TITLE: **Defining Clinical Endpoints in LGMD**

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CLINICAL RESEARCH PROTOCOL

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Summary of Changes from Previous Version:

Affected Section(s)	Summary of Revisions Made	Rationale
All	Reformat	Ease of reference between Arm 1 and Arm 2
5, 6, 2	Addition of Sarcoglycan Cohort	Expanded knowledge for cohort
3	Study Aim changed from 12 months to 24 months	Inclusion of Sarcoglycan Cohort
Appendix 2	Added follow-up telemed assessments and visit windows	For clarification purposes

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STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Council on Harmonization Good Clinical Practice (ICH GCP) and the following:

2.1. United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, **and/or** 21 CFR Part 812).

The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the funding agencies and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection and ICH GCP Training. The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form(s) must be obtained before any participant is consented. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form(s) will be IRB approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form

INVESTIGATOR AGREEMENT:

I have read the protocol and agree to conduct the study as outlined in the protocol.

Signature: _____ **Date:** _____

Name (print): _____

Institution Name and Address:

_____

_____

_____

1. PROTOCOL SUMMARY

Title:	Defining Clinical Endpoints in LGMD	
Study Description:	Developing COAs in LGMD to hasten therapeutic drug development.	
Objectives	Primary Objective:	To define a common set of pelvic and shoulder girdle COAs and COAs useful for capturing phenotypic diversity.
	Secondary Objective:	To determine the sensitivity to longitudinal disease progression
		To refine clinical strategies based on baseline and longitudinal phenotypic characteristics
		To validate exploratory telemedicine remote assessments in Arm 2.
Endpoints	100-meter walk, 10-meter walk, supine FVC, NSAD, TUG, PUL	
Study Population	Individuals with LGMD type CAPN3, ANO5, DYSF, DNAJB6, SGCA, SGCB, SGCD, and SGCG	
Study Duration	4 years	
Participant Duration	24 Months	
Co-Investigators:	Anthony Amato, MD	Brigham and Women's
	Jeffery Statland, MD	Kansas University Medical Center
	Kathryn Wagner, MD	Kennedy Krieger Institute
	Linda Lowes, DPT, PhD	Nationwide Children's Hospital
	Volker Straub, MD	Newcastle University
	Katherine Mathews, MD	University of Iowa
	Matt Wicklund, MD	University of Colorado
	Tahseen Mozzafar, MD	University of California-Irvine
	Peter Kang, MD	University of Florida
	Conrad Weihl, MD, PhD	Washington University

2. INTRODUCTION

Limb Girdle Muscular Dystrophy comprise a group of disorders made up of over 30 mutations which share a common phenotype of progressive weakness of the shoulder and hip girdle muscles. While the individual genetic mutations are rare, as a cohort, LGMDs are one of the four most common muscular dystrophies. The overall goal is to define the key phenotypes as measured by standard clinical outcome assessments (COAs) for limb girdle muscular dystrophies (LGMD) to hasten therapeutic development.

2.1. STUDY RATIONALE

The rationale for this study is defining COAs where LGMDs converge, and COAs where LGMDs diverge in performance will help hasten therapeutic development and ensure properly powered clinical trials. Recent advances in gene testing have enabled several large, free genetic testing programs in the United States, increasing the pool of genetically defined LGMDs. In collaboration with LGMD advocacy groups we have identified strategies to reach out and mobilize this genetically defined LGMD community to enter a large trial preparedness study.

2.2. BACKGROUND

The genetic heterogeneity has been a barrier to broad natural history efforts, with prior investigations often limited to single gene mutations. Much attention is paid to the variability within individual mutations (e.g. distal presentations), as opposed to defining the best strategy for measuring change in overall LGMD disease burden. This presents a major dilemma for LGMD rare disease research: how to balance diverse genes leading to overlapping phenotypes, versus variants in the same gene leading to divergent phenotypes. What is clear, is as a group, LGMDs are chronic and progressive leading to significant lifetime morbidity and represent a large unmet clinical need.

Recent developments in our genetic understanding of LGMD and molecular approaches to therapy have led to proposed gene replacement therapies for at least three of the LGMD mutations. Several of these gene replacement therapies are currently in pre-clinical/phase 1 testing, leading to an urgent need for natural history data. In addition, non-specific therapies which target muscle mass or function are being tested in other muscular dystrophies and may prove beneficial for LGMD.

2.3. RISK/BENEFIT ASSESSMENT

2.3.1. KNOWN POTENTIAL RISKS

This study provides a minor increase over minimal risk.

2.3.2. OVERVIEW OF RISKS

- During the collection of blood samples, the participant may experience pain and/or bruising at the needle site. An anesthetic cream may be applied on the arm to make the area numb and reduce discomfort. Although rare, localized clot formation and infections may occur. Light-headedness and/or fainting may also happen during or shortly after having blood drawn.
- During the functional testing and motor testing, there is the potential for the participant to fall. Two members of the study staff will be present to minimize this risk.
- Muscle strength testing may cause the participant's muscles to be sore
- Breathing tests may cause the participant to have difficulty breathing or he/she may feel fatigued during the test.

- Completing questionnaires about the participant's symptoms could cause the participant to become tired after concentrating for a long period of time. Some questions may cause minor psychological stress.
- Release of medical information could result in a potential loss of privacy. There is a small chance that some research may yield results that will have a negative impact on participants, family members, other individuals, or groups. This impact may include ability to be insured or employed, or changes in family relationships.

