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AWARD NUMBER: W81XWH-17-1-0477

TITLE: Validating Community-Based Measures of Activity in Ambulatory Duchenne Muscular Dystrophy

PRINCIPAL INVESTIGATOR:

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RECIPIENT: University of California, Davis

REPORT DATE: September 2020

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command

Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
Sept 2020	Annual	Sept 1 2019 – Aug 31, 2020

4. TITLE AND SUBTITLE

Validating Community-Based Measures of Activity in Ambulatory Duchenne Muscular Dystrophy

5a. CONTRACT NUMBER

5b. GRANT NUMBER
W81XWH-17-1-0477

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
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5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

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8. PERFORMING ORGANIZATION REPORT NUMBER

MD160094Y2

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT

Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

This research project will validate use of patient generated step and activity data for data collection at the point-of-care to support use of stride rate patterns as an outcome measure for ambulatory patients with DMD. We will include step activity monitoring by laboratory and consumer level step monitoring devices that can feed data through
Apple HealthKit into the UC Davis instance of the Epic electronic medical record system. Up to 60 ambulatory patients with DMD will be recruited to represent the early, middle and late stages of the progressive loss of ambulation in DMD. Up to 150 control patients will be recruited and split into similar age ranges. Participants will be assessed using step monitoring devices and traditionally performed clinical outcome measures, followed by community monitoring. StepWatchTM data collected from two previously enrolled cohorts of children with DMD will also be used for longitudinal analyses and determination of responsiveness to steroid treatment.

15. SUBJECT TERMS

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
Unclassified	Unclassified	Unclassified	Unclassified		19b. TELEPHONE NUMBER *(include area code)*

TABLE OF CONTENTS

1. INTRODUCTION: Narrative that briefly (one paragraph) describes the subject, purpose and scope of the research.

Background: Development of novel technologies and therapeutic agents to treat Duchenne muscular dystrophy (DMD) have increased interest by regulatory bodies such as the Food and Drug Administration in the development of "clinically-meaningful" study endpoints for clinical trials. There is a need for the development of valid measures of ambulatory ability in very young children while effectively evaluating treatment effects in clinical trials.

Objective: This proposal focuses on validating the use of patient generated step and activity data to facilitate future data collection at the point-of-care to support the development of stride rate patterns as an outcome measure for ambulatory patients with DMD. It is to include step activity monitoring by StepWatch™ and a consumer level step monitoring devices (Garmin VivoActiveHR and Polar M400 activity watches and the Polar StrideSensor activity monitor) that can feed data through Apple HealthKit into the UC Davis instance of the Epic electronic medical record system. Up to 60 ambulatory patients with DMD will be recruited to represent the early, middle and late stages of the progressive loss of ambulation in DMD. Patients will be sorted into three age groups of (n=20) participants: early (ages 2-6), middle (ages 7-11) and late (ages 12-16). Up to 150 control participants will be recruited and split into similar age ranges. Participants will be assessed using step monitoring devices and traditionally performed clinical outcome mesures (6MWT, TFTs, NSAA), followed by community monitoring. StepWatch™ data collected from two previously enrolled cohorts of children with DMD will also be used for longitudinal analyses and determination of responsiveness to steroid treatment. We will develop model plans for data collection, validation, visualization, transfer, archival and lock of raw instrument data, as well as guidelines for integration with existing data platforms including EPIC electronic health records and I2B2 NIH data repository.

Applicability: Well-designed community mobility measures can be used in both clinical trials and day-to-day clinical practice. For clinical trials, they provide researchers with the ability to measure day-to-day walking ability across a broad range of ages, including very young children with DMD. Those results can then also be compared to other clinical trial measures such functional evaluations and timed function tests to help teach researchers and regulatory authorities about how "in clinic" tests commonly used in clinical trials relate to a persons' mobility in their daily life and whether those tests are "clinically meaningful". Within 3 years, this project will be able to produce such a tool.

Impact and Contributions: Data from this project will provide the basis for development of a "clinical trialready" community mobility measure that has been constructed against a background of comprehensive clinical assessments of functional ability across the range of ambulatory ability. This measure will be rapidly usable as a sensitive measure for use in the growing field of DMD clinical trials, and will help to demonstrate "clinically meaningful" results to regulatory agencies in charge of new drug approval.

