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TITLE: Assessing Arrhythmic Risk in Adult Patients with Duchenne Muscular Dystrophy

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CONTRACTING ORGANIZATION: Johns Hopkins University, Baltimore, MD

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6. AUTHOR(S)

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7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
Johns Hopkins University, 720 Rutland Ave, Ross 871,
Baltimore, MD, 21205

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13. SUPPLEMENTARY NOTES

14. ABSTRACT

Background: Cardiac involvement is common in Duchenne Muscular Dystrophy (DMD). By the end of the second decade, cardiomyopathy is observed in >30% of men and can lead to heart failure, heart rhythm abnormalities and sudden cardiac death. Many men with DMD die suddenly, however, it remains unclear whether they die of arrhythmias. **Objective and Study Design:** We propose *to study the natural history of the rhythm abnormalities in DMD by implanting miniaturized cardiac monitors* (ILRs) in 75 DMD patients at risk for developing potentially life-threatening heart rhythm disorders (*Specific Aim 1*). Additionally, we will use computer simulations in personalized 3D heart models generated from cardiac MRI images obtained during clinical visits, to examine whether scar tissue found in DMD hearts will allow for a better identification of patients at highest risk for arrhythmias who may benefit from implantation of a cardioverter-defibrillator (*Specific Aim 2).* **Major Findings:** We have completed IRB/HRPO approval at this time and are actively enrolling patients. An alternative protocol which includes prolonged ambulatory rhythm monitoring with Ziopatches and Event monitors in addition to ILRs is proposed to help to meet enrollment goals during the COVID-19 pandemic.

15. SUBJECT TERMS
Duchenne Muscular Dystrophy, Sudden Cardiac Death, Ventricular Tachycardia, Computational Modeling

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
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1. INTRODUCTION:

Background: Cardiac involvement is common in Duchenne Muscular Dystrophy (DMD) and can lead to heart failure, arrhythmias and sudden cardiac death. Many men with DMD die suddenly, however, it remains unclear whether they die of arrhythmias. **Objective:** We propose *to study the natural history of the rhythm abnormalities in DMD by implanting miniaturized cardiac monitors* (ILRs) in 75 DMD patients at risk for developing potentially life-threatening heart rhythm disorders (*Specific Aim 1*). Additionally, we will use computer simulations in personalized 3D heart models generated from cardiac MRI images to examine whether scar tissue found in DMD hearts will allow for a better identification of patients at highest risk for arrhythmias who may benefit from implantation of a cardioverter-defibrillator (*Specific Aim 2).*

2. KEYWORDS:

Duchenne muscular dystrophy, sudden cardiac death, ventricular tachycardia, computational modeling, left ventricular fibrosis, implantable loop recorders, ambulatory EKG monitoring.

3. ACCOMPLISHMENTS:

What were the major goals of the project?

Major Task 1: Ensure Regulatory Documents and Research Protocol are uptodate.

- Coordinate with sites for annual IRB report for continuing review
  Projected: Annually
  Status: ongoing
- Submit IRB amendments, adverse events and protocol deviations as needed
  Projected: Q1
  Status:
  IRB approval for Nationwide Children's site obtained 08/12/2019. HRPO approval obtained 5/28/2020.
  IRB approval for Hopkins site obtained 1/24/2020. HRPO approval obtained 5/28/2020.
  IRB approval for Northwestern site obtained 3/13/2020. HRPO approval obtained 8/7/2020.

Major Task 2: Recruitment and Training of Research Study Support Staff

- Advertise and interview for project-related staff:
  Projected: Q1
  Status: Completed
- Hiring and training of project-related staff:
  Projected: Q1
  Status: Completed

Major Task 3: Enroll patients and implant ILRs

- Begin subject recruitment and implantation of ILRs:
  Projected: Q3 onwards.
  Status: **Delayed due to COVID-19. All patient related research protocols were halted by the Hopkins IRB due to the COVID-19 pandemic.**

Specific Aim 2: Arrhythmia Risk Stratification Using Personalized Heart Models:
Projected: Q3 onwards.
Status: all these goals not completed given pending IRB approval.