2.3.3. KNOWN POTENTIAL BENEFITS

There are no direct benefits that the participant can expect to receive as a result of participating in this study. Society will benefit with a greater understanding of the disease process and potential clinical trial preparedness.

2.3.4. ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

The site study coordinator and investigators will monitor all participants for potential risks and benefits. All adverse experiences will be documented, and serious adverse events will be reported per institutional IRB SAE reporting guidelines.

3. OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
To define a common set of pelvic and shoulder girdle COA's	100-meter walk, NSAD, TUG, 10-meter walk, supine FVC	These measures have previously been evaluated as sensitive to change in other forms of muscular dystrophy
Secondary		
To determine the sensitivity of the COAs to longitudinal disease progression	100-meter walk, NSAD, TUG, 10-meter walk, supine FVC	These measures have been previously evaluated as sensitive to change in other forms of muscular dystrophy
Tertiary		
To validate exploratory telemedicine remote assessments in Arm 2.	TUG, PUL	This measure will capture the changes associated with LGMD as reported by patients self-reporting and testing measures

3.1. OVERALL STUDY AIM

Our approach is to enroll large cohorts from each of the four most prevalent, amenable to therapy, LGMDs (n=20 each): CAPN3, ANO5, DYSF, and DNAJB6 and (n=18 each): SGCA, SGCB, SGCD, SGCG. We will perform a 24-month longitudinal study using 11 sites in our LGMD Research

Consortium. We hypothesize that COAs representing the major shoulder and pelvic girdle functional burden can be shared across all LGMDs, and genetic variability can be addressed by adding select mutation-relevant COAs to create a LGMD COA toolbox for future trials.

3.2. SPECIFIC STUDY AIMS

3.2.1. To define a common set of pelvic and shoulder girdle COAs, and COAs useful for capturing phenotypic diversity. Participants will have visits for a minimum of 12-months. The baseline visit will occur over two days to allow for test-retest reliability. We will use standard measures (defined below) of motor strength and evaluator-administered functional motor tasks, which target proximal, mid-limb, and distal upper and lower extremity function. We will also assess pulmonary capacity and patient-reported measures of functional disease burden. We will collect biological samples and assess AAV-rh 74 seroreactivity and store them for future biomarker discovery. Cross sectional analysis will assess variance between cohorts and within cohorts on select COAs to determine convergent and divergent phenotypes.

3.2.2. To determine the sensitivity of the COAs to longitudinal disease progression. We will determine the responsiveness of our COAs at 3, 6, and 12 months. We will use statistical and anchoring methods to determine what will be a minimally important clinical difference. We will use factor analysis to identify COAs that capture variation in disease severity across the cohort.

3.2.3. To define clinical trial strategies based on baseline and longitudinal phenotypic characteristics. We will focus on COAs that are applicable across cohorts. We will determine which baseline characteristics, mutation, age, gender and baseline functional status are most likely to predict progression over 12 months using regression trees to assess subgroups likely to progress.

3.2.4. To validate an exploratory telemedicine remote assessment in the SGCA, SGCB, SGCD, and SGCG cohort. We will compare two telemedicine captured upper extremity functional measures to in-person visits at month 1, 6, 9 months, 12 months and then extend follow up at after 12 months by collecting telemedicine visits every 3 months for an additional12 months.

3.3.SIGNIFICANCE

3.3.1. Prevalence of LGMD's

There are limited LGMD epidemiological studies, with a meta-analysis of studies published since 1991 yielding a world-wide incidence of 0.7/100,000, and prevalence of 3/100,000.[1] There are no prevalence studies in the United States but using the projected worldwide estimates would yield approximately 10,500 affected individuals in the US. While there are limited studies documenting the population prevalence of the LGMDs, many studies have looked at the relative frequency of different LGMD subtypes. A study from 2006 found a US distribution of LGMD mutations: 18% DYSF (LGMD2B), 15% SGCA (LGMD2C-F), 15% FKRP (LGMD2I), 12% CAPN3 (LGMD2A), and 1.5% CAV3 (LGMD1C).[2] Recently, programs by the Muscular Dystrophy Association, the Jain Foundation, and others have provided free genetic testing for individuals with LGMD in the US. The programs were designed to eliminate a previous barrier to diagnosis, the high cost of genetic sequencing. The 35-gene LGMD panel, performed through Emory University, has provided a relative prevalence of mutations within the 6177 individuals who had genetic testing.

The four most common recessive LGMD mutations which might be amenable to gene replacement were in CAPN3 (LGMD2A), DYSF (LGMD2B), the combined sarcoglycan

mutations (LGMD2C-F), and ANO5 (LGMD2L; **Figure 1**). *These LGMDs are prime candidates for gene therapy and ideal LGMD subtypes to focus on for Project 1.*

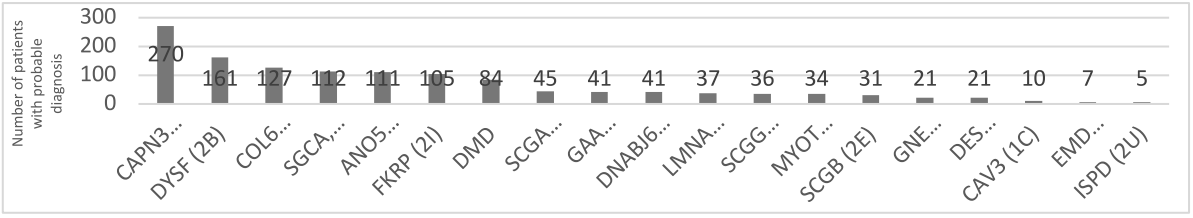

Figure 1. Prevalence of pathogenic mutations and likely pathogenic variants in a IS-based free LGMD testing program