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

Duchenne muscular dystrophy
Community Mobility
mHealth
Patient Generated Health Data
Accelerometers
Clinical Trial Outcomes Development
DMD Natural History

3. ACCOMPLISHMENTS: The PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction.

What were the major goals of the project?
List the major goals of the project as stated in the approved SOW. If the application listed milestones/target dates for important activities or phases of the project, identify these dates and show actual completion dates or the percentage of completion.

Aim 1: Comparison of accuracy and validity of both laboratory- and consumer-grade step activity monitoring devices, and comparison to traditional clinical evaluator determined laboratory-based measures.

- Aim 1.1: Evaluate validity and correlation of stride activity data using laboratory and consumer grade devices.
- Aim 1.2: Determine concurrent validity of stride rate patterns by accelerometry as compared to the 6-minute walk test, North Star Ambulatory Assessment and Timed Motor Performance Tests in DMD patients who are able to perform these assessments.

Aim 2: Evaluation of age-related patterns in community step monitoring data in DMD and typically developing youth controls.

- Aim 2.1 Evaluate differences between DMD and TDY in overall daily patterns of activity by age group
- across all levels of stride rate activity.
- Aim 2.2 Evaluate differences between DMD and TDY for area under the curve for total time and height-adjusted distance overall and at each stride rate and stride activity level group.
- Aim 2.3 Evaluate Differences between age groups that represent disease progression in DMD for area under the curve for total time and height-adjusted distance overall and at each stride rate and stride activity level group.

Aim 3: Evaluation of historical community stride monitoring data from natural history studies and clinical trials to evaluate longitudinal change and steroid response characteristics.

- Aim 3.1 Evaluate longitudinal rate of change characteristics of stride activity monitoring in DMD using
- historical natural history data.
- Aim 3.2 Evaluate longitudinal rate of change characteristics of stride activity monitoring to identify
- differences due to glucocorticoid therapy using historical clinical trial data.

Aim 4: We will develop, evaluate and provide recommendations for a framework to collect, and track patient generated health data in the electronic health record for clinical care and to transfer this data into a database to meet Federal 21CFR11 compliance for clinical research.

- **Aim 4.1:** Develop guidelines for developing a platform to collect PGHD, guidelines for storage,
- visualization and providing clinical care in the EPIC electronic health record.
- **Aim 4.2:** Provide guidelines for the transfer of de-identified patient-generated health data (PGHD) collected via this methodology to meet FDA 21CFR11 compliance. In addition develop guidelines for sharing deidentified PGHD using a platform like the I2B2 NIH data repository for clinical research.

What was accomplished under these goals?

Phase I Activities: Study Preparation and Initiation

Task 1 – Human Subject Protection Approval Submission to DoD (Months 1-3): The project PI and co-investigators will develop a human subjects protocol and consent documentation for clinical evaluations and will obtain IRB approval from UC. Institutional IRB approvals will be submitted to DoD HRPO for revision and approval. DoD revisions will be reviewed and approved by the Institutional IRB. This task will be completed by Drs. McDonald and Henricson and Mr. Owens. COMPLETE

Task 2 – Equipment Procurement and Distribution (Months 1-3): The project coordinator will obtain stride rate monitor systems and other materials required to conduct study evaluations. This task will be completed by Ms. Nicorici and Mr. Branum. COMPLETE

Task 3 – Clinical evaluator methodological training for clinical assessments (Month 3): The project investigators and clinical evaluators will meet centrally to harmonize evaluation techniques. This task will be completed by Dr. McDonald, Dr. Henricson, and Ms. Nicorici. COMPLETE

Task 4 – RedCap database and electronic data capture system design (Months 2-3): The project data manager will construct a study database and online web-accessible electronic case report form system to ensure accuracy and completeness of data entry. All study evaluation data will be captured using paper-and-pencil clinic worksheets and will be transcribed into electronic forms by study clinical evaluators and study coordinators. Raw data from stride rate monitors will be uploaded and archived as individual files and will be associated with specific participants and visits to facilitate later compilation and analysis. RedCap enables data monitoring and editing features that are compliant with FDA requirements for electronic recordkeeping in clinical trials. The RedCap system is provided free of charge for UC-associated studies via the UC Davis Clinical and Translational Science Center. Additional technical details are available at http://www.ucdmc.ucdavis.edu/ctsc/redcap/. This task will be completed by Mr. Owens. COMPLETE