- Collect data on arrhythmias from ILRs and correlate with cMRI-LGE data, when clinically available (n=20 subjects with documented ventricular arrhythmias and n=20 subjects without VT)
- Transfer cMRI-LGE data from NCH and NWU to HIPAA-compliant workstation for creation of 3D heart models
- Creation of 3D heart models and virtual electrophysiology study (n=20 subjects with documented ventricular arrhythmias and n=20 subjects without VT/VF)

Major Task 4: Data Analysis

- Coordinate with Sites & Data Core for monitoring data collection rates and data quality; Bi-monthly teleconferences
  Projected: Q3 onwards
  Status: Delayed due to COVID-19 pandemic. Projected to start once 25% of study patients have been enrolled.

What was accomplished under these goals?

1) **Major activities:** HRPO approval of IRB protocols obtained for all 3 study sites.
2) **Specific objectives**: Enrollment of patients was on hold during Q3 and Q4 due to COVID-19 pandemic and halting of clinical research activities across all three participating study sites.
3) **Significant results or key outcomes, including major findings, developments, or conclusions:** Enrollment of patients was on hold during Q3 and Q4 due to COVID-19 pandemic and halting of clinical research activities across all three participating study sites
4) **Other achievements:** N/A.

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

Nothing to report.

How were the results disseminated to communities of interest?

Nothing to report.

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

- modified enrollment criteria (approval from IRB pending) as discussed with DOD Program Manager will allow for meeting enrollment goals during COVID-19 pandemic
- restart patient enrollment and analysis of cardiac MRI data in personalized heart models.

4. IMPACT:

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?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe ways in which the project made an impact, or is likely to make an impact, on commercial technology or public use, including:

- *transfer of results to entities in government or industry;*
- *instances where the research has led to the initiation of a start-up company; or*
- *adoption of new practices.*

Nothing to report.

What was the impact on society beyond science and technology?

Nothing to report.

5. CHANGES/PROBLEMS:

Current problems:
1) Given the current COVID-19 pandemic, our local IRB at Hopkins had halted all patient-related research for more than 4 months.
2) Likewise, the COVID-19 pandemic has resulted in increased reluctance of DMD patients to present for in-patient clinic visits, cMRIs and procedures/implantation of loop recorders, as most DMD patients are considered high risk given their comorbidities and immunosuppression.
Mitigation strategies: Discussed below.

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

Anticipated problems: Even after our local IRB has allowed for resumption of patient-related research in September 202, we are still expecting difficulties with patient enrollment due to the fact that most patients with Duchenne muscular dystrophy are very reluctant to come in to clinic for in person visits or have procedures like ILR implantation. Given their immunosuppressed state and comorbidities, DMD patients are at significantly increased risk of complications should they contract COVID-19.

Mitigation strategies: Based on discussion with the other study centers, an alternative path to meet enrollment and study goals is by

1) Expanding enrollment criteria (accepting patients with other forms of prolonged ambulatory EKG monitoring, including Ziopatches and 30 day event monitors, rather than only implantable loop recorders for rhythm monitoring). While Ziopatches can only record 14 days of continuous EKG monitoring, they have the unique advantage that they can be mailed directly to the patient's home. Thus, it does not require in person clinic visits to apply Ziopatches which **makes us independent of future developments of the COVID-19 pandemic**. We could mail up to two Ziopatches per year to patients, if clinically indicated. While we potentially are able to recruit less patients with ILRs due to the COVID-19 pandemic, we anticipate that including patients with Ziopatch EKG monitoring will allow us to meet (or potentially even exceed) the number of patients who will be eligible for computational modeling (Aim 2: personalized heart models to assess risk for VT and sudden death). We anticipate to recruit a mix of patients with ILRs and Ziopatches. We are currently working on including all 7 patients from all three sites who have ILRs already.

2) Accepting patients from more PPMD-certified centers (PPMD, Parent Project Muscular Dystrophy is the study sponsor for the Northwestern Site). We are planning to advertise the study on the PPMD website and **recruit patients from other PPMD-certified Duchenne centers who already have ILRs.**

Changes that had a significant impact on expenditures

N/A.