3.3.2. Urgent need for Clinical Trial Readiness

The rapid advancement of molecular based therapeutics in inherited neuromuscular disorders, and gene-based therapies for LGMD create a pressing need to develop robust COAs for LGMD. In spinal muscular atrophy, the recent FDA approval of an antisense oligonucleotide therapy (Spinraza), and ongoing, successful efforts with gene therapy suggests that therapies that directly modify genetic mutations are possible.[3–5] In Duchenne muscular dystrophy (DMD), another antisense oligonucleotide therapy (exon 51-skipping therapy) has approval in the United States, and a drug which causes read-through of premature stop mutations is provisionally approved in Europe.[6,7] Phase 1 studies of AAV-delivered gene therapy for LGMD 2C, D (sarcoglycan) have demonstrated proof-of-principle for delivery in an isolated muscle, and showed sarcoglycan staining in muscle biopsies post therapy (**Figure 2**).[8–11] Preclinical efforts to develop gene therapies for FKRP mutations (LGMD2I) and sarcoglycan B mutations (LGMD2E) are underway (see letter of support). For the dominant LGMDs which are not amenable to gene replacement, we have also shown evidence that small molecules can affect the pathology associated with *DNAJB6* mutations (LGMD1D, **Figure 2**).[12] In addition to molecularly based therapies many therapies are currently in clinical trials in muscular dystrophy which may provide a benefit which are not disease specific. Such approaches include targeting the myostatin pathway, muscle inflammation, regeneration, or fibrosis. Recently completed early phase studies of non-specific therapies in LGMD include anti-myostatin drug to improve muscle growth (NCT02841267), a steroid to target inflammation (NCT00527228), and a tRNA synthetase to target muscle inflammation and regeneration (NCT02836418).

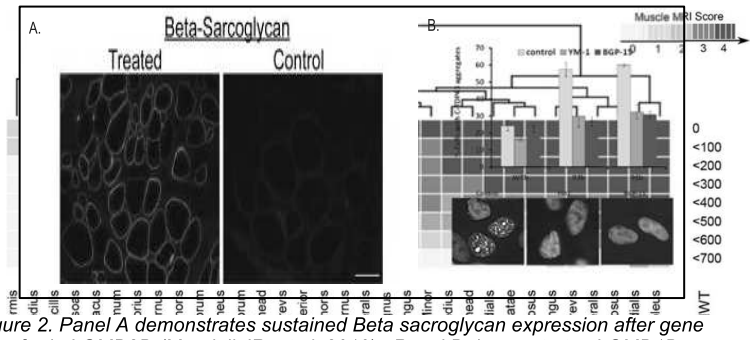

Figure 2. Panel A demonstrates sustained Beta sacroglycan expression after gene transfer in LGMD2D (Mendell JR, et al, 2010). Panel B demonstrates LGMD1D mutations (93b and 96b) in DNAJB6 impair clearance of TDP43 nuclear inclusions. Treatment with small molecules that modulate chaperone function (YM1, BGP-15) rescue this in cell culture. In fact, BGP-15 is an analog of arimoclomol which is clinical trials for IBM, which has active or recently completed studies in IBM and ALS.

Figure 3. Heat map from dysferlin study shows relationship between MRI fibro-fatty changes in muscle (darker green color) and decreased distance traversed on the 6 minute walk test (right y-axis). In addition, note early involvement in both hamstring and gastrocnemius muscles. (Diaz-Manera J, et al., 2018)

Discussions with academic researchers and industry partners have identified gaps to overcome in LGMD trial preparedness, as candidate therapeutics will be entering larger studies in the next 5 years. In particular there is a need for: 1) better diagnostics; 2) refined trial strategies for inclusion or exclusion criteria; 3) biomarkers for early phase studies; 4) COAs and patient-reported outcomes for later phase studies and drug registration trials; 5) understanding baseline variables which may predict more consistent progression over timeframes typical for clinical trials (e.g. 1 year); and 6) exploratory techniques like telemedicine for remote assessments to reduce patient burden and expand the LGMD population that can be reached for clinical trials.

A major barrier to therapy development for LGMD is lack of standard COAs, and an inability to determine the natural history of LGMD as measured by COAs. In addition, there is limited data regarding which COAs will be common to all LGMDs, and which may provide more specificity for atypical phenotypic presentation.