Task 5 – Annual IRB Review (Years 2&3, Month 1 *approximately*): Annual human subject protection review activities will be conducted as required by institution IRB and DoD committees. This task will be completed by Drs. McDonald and Henricson and Mr. Sarwari. COMPLETE

Task 6- Study Recruiting, Advertising and Outreach via clinic networks, advocacy organizations, patient registries and social media outlets (Year 3, Month 6 – Year 4, Month 6) IN PROGRESS

Phase II Activities

Task 1 - Recruit and collect data on 60 DMD and 150 typically-developing children (2-16 years) (Year 3, Month 6 – Year 4, Month 6): Participants will be evaluated per the study evaluation protocol at UC. This task will be completed by Ms. Goude, Ms Nicorici, the project specialist (TBD) and Drs. McDonald and Henricson. IN PROGRESS

Task 2 - RedCap electronic data capture (Year 3, Month 6 – Year 4, Month 6): Data from clinical evaluations will be entered into the electronic case report form system. This task will be completed by clinical study team. IN PROGRESS

Phase III Activities: Retrospective Data Analysis and Publications

Task 1-2 – Data analysis and development of publications (Year 3-4): Data analysis will be conducted for Aim 3 activities per the study data analysis plan. Investigators will draft manuscripts for publication in a reputable peer-reviewed journal. This task will be completed by Drs. McDonald and Henricson and the study team. IN PROGRESS

Phase IV Activities: Development of Data Integration Platform Guidelines

Task 1 - Develop guidelines for electronic data transfer and storage platform construct for community-derived mobile health data for medical records (Year 3-4). As stated in Aim 4.1 activities, investigators will develop guidelines for developing a platform to collect PGHD, guidelines for storage, visualization and providing clinical care in the EPIC electronic health record. This task will be completed by Dr. Dharmar, with input from Drs. McDonald and Henricson. IN PROGRESS

Task 2 - Provide guidelines for the transfer of de-identified patient-generated health data (PGHD) to meet FDA 21CFR11 compliance (Year 3-4). As stated in Aim 4.2 activities, investigators will develop guidelines for 21 CFR 11-compliant electronic data transfer and storage platform construct for community-derived mobile health data for research. In addition they will develop guidelines for sharing de-identified PGHD using a platform like the I2B2 NIH data repository for clinical research. This task will be completed by Dr. Dharmar, with input from Drs. McDonald and Henricson. IN PROGRESS

Task 3 – Develop a guidance document and manuscript reflecting system design recommendations and implementation (Year 3-4). Investigators will draft a manuscript for publication in a reputable peer-reviewed journal. This task will be completed by Dr. Dharmar, with input from Drs. McDonald and Henricson. IN PROGRESS

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

Nothing to Report

How were the results disseminated to communities of interest?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how the results were disseminated to communities of interest. Include any outreach activities that were undertaken to reach members of communities who are not usually aware of these project activities, for the purpose of enhancing public understanding and increasing interest in learning and careers in science, technology, and the humanities.

Nothing to Report

What do you plan to do during the next reporting period to accomplish the goals?

Within constraints due to COVID-19-related clinical research safety practices (see Actual or Anticipated Problems section below), we are presently enrolling and testing study participants per the approved study protocol and the revised Statement of Work.

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?

Nothing to Report

What was the impact on other disciplines?

Nothing to Report

What was the impact on technology transfer?

Nothing to Report

What was the impact on society beyond science and technology?

Nothing to Report

5. CHANGES/PROBLEMS: The PD/PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official 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

Nothing to Report

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

In our previous report, we experienced significant delays in project implementation due to movement of our Davis campus laboratory, which involved demolition of our old space and construction and configuration of the new space, which is now complete and operational. As previously noted, the Sacramento campus lab was to be being moved during the summer of 2019, but construction of the new lab has been delayed. Regardless of the delay, we have not experienced any facility-related impacts on our operations or resources, nor do we anticipate any in the coming months. Previous project staffing issues have been resolved through coordination with the clinical trial staff in the UC Davis Neuromuscular Research Center.