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

Given the COVID-19 pandemic we are experiencing difficulties with patient enrollment due to the fact that most patients with Duchenne muscular dystrophy are very reluctant to come in to clinic for in person visits or have procedures like ILR implantation due to their immunosuppressed state and comorbidities which significantly increase their risk of complications should they contract COVID-19.

Mitigation strategies: Based on discussion with the other study centers, an alternative path to meet enrollment and study goals is by
1) Expanding enrollment criteria (accepting patients with other forms of prolonged ambulatory EKG monitoring, including Ziopatches and 30 day event monitors, rather than only implantable loop recorders for rhythm monitoring). While Ziopatches can only record 14 days of continuous EKG monitoring, they have the unique advantage that they can be mailed directly to the patient's home. Thus, it does not require in person clinic visits to apply Ziopatches which **makes us independent of future developments of the COVID-19 pandemic**. We could mail up to two Ziopatches per year to patients, if clinically indicated. While we potentially are able to recruit less patients with ILRs due to the COVID-19 pandemic, we anticipate that including patients with Ziopatch EKG monitoring will allow us to meet (or potentially even exceed) the number of patients who will be eligible for computational modeling (Aim 2: personalized heart models to assess risk for VT and sudden death). We anticipate to recruit a mix of patients with ILRs and Ziopatches. We are currently working on including all 7 patients from all three sites who have ILRs already.
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IRB protocol has been submitted.

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:

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

  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: *Andreas S. Barth, MD, PhD*
Project Role: *PI*
Researcher Identifier (e.g. ORCID ID): 0000-0001-5275-8049
Nearest person month worked: *1*
Contribution to Project: *Wrote IRB protocol at Johns Hopkins*
Overseeing recruitment of study members
Coordinated activity between centers.

Name: *Natalia Trayanova, PhD*
Project Role: *co-PI*
Researcher Identifier (e.g. ORCID ID): 0000-0002-8661-063X
Nearest person month worked: *1/2*
Contribution to Project: *coordination with other study centers re:transfer of cardiac MRI data for personalized heart models*

Name: *Linda Cripe MD*
Project Role: *local site-PI, Nationwide Children's Hospital*
Researcher Identifier (e.g. ORCID ID): 0000-0003-0524-9908
Nearest person month worked: *1*
Contribution to Project: *Wrote IRB protocol at Nationwide Children's Hospital*
Overseeing recruitment of study members
Coordinated activity between centers.

Name: *Elizabeth McNally, MD, PhD*
Project Role: *local site-PI, Northwestern University*
Researcher Identifier (e.g. ORCID ID): 0000-0002-1221-719X
Nearest person month worked: *1*
Contribution to Project: *Wrote IRB protocol at Northwestern University*
Overseeing recruitment of study members
Coordinated activity between centers.

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

Key Personnel change:

1) Kennedy Krieger Institute (KKI): Kathryn Wagner, MD, PhD will be leaving KKI at the end of October 2020 to assume a role in Duchenne Research outside of academia. Dr. Doris Leung will be become the Director of the Genetic Muscle Clinic at KKI and will be replacing Dr. Wagner's role in this grant. We do not anticipate any change with respect to the Specific Aims of this project.

What other organizations were involved as partners?

1. Kennedy Krieger Institute: Outpatient Center, Broadway Campus, 801 North Broadway Baltimore, MD 21205
   Contribution: Main study site together with Johns Hopkins University. Patient recruitment. Coordinating center.

2. Nationwide Children’s Hospital. 700 Children's Dr, Columbus, OH 43205
   Contribution: Patient recruitment, study site.

3. Northwestern University, Feinberg School of Medicine, Chicago, IL
   Contribution: Patient recruitment, study site.

4. Parent Project Muscular Dystrophy (Non-Profit Organization): 401 Hackensack Avenue, 9th Floor, Hackensack, NJ 07601.
   Contribution: provides sponsoring/financial support for Northwestern University site for this project.

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.