3.3.3 Prior COA Development in LGMDs

There are many cross-sectional studies in LGMD that seek to describe the genotype-phenotype spectrum associated with individual mutations. Some strategy f or grouping mutations by type is required, for example nonsense mutations, microdeletions or insertions, missense mutations. On average the ability for specific mutations to predict the clinical severity, age at diagnosis, or age at first wheelchair use, is not strong.[13–15] This helps support the notion that we will be able to group LGMD patients by phenotype, age, or baseline functional status to validate a set of common COAs, with some adjustment for those LGMD subtypes where we know from the prior studies additional outcomes may be required to monitor respiratory or cardiac status. For example the sacroglycanopathies typically have a younger age of onset with more prominent respiratory and cardiac morbidity, than the LGMDs due to dysferlin or calpain mutations.[16] While there are many cross-sectional or retrospective LGMD studies, there are few longitudinal studies. There have been prospective longitudinal studies in individuals with CAPN3, *FKRP* and *DSYF* mutations (LGMD2A, 2I, and 2B, respectively).[13,17,18] It is difficult to compare across studies because inclusion criteria (e.g. age or functional status), number of individuals included, procedures performed and evaluator training, or follow up time are not uniform. That said it is encouraging that studies overall have demonstrated an ability to use common muscular dystrophy COAs and shown such common COAs are reliable in LGMD and relate in a cross-sectional fashion to overall severity of weakness, or disability. Both manual muscle testing and quantitative myometry have been used to describe patterns and degree of muscle involvement. As expected some common features include limb-girdle patterns of weakness, with variable thigh or arm involvement.[13,17,18] Interestingly for LGMD2I (FKRP) and LGMD2B (DSYF) use of MRI has reinforced this expected distribution of muscle involvement; but has also revealed early and frequent involvement of more distal muscles (e.g. the gastrocnemius), suggesting that some separately defined phenotypes, like distal myopathies, may actually represent a LGMD spectrum (**Figure 3**).[19] Indeed at 1 year of follow up in LGMD2I changes in quantitative fat on MRI revealed expected evolution in changes in muscles in the posterior thigh, but also changes in the gastrocnemius.[18] Some common timed functional measures being used in LGMD studies include the 6 minute walk test, the timed up and go, the 10 meter walk/run. These outcomes have a broad experience of use in many dystrophies, including the three most prevalent DMD, FSHD, and myotonic dystrophy.[20–22] In LGMD2B these outcomes consistently showed small, but significant progression over 1 year of follow up (see Approach), supporting the notion that a set of functional motor outcomes will be important for LGMD. MRI has been proposed in LGMD as an early biomarker to track disease progression over timeframes where strength or function might not be expected to change, or in smaller cohorts of subjects. The most common methods used include quantitative fat as measured by the DIXON technique, or quantitative T2. One study has shown changes on MRI in LGMD2I over 1 year, where strength and function did not change.[18] MRI is likely a tool which will be important in LGMD therapeutic development; however, several limitations prohibit its widespread use at this time: 1) high recurrent costs; 2) lack of common equipment and protocols; 3) patient limitations on ability to tolerate MRI (e.g. respiratory status, contractures); 4) uncertain regulatory acceptance; and 5) extensive post-processing costs in terms of time and money. Patient reported outcomes become important as therapeutic development gets closer to registration, and the patient-reported health impact of disease becomes important. There are only limited studies of patient-reported disease impact. One study used common non-disease specific PROs in LGMD, including the SF-36, the Individual Neuromuscular Quality of Life scale, and screens of fatigue or sleepiness. Not surprisingly they showed LGMD impacted quality of life mainly in physical areas (weakness,

fatigue, and independence), with less consistent findings on emotional or social relationship domains.[23]

Taken together clear themes for LGMD outcome development are emerging:

- While genetic diversity is a concern, LGMDs do not demonstrate strong single gene predictors of severity, enabling a broader approach like that proposed in Project 1
- Standard techniques for measuring strength and function will likely be reliable, pertinent for LGMD, and amenable to roll out in a multi-site study
- While changes in timeframes of 12 months may not be large, they are likely detectible in LGMD using motor function outcomes
- The COAs determined in Project 1 can be complimentary to any additional studies of outcomes like MRI, which may also have an important role in LGMD

Importantly, while individual subtypes may have had prior natural history studies, it is unclear how generalizable these data are across LGMDs or the multi-site reproducibility of the results, so a larger effort, like that proposed here is vital for therapeutic development for LGMD. Several therapeutics have the potential to be broadly applicable to all LGMDs. Based on the pathogenesis, anything stabilizing or repairing the sarcolemmal membrane would also be applicable across LGMDs. Therefore, it would be important to understand if the COAs sensitive for LGMD2B progression would be sensitive in people with LGMD2A mutations.

3.4. Barriers to COA development in LGMDs

Prior efforts to develop COAs have focused on individual subtypes of LGMD. This has limited the power to detect changes in slowly progressive conditions and is further hampered by the variability within a specific subtype. In addition, prior efforts have been conducted by a small number of sites limiting our ability to define the multi-site reliability and performance of outcome measures. Our hypothesis for this project is that a core set of clinical outcome assessments can be shared between LGMD subtypes, a so-called 'LGMD clinical trial toolbox.' The ability to use a shared set of COAs across LGMDs provides efficiency for clinical trial planning. Within certain LGMD subtypes, it will be helpful to assess phenotypic variation (e.g., distal onset) and contrast this with a shared, convergent, phenotype across LGMDs. This approach will allow us to better define where other outcomes like respiratory and cardiac status, distal function, or measures of contractures may be required. Finally, LGMDs are rare disease with relatively low population density at any one clinical center, requiring collaborations across multiple sites to study the disease. Remote assessments refer to outcome measures that are administered remotely from the study site. The use of follow up questionnaires or even phone calls has been a long-standing practice in clinical trials. More recently, the advent of high-quality video conferencing has enabled researchers to explore the use of more sophisticated remote assessments. Tools to remotely assess physical function have been validated in stroke, Parkinson's disease, Huntington's disease, and spasticity.[24–28] Research participants and clinic patients both report increased satisfaction with this methodology. To date, these remote assessments have not been validated for LGMD: Project 1 allows for validation of the approach.