Due to the COVID-19 pandemic, human participant clinic visits were temporarily put on hold on a university-wide basis at UC Davis and throughout the UC system, and this impacted our ability to enroll study participants. Our lab experienced no cessation of *interventional* human studies with prospects for direct benefit to participants, but all other studies were placed on hold pending development of laboratory-specific safety SOPs. The university implemented a phased re-start of project elements requiring direct human interaction. This project was designated as a "high-priority" clinical study by the Dean's Office and was one of the first to be allowed to resume in June with targeted enrollment of study participants who have been scheduled for regular clinical care visits. This has enabled us to enroll an initial cohort of individuals with Duchenne muscular dystrophy, as well as typically-developing siblings. While we have not yet reached full enrollment capacity, we anticipate further relaxation of research restrictions in the coming months that will allow us to gather more data. With the help of our institution's telemedicine and telehealth program leaders, we are presently exploring ways to extend the study into the community using telehealth visits and connected devices to enable us to conduct common clinical evaluations (such as the six-minute walk test and timed motor performance tests) remotely in the home/community environment where we expect we will be able to recruit participants more rapidly. If we are successful at developing these methods, and if they are approved by our University in concordance with present COVID-19 research policies, we will introduce a protocol modification prior to implementation.

Given these events and challenges, our present plan is to continue in a no-cost extension year per our last approved revision of our project Statement of Work.

Changes that had a significant impact on expenditures

Nothing to Report.

Nothing to Report

Significant changes in use or care of human subjects

Nothing to Report

Significant changes in use or care of vertebrate animals

Nothing to Report

Significant changes in use of biohazards and/or select agents

Nothing to Report

6. PRODUCTS: List any products resulting from the project during the reporting period. If there is nothing to report under a particular item, state "Nothing to Report."

Publications, conference papers, and presentations

Nothing to Report

Journal publications

Nothing to Report

Books or other non-periodical, one-time publications.

Nothing to Report

Other publications, conference papers and presentations.

Nothing to Report

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: Craig McDonald, MD (PI) - No Change
Name: Erik Henricson, MPH (Co-Investigator) - No Change
Name: Madan Dharmar, PhD (Co-Investigator) - No Change
Name: Alina Nicorici, BS (Clinical Evaluator) - No Change

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

What other organizations were involved as partners?

Nothing to Report

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: For collaborative awards, independent reports are required from BOTH the Initiating Principal Investigator (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.

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

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.

APPENDIX 1: Revised Study Timeline

Objectives and Specific Aims

This proposal focuses on validating the use of patient generated step and activity data to facilitate future data collection at the point-of-care to support the development of stride rate patterns as an outcome measure for ambulatory patients with DMD. It is to include step activity monitoring by StepWatch™ and a consumer level step monitoring devices (Garmin VivoActiveHR and Polar M400 activity watches and the Polar StrideSensor activity monitor) that can feed data through Apple HealthKit into the UC Davis instance of the Epic electronic medical record system. Up to 60 ambulatory patients with DMD will be recruited to represent the early, middle and late stages of the progressive loss of ambulation in DMD. Patients will be sorted into three age groups of (n=20) participants: early (ages 2-6), middle (ages 7-11) and late (ages 12-16). Up to 150 control patients will be recruited and split into similar age ranges. Participants will be assessed using step monitoring devices and traditionally performed clinical outcome measures (6MWT, TFTs, NSAA), followed by community monitoring. StepWatch™ data collected from two previously enrolled cohorts of children with DMD will also be used for longitudinal analyses and determination of responsiveness to steroid treatment. We will address the following specific aims:

Aim 1: Comparison of accuracy and validity of both laboratory- and consumer-grade step activity monitoring devices, and comparison to traditional clinical evaluator determined laboratory-based measures.

Aim 1.1: Evaluate validity and correlation of stride activity data using laboratory and consumer grade devices.

Aim 1.2: Determine concurrent validity of stride rate patterns by accelerometry as compared to the 6-minute walk test, North Star Ambulatory Assessment and Timed Motor Performance Tests in DMD patients who are able to perform these assessments.

Aim 2: Evaluation of age-related patterns in community step monitoring data in DMD and typically developing youth controls.

