACTIVE workspace volume video game quantifies upper extremity function in individuals with neuromuscular disease. 70th Annual American Academy of Neurology Annual Meeting. Los Angeles, CA.

Alfano, L.N., Miller, N.F., Iammarino, M.A., Dugan, M.E., Lowes, L.P. (April, 2018). ACTIVE: Utilizing video game technology to quantify function and measure change across the lifespan. OPTA Annual Conference. Columbus, OH.

Alfano, L.N., Lowes, L.P., (2018, August). Clinical outcome measures. Seventh Annual Nationwide Children's Hospital/ OSU Myology Course. Columbus, OH.

Lowes, L.P., (2018, January). More than just fun and games: ACTIVE workspace volume video game quantifies upper extremity function in individuals with spinal muscular atrophy. International Scientific Congress on Spinal Muscular Atrophy. Krakow, Poland.

Lowes, L.P. (2018, July). Outcome measure selection. Post-Approval Evidence for Drugs for Rare Diseases Stakeholder Meeting Monday. Boston, MA.

Lowes, L.P. (2018, October). Determining trial outcome measures. Coalition to Cure Calpain 3 Scientific Meeting. Arlington, VA.

Lowes LP. (June 2017). Utility of ACTIVE Workspace Volume as a Clinically Meaningful Measure of Upper Extremity Function. Lecture at the 21st Annual Cure SMA International Researcher Meeting. Orlando, FL.

Alfano LN. (July 2017). Motion assessments in individuals with XLMTM. Lecture at the 2017 MTM-CNM Family Conference. Nashville, TN.

Lowes LP, Alfano LN. (August 2017). Clinical outcome measures in neuromuscular disease. Lecture at the Sixth Annual Nationwide Children's Hospital/OSU/Wellstone Myology Course. Columbus, OH.

Alfano LN. (September 2017). Novel functional outcome measures. Lecture at the 2017 Muscle Study Group Annual Scientific Meeting. Snowbird, UT.

Posters:

Capturing function across the lifespan: Identifying outcome measures to expand clinical trials
Megan A Iammarino PT, DPT, Lindsay N Alfano, PT, DPT, PCS, Natalie F Miller, PT, DPT,

Linda P Lowes, PT, PhD.
2018 Parent Project Muscular Dystrophy Annual Conference. Scottsdale, AZ June 2018

Utility of ACTIVE workspace volume as a clinically meaningful measure of functional capacity in individuals with neuromuscular disease
Megan A Iammarino PT, DPT, Lindsay N Alfano, PT, DPT, PCS, Natalie F Miller, PT, DPT, Margaret E Dugan, BS, Melissa Moore-Clingenpeel, Samiah Al-Zaidy, MD, Chang-Yong Tsao, MD, Kevin M Flanigan, MD, Louise R Rodino Klapac, PhD, Jerry R Mendell, MD, Linda P Lowes, PT, PhD.
The 23rd International Congress of the World Muscle Society. Mendoza, Argentina October 2018

More than just fun & games: ACTIVE workspace volume quantifies meaningful change in spinal muscular atrophy
Lindsay N Alfano, PT, DPT, PCS, Natalie F Miller, PT, DPT, Megan A Iammarino PT, DPT, Melissa Moore-Clingenpeel, Suzanne Lowes, Margaret E Dugan, BS, Megan Waldrop, MD, Kevin M Flanigan, MD, Garey Noritz, MD, John Kissel, MD, Samiah Al-Zaidy, MD, Chang-Yong Tsao, MD, Linda P Lowes, PT, PhD.

The 23rd International Congress of the World Muscle Society. Mendoza, Argentina October 2018

Megan A Iammarino, Lindsay N Alfano, Natalie F Miller, Margaret E Dugan, Melissa Moore-Clingenpeel, Kevin M Flanigan, Samiah Al-Zaidy, Jerry R Mendell, Linda P Lowes. Utility of ACTIVE Workspace volume as a clinically meaningful measure of upper extremity function in individuals with spinal muscular atrophy. The 2017 Muscle Study Group Scientific Annual Meeting, September 2017, Snowbird, Utah.
Lowes LP. (June 2017). Utility of ACTIVE Workspace Volume as a Clinically Meaningful Measure of Upper Extremity Function. Lecture at the 21st Annual Cure SMA International Researcher Meeting. Orlando, FL.

- **Journal publications.**
  Nothing to Report

- **Books or other non-periodical, one-time publications.**
  Nothing to Report

- **Other publications, conference papers, and presentations**.

- **Website(s) or other Internet site(s)**

  Nothing to Report

- **Technologies or techniques**

  Nothing to Report

- **Inventions, patent applications, and/or licenses**

  Nothing to Report

- **Other Products**
  Nothing to Report

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name:	Linda P. Lowes
Project Role:	Principal Investigator
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	4

Contribution to Project: Dr. Lowes has performed work in the area of study design, data collection, data analysis, and collaboration with other disciplines.

Funding Support:

Name: Lindsay A. Alfano
Project Role: Co-Investigator
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: 2

Contribution to Project: Dr. Alfano has performed work in the area of study design, data collection, data analysis, and collaboration with other disciplines.

Funding Support:

Name: Margaret Dugan
Project Role: Research Aide
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: 6

Contribution to Project: Ms. Dugan has performed work in the area of data collection, data cleaning, and administrative tasks.

Funding Support:

Name: Natalie Miller
Project Role: Key Personnel
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: 0.4

Contribution to Project: Ms. Miller has performed work in the area of data collection and analysis.

Funding Support:

Name: Furrukh Khan
Project Role: Consultant
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: 2

Contribution to Project: Dr. Khan has performed work in the area of data collection and development of the Soliton system.

Funding Support:

Name: Jessie Zhao
Project Role: Consultant

Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: 2

Contribution to Project: Ms. Zhao has performed work in the area of data collection and development of the Soliton system.

Funding Support:

Name: Jeremy Patterson
Project Role: Consultant
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: 2

Contribution to Project: Mr. Patterson has performed work in the area of ACTIVE-Soliton game development and Soliton calibration process improvement.

Funding Support:

Name: John Luna
Project Role: Graduate Student/ Intern
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: 2

Contribution to Project: Mr. Luna has performed work in the area of ACTIVE-Soliton game development and Soliton calibration process improvement.

Funding Support:

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period? Nothing to report

What other organizations were involved as partners?

IKOVE Venture Partners:
Columbus, OH
Partner's contribution to the project

- In-kind support
- Collaboration

The Ohio State University Advanced Computing Center for the Arts and Design Motion Lab:
Columbus, OH
Partner's contribution to the project

- Facilities

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: For collaborative awards, independent reports are required from BOTH the Initiating PI and the Collaborating/Partnering PI. A duplicative report is acceptable; however, tasks shall be clearly marked with the responsible PI and research site. A report shall be submitted to **https://ers.amedd.army.mil** for each unique award.

Not Applicable

QUAD CHARTS: If applicable, the Quad Chart (available on https://www.usamraa.army.mil) should be updated and submitted with attachments.

Not Applicable

9. APPENDICES: Attach all appendices that contain information that supplements, clarifies or supports the text. Examples include original copies of journal articles, reprints of manuscripts and abstracts, a curriculum vitae, patent applications, study questionnaires, and surveys, etc.