4. STUDY DESIGN

4.1. OVERALL STUDY DESIGN

This study will enroll 152 subjects at 11 participating sites part of the established LGMD Research Consortium. No Treatment will be administered as part of this study. Patients will receive standard of care as determined by their treating physician.

4.1.1. ARM 1

Study visits will occur at baseline, month 6 and month 12 in all cohorts except the LGMD1D cohort, where the visits will be at baseline and 12 months. Up to 20 subjects, both male and female, will be enrolled from each cohort below:

- CAPN3 (LGMD2A)
- DYSF (LGMD2B)
- ANO5 (LGMD2L)
- DNAJB6 (LGMD1D)

4.1.2. ARM 2

In person study visits will occur at baseline, month 3, month 6, and month 12. Telemedicine assessments will occur at month 1, month 6, month 9, month 12 and will .continue every 3 months for 12 additional months. Up to 18 subjects, both male and female will be enrolled in each cohort below:

- SGCA (LGMD2D)
- SGCB (LGMD2E)
- SGCD (LGMD2C)
- SGCG (LGMD2F)

4.2. SCIENTIFIC RATIONALE FOR STUDY DESIGN

As the primary objective of the proposal is to develop clinical trial outcome measures, the subject selection criteria mirror the types of subjects likely to be selected for LGMD clinical trials. However, as there are still questions about ideal eligibility criteria, we have left our criteria broad enough to investigate demographic and genetic associations with disease progression.

4.3. END OF STUDY DEFINITION

At the completion of this study we will have: 1) Determined which COAs are most appropriate for therapeutic trials; 2) established the variability in common COAs for power and sample size planning; 3) determine the sensitivity of the COAs to longitudinal disease progression; 4) validated exploratory telemedicine remote assessments in Arm 2.

5. STUDY POPULATION

Study participants will be identified through self-selection and direct recruitment options. Participants will be identified from the population of individuals who are followed at the neuromuscular clinics at the Virginia Commonwealth University, Washington University in St. Louis, University of Iowa, Kansas University, Nationwide Children's Hospital, University of Colorado, University of California Irvine, University of Florida, Brigham and Women's, Kennedy Krieger Institute, and Newcastle University.

5.1. INCLUSION CRITERIA

5.1.1. Arm 1

- Age between 6-65 at enrollment
- Clinically affected (defined as weakness on bedside evaluation in either a limb-girdle pattern, or in a distal extremity)
- A genetically or functionally confirmed mutation in ANO5, CAPN3, DYSF, or DNAJB6.
- Ambulatory

5.1.2. Arm 2

- Age between 4-50 at enrollment
- Clinically affected (defined as weakness on bedside evaluation in either a limb-girdle pattern, or in a distal extremity)
- a genetically confirmed mutation in SGCA-G

5.2. EXCLUSION CRITERIA

5.2.1. Arm 1

- Any other illness that would interfere with the ability to undergo safe testing or would interfere with interpretation of the results in the opinion of the site investigator.
- History of a bleeding disorder, platelet count <50,000, current use of an anticoagulant.
- Positive pregnancy test at time any timepoint during the trial.

5.2.2. Arm 2

- Any other illness that would interfere with the ability to undergo safe testing or would interfere with interpretation of the results in the opinion of the site investigator.
- History of a bleeding disorder, platelet count <50,000, current use of an anticoagulant
- Positive pregnancy test at time any timepoint during the trial.

5.3. Rationale of Inclusion and Exclusion Criteria

Arm 1: The age range is designed to be broad to capture the full range of disease severity associated with ambulation status and reflect potential clinical trial populations. The younger age limit was chosen to ensure the ability to comprehend the outcome measures proposed. Those with an *ANO5* (LGMD2L) mutation may not lose ambulation or even be clinically affected until late in life, necessitating an age range of up to 65. The upper age limit reflects the potential exclusion criteria of future therapeutic trials.

Arm 2: The age range is designed to be broad to capture the full range of disease severity associated with ambulation status, and reflect potential clinical trial populations. Individuals with sarcoglycan mutations (LGMD2C-F) may lose ambulation early in life and therefore require a younger age of onset to capture ambulation.[29] The younger age limit was chosen to ensure the ability to comprehend the outcome measures proposed. The upper age limit reflects the potential exclusion criteria of future therapeutic trials.
The inclusion criteria dos not stipulate ambulation status. Participants at risk for losing ambulation (or non-ambulatory) (10-meter walk>12 sec) will be allowed to enroll but will be no more than 20% of the overall participant enrollment. This will improve our understanding of the phenotypic spectrum and begin to evaluate clinical outcome assessments in more functionally limited individuals.

5.4. SCREEN FAILURES

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened up to 2 additional times. The interval between rescreening should be at least 4 weeks after the prior consent was signed. Each time a rescreening is performed, the individual must sign a new consent form and will be assigned a new identification number.

5.5.DEVIATION FROM INCLUSION/EXCLUSION CRITERIA

Deviations from Inclusion/Exclusion criteria is not authorized. Sites should take all reasonable efforts to comply with the protocol.