Aim 2.1 Evaluate differences between DMD and TDY in overall daily patterns of activity by age group across all levels of stride rate activity.

Aim 2.2 Evaluate differences between DMD and TDY for area under the curve for total time and height-adjusted distance overall and at each stride rate and stride activity level group.

Aim 2.3 Evaluate Differences between age groups that represent disease progression in DMD for area under the curve for total time and height-adjusted distance overall and at each stride rate and stride activity level group.

Aim 3: Evaluation of historical community stride monitoring data from natural history studies and clinical trials to evaluate longitudinal change and steroid response characteristics.

Aim 3.1 Evaluate longitudinal rate of change characteristics of stride activity monitoring in DMD using historical natural history data.

Aim 3.2 Evaluate longitudinal rate of change characteristics of stride activity monitoring to identify differences due to glucocorticoid therapy using historical clinical trial data.

Aim 4: We will develop, evaluate and provide recommendations for a framework to collect, and track patient generated health data in the electronic health record for clinical care and to transfer this data into a database to meet Federal 21CFR11 compliance for clinical research.

Aim 4.1: Develop guidelines for developing a platform to collect PGHD, guidelines for storage, visualization and providing clinical care in the EPIC electronic health record.

Aim 4.2: Provide guidelines for the transfer of de-identified patient-generated health data (PGHD) collected via this methodology to meet FDA 21CFR11 compliance. In addition develop guidelines for sharing de-identified PGHD using a platform like the I2B2 NIH data repository for clinical research.

Project Timeline (REVISED)

Study-specific tasks and activities are displayed in the table below.

Project/Task	Year 1				Year 2				Year 3				Year 4			
	1	2	3	1	2	3	4	4	1	2	3	4	1	2	3	4
Phase I: Study Preparatory and Initiation Activities																
Develop Study Protocol and obtain IRB approvals (Institutional and DoD)	C															
Equipment Procurement and Distribution	C															
Site evaluator methodological training for functional assessments	C															
Database and electronic data capture system setup	C															
Annual IRB Review					C				X				X			
Study Recruiting, Advertising and Outreach via clinic networks, advocacy organizations, patient registries and social media outlets.		X	X	X	X	X	X	X	X	X	X	X	X	X		
Phase II: Clinical Study Conduct (Aims 1 and 2)																
Recruit and collect data on 60 DMD children and 150 controls (age 2-16 years).		X	X	X	X	X	X	X	X	X	X	X	X	X		
Electronic data capture, data monitoring and cleaning.		X	X	X	X	X	X	X	X	X	X	X	X	X		
Database lock									X				X			
Analyze data. Write up paper regarding Aim 1.1 on reliability and validity data.									X	X	X		X	X	X	
Analyze data. Write up paper regarding Aim 1.2 on comparisons with community and clinical measures.									X	X	X		X	X	X	
Analyze data. Write up paper regarding Aim 2.1 and 2.2 on comparison of activity patterns in DMD vs controls.										X	X	X		X	X	X
Analyze data. Write up paper regarding Aim 2.3 on comparison of activity patterns with DMD progression										X	X	X		X	X	X
Phase III: Retrospective Data Analysis and Publications (Aim 3)																
Analyze data. Write up paper regarding Aim 2.1 on 1-year longitudinal change using McDonald Shriner's Hospital consortium data.		X	X	X					X	X	X	X	X	X	X	X
Analyze data. Write up paper regarding Aim 2.2 on magnitude of glucocorticoid effect using PTC Therapeutics clinical trial group data.					X	X	X		X	X	X	X	X	X	X	X
Phase IV: Development of data integration platform guidelines (Aim 4)																
Develop guidelines for electronic data transfer and storage platform construct for community-derived mobile health data for medical records.	X	X	X	X					X	X	X	X	X	X	X	X
Develop guidelines for 21 CFR 11-compliant electronic data transfer and storage platform construct for community-derived mobile health data for research.				X	X	X	X		X	X	X	X	X	X	X	X
Simulate and test community step data transfer process from consumer device through EPIC EMR and research databases.							X	X	X	X	X	X	X	X	X	X
Write up paper regarding Aim 4 platform guidelines and recommendations.									X	X	X	X	X	X	X	X