5.6. STRATEGIES FOR RECRUITMENT AND RETENTION

Participants will be recruited from the respective Neuromuscular Disease Centers. Other options include: recruitment newsletters (from the Muscular Dystrophy Association), JAIN foundation, Coalition to Cure Caplain-3, LGMD2D Foundation, LGMD2L foundation, Kurt & Peter Foundation, and the FKRP registry. All registries are databases of clinical patients and prior research participants who consented to receive direct notification regarding future research studies in which they may be interested. We will contact those patients who previously participated in the MDA and JAIN foundation free genetic testing programs who would qualify. Interested potential participants and parents will be contacted by phone by the study coordinator and questioned about health status. Interested potential participants and parents will be contacted by phone by the study coordinator and questioned about health status. Interested participants who appear to fit the inclusion/exclusion criteria will be asked to come for a screening/baseline visit. Finally, we will register the study on www.clinicaltrials.gov.

6. STUDY ASSESSMENTS AND PROCEDURES

6.1. WRITTEN INFORMED CONSENT

Participants will be provided with a copy of the consent form and assent form for review prior to their screening visit when possible. Informed consent (and assent for the older cohort) will be obtained by the principal investigator or study coordinator after complete description of the study and an opportunity to ask questions and have their questions answered. This information includes the purpose, procedures, risks, benefits, contact persons, compensation, care for injury, and voluntary participation in the study. The parent or legal guardian of the subject will sign an IRB approved consent form. The investigator will retain the original with a copy for the subject.

6.2.STUDY ASSESSMENTS

For each patient, all study procedures should be conducted according to the Schedule of Events (Appendix 1) and following the study-specific recommendations included in the Study Manual of Operations.

6.3. SAFETY ASSESSMENTS

Safety assessments include monitoring of adverse events, concomitant medications, vital signs and physical exam findings.

6.4. CLINICAL ASSESSMENTS

6.4.1. MEDICAL AND SURGICAL HISTORY

A complete medical and surgical history will be used to capture other medical comorbidities, age of onset, and family history

6.4.2. VITAL SIGNS

Blood pressure (systolic and diastolic), respiratory rate, pulse rate, body temperature, body weight, and height will be collected at each study visit.

6.4.3. PHYSICAL EXAM

A brief physical exam will be conducted at each study visit to establish baseline values

6.4.4. URINE PREGNANCY TESTING

For females of childbearing potential only

6.4.5 TELEMEDICINE ASSESSMENTS

Participants will be asked to complete the Performance of Upper Limb v2.0 (6.5.4) or the TUG (6.5.5) via Zoom with a Clinical Evaluator at months 1,6,9,12,15,18, 21 and 24 of participation.

6.5. EFFICACY ASSESSMENTS

6.5.1. 100-Meter Timed Test (100m)

The participant will be asked to complete 2 laps around 2 cones set 25 meters apart as quickly as safely possible, running if able and the time in seconds is recorded. This will not be assessed in participants with a 10-meter walk time greater than 12 seconds.

6.5.2. 10-Meter Walk

Participants will complete three trials of the 10-meter walk test. The fastest time will be recorded, in addition to the average of the three trials. The test will be conducted in a quiet hallway and the participant will be instructed to walk their normal self-selected pace from one cone to the next along the 10-meter course marked on the floor. No assistive devices or flip-flops are allowed, and the test will be performed either barefoot or in well-fitting shoes. Orthoses and ankle braces will be allowed.

6.5.3. North Star Assessment for Dysferlinopathy (NSAD)

The NSAD is a functional scale specifically designed to measure motor performance in individuals with LGMD. It consists of 29 items that are considered clinically relevant items from the North Star Ambulatory Assessment and the Motor Function Measure 20 with a maximum score of 54 and higher scores indicate higher functional abilities. The test needs to be completed in the order provided with the test being performed on the same flooring each visit; preferably the same room.

6.5.4. Performance of Upper Limb 2.0 (PUL)

The PUL is a tool designed for assessing upper limb function in persons with neuromuscular disorders.[39] It was developed as a conceptual framework reflecting the progression of weakness and natural history of functional decline in DMD. There are 22 scored items; a score of 42 indicates the highest level of independent function and 0 the lowest

6.5.5. Timed up-and-go (TUG)

Participants will perform this test three times in accordance with previous studies.[2] The TUG will be administered using the appropriate stable seating surface (i.e., cube chair or straight back chair) to achieve 90 degree of both hip and knee flexion when participant is seated with both feet flat on the floor to start. No flip flops will be allowed, and the test should be performed either barefoot or will well-fitting shoes on. Assistive devices, orthoses and ankle braces will be allowed.

6.5.6. Timed 4 stair climb

Participants will perform the 4-stair climb with instructions to ascend 4 steps as quickly

as safely possible using handrails if needed. The time to ascend the 4 steps will be recorded. This will not be assessed in participants with a 10 meter walk time greater than 12 seconds.

6.5.7. 9 Hole Peg Test

The 9HPT is a quantitative measure of distal upper extremity function. It measures the ti me required for patients to place 9 pegs in the 9 holes on the board and then remove them as quickly as possible. The total time to complete the task is recorded.

6.5.8. Hand Held Dynamometry (HHD)

Hand held dynamometry using the MicroFET2 myometer will be utilized to capture isom etric strength in target muscle groups. Maximum strength in kilograms will be reported fo r each muscle group provided a continuous scale variable for analysis. CITEC attachments will be placed on the MicroFET2 to measure the Pinch and Grip of the subject. These pinch and grip techniques will also capture the maximum strength in kilograms for the muscle groups involved.

6.5.9. Measures of Pulmonary Function

Spirometry will be performed in a sitting and supine position using standardized equipment. Forced vital capacity (FVC), Forced expiratory volume in 1 second (FEV1), and maximal expiratory pressure (MEP) will be assessed. Use of nocturnal or daytime positive pressure ventilation (PPV) (e.g., BiPAP or CPAP) will also be recorded. Viral filters may be used, open or closed methods may be used during expiration, pediatric masks or adaptive oval mouthpieces may be used as needed according to participants level of ability to maintain a good lip seal on the testing device. Nose clips will be worn for all trials to prevent air flow loss.

6.5.10. ACTIVLIM

This patient-reported measure of activity limitations is to assess individuals with upper and/or lower limb impairments, which measures the ability to perform daily activities.

6.5.11. DASH

The Disabilities of the Arm, Shoulder, and Hand Questionnaire (DASH), measures levels of disability in an individual's upper extremity.

6.5.12. PROMIS

This is a set of patient-reported measures developed by a National Institute of Health evaluates physical, mental, and social health.

6.5.13. The Limb Girdle Muscular Dystrophy Health Inventory (LGMDHI)

This questionnaire is a disease specific patient reported outcomes

6.5.14. Domain Delta Questionnaire

This patient reported measure will be used to report that their health over 12 months. It will provide a benchmark for the smallest detectable clinically meaningful change on PROs and functional outcome measures.

6.6. BIOMARKER ASSESSMENTS

6.6.1. Blood, Urine, and Tissue Samples

A blood sample will be collected at the baseline visit to obtain DNA samples for biomarker discovery. Serum and urine (for fibroblasts) will be collected at each in-person visit for other exploratory biomarkers. Individuals with a prior muscle biopsy will be asked to provide this sample for future research and discovery into biomarkers. These samples will be stored in the biorepository, and provide the foundation for future pilot projects, and serve as a resource to the greater LGMD community.

6.7.CONCOMITANT MEDICATION

Clinically relevant prior treatments received by the patient including (1) previous LGMD treatments (including SoC) with patient's response and reason for changing treatment/dose in the last 12 months and (2) non-LGMD treatment in the last 6 months must be recorded in the eCRFs. Information should include start and stop dates and tick box for those continuing as concomitant medication. All concomitant medications whether allowed or not must be recorded in the eCRFs.

7. ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

7.1.DEFINITIONS

7.1.1. ADVERSE EVENT

For this study, an adverse event (AE) is any untoward medical occurrence in a subject during participation in the clinical study or with use of the experimental agent being studied. An adverse finding can include a sign, symptom, abnormal assessment (laboratory test value, vital signs, etc.), or any combination of these regardless of relationship to participation in the study.

Abnormal investigational findings (e.g., physical exam) should not be reported as AEs unless they are associated with clinical signs and symptoms, lead to study discontinuation, or are otherwise considered clinically relevant by the investigator. In cases of surgical or diagnostic procedures, the condition/illness leading to such a procedure is considered as the AE rather than the procedure itself. In the case of a fatality, the cause of death is considered as the AE, and the death is considered as its outcome.

7.1.2. SERIOUS ADVERSE EVENTS (SAE)

A serious adverse event (SAE) is any event that meets any of the following criteria:

- Results in Death
- Is life threatening
- Is an important medical event that may not result in death, be life-threatening, or require hospitalization but may not be considered an SAE.
- Results in persistent or significant disability

An important medical event that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

7.1.3. UNANTICIPATED PROBLEMS (UP)

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to subjects or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

7.2. EVENTS NOT CONSIDERED TO BE ADVERSE EVENTS

Pre-existing medical conditions/signs/symptoms present before enrollment that do not worsen in severity or frequency during the study are defined as baseline medical conditions and are not to be considered AEs.

7.3. TIME PERIOD AND FREQUENCY FOR ASSESSMENT FOLLOWUP

The PI will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.
Any follow-up information on a previously reported SAE will be reported within 24 hours. The investigator will treat participants having adverse experiences appropriately and observe them at suitable intervals until the experiences resolve. The investigator must respond to requests for follow-up information the Protocol Manager may have on the AE within 24 hours.

7.4. CHARACTERISTICS OF AN ADVERSE EVENT

To assess relationship of an event to study procedures, the following guidelines are used:

7.4.1. Related (Possible, Probable, Definite)

- The event is known to occur with the study procedures.
- There is a temporal relationship between the intervention and event onset.
- The event abates when the intervention is discontinued.
- The event reappears upon a re-challenge with the study procedures.

7.4.2. Not Related (Unlikely, Not Related)

- There is no temporal relationship between the intervention and event onset.
- An alternate etiology has been established.

The Study PI and Safety Monitor will be responsible for determining whether an SAE is expected or unexpected. An adverse event will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the intervention.

7.5. SEVERITY OF EVENT

The following scale will be used to grade adverse events:

- Mild: no intervention required; no impact on activities of daily living (ADL)
- Moderate: minimal, local, or non-invasive intervention indicated; moderate impact on ADL

- Severe: significant symptoms requiring invasive intervention; subject seeks medical attention, needs major assistance with ADL

7.6. RECORDING OF ADVERSE EVENTS

It is the responsibility of the investigator to document all AEs that occur during the study. Patients will be evaluated and questioned at each study visit by study staff. All AEs spontaneously reported by the patient and/or in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic procedure will be recorded on the AE CRF and entered in the electronic data capture system.

If an investigator determines that an event meets the protocol definition of a Serious Adverse Event (SAE), the SAE will be reported to the Protocol Manager within 24 hours. The SAE Report Form must be completed with as much information as possible and include all relative information to the evening including but not limited to:

- Progress notes
- Laboratory reports
- Diagnostic reports

7.7. REPORTING PROCEDURES

All AEs will be followed in the electronic data capture (EDC) system until the event has been stabilized or until the investigator determines that follow-up is no longer needed. Each AE report will include a description of the event, duration (onset and resolution dates), severity, any other potential causal factors, any treatment given, or other action taken and outcome.

If an SAE occurs during the reporting period, the investigator must immediately (i.e., within a maximum 24 hours after becoming aware of the event) inform the Study PI and Protocol Manager. All written reports should be transmitted using the study-specific SAE Report Form, which must be completed by the investigator following specific completion instructions. Names, addresses, telephone and fax numbers for SAE reporting are located on the SAE Report Form and in the completion instructions provided in the Study Manual. When an SAE (or follow-up information) is reported by telephone, a written report must be sent immediately thereafter by fax or e-mail.

7.8.REPORTING FOR MULTI-CENTER TRIALS

The site PI must immediately report to the coordinating center PI and Protocol Manager any serious adverse event, whether or not considered study related, including those listed in the protocol and must include an assessment of whether there is a reasonable possibility that the study caused the event within 48 hours of PI awareness of the event.

They must also report any unanticipated problems within 24 hours. The Site PI must also report any protocol deviations or violations to the coordinating center PI within 7 days of PI awareness. Participating centers must also submit all reports to their local IRB in accordance with their institutional policies.

7.9. PREGNANCY

Female patients, over the age of 12 and who are of childbearing potential at the time of consent are excluded from participating in this study. If a female patient becomes pregnant during the study, the patient must be withdrawn. All pregnancies occurring during the study must be reported to the investigator. The investigator must report the pregnancy and withdraw the patient within 5 business days.

7.10. UNANTICIPATED PROBLEM REPORTING

Site Investigators will include the following information when reporting an adverse event, or any other incident, experience, or outcome as an unanticipated problem to the IRB:

- Appropriate identifying information for the research protocol, such as the title, investigator's name, and the IRB project number;
- A detailed description of the adverse event, incident, experience, or outcome;
- An explanation of the basis for determining that the adverse event, incident, experience, or outcome represents an unanticipated problem;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the unanticipated problem.

To satisfy the requirement for prompt reporting, unanticipated problems will be reported using the following timeline:

- Unanticipated problems that are serious adverse events will be reported to the VCU IRB, within 5 days of the coordinating center PI and Protocol Manager becoming aware of the event.
- Any other unanticipated problem will be reported to the VCU IRB within 5 days of the coordinating center PI and Protocol Manager becoming aware of the problem.

All unanticipated problems should be reported to appropriate institutional officials as required by an institution's written reporting procedures.

7.11. FOLLOW UP

All adverse events will be followed up until full resolution or stabilization. Stabilization is defined as no further changes are documented after at least 4 weeks follow up.

8. STATISTICAL CONSIDERATIONS

8.1. STATISTICAL HYPOTHESES

8.1.1. Aim 1

Reliability and Validity of the COAs, for each site and overall

Reliability measures the consistency between COAs at two separate occasions and will be measured using methods described in Fleiss and those in Altman and Bland.[16,17] These analyses include the mean absolute difference, technical error, and intra-class correlation coefficients to account for the degree of partitioned variance between the subjects and the methods.[16] The mean absolute difference is the sum of the absolute paired differences divided by the total number of subjects. The technical error is the square root of the sum of squares of the differences between paired measurements. Intra-class correlation coefficients (CR%) are obtained from a nested analysis of variance of a random effects model in which the repeated measurements are nested within subjects. The CR% is the percentage of the total variation, sum of the between- and within-subject variance, explained by the between-subject variance. The larger the between-subject variance, the smaller the proportion of the total variation contributed by the within-subject variation (paired measurements from different days) and thus, the better consistency between the 2 days. Ninety-five percent lower confidence bounds will be computed for these quantities

Analysis of Baseline Measures

The cross-sectional data obtained in 152 LGMD patients at baseline will be used to describe the sample and examine the relationships between the COAs and genetic mutation. A factor analysis will be performed to examine the structure of the different COAs, proximal hip girdle or distal, and to determine whether the different components group together in a logical manner; Cronbach's α will be used to assess the internal consistency of the scale. We will also compute a 95% confidence interval (CI) for the statistics. We will compare baseline differences among groups using analyses of covariance (ANCOVA). The variables to be compared are those with potential effects on COAs. If baseline differences in these variables exist, adjustments will be made by incorporating these variables as covariates in the analysis.

Relationships between the COAs and other variables such as age, gender, age at symptom onset, years since symptom onset, and years since diagnosis will be similarly examined, but these analyses will be exploratory in nature since these associations are not necessarily expected to be strong. For example, it may be that subjects who have a longer duration of symptoms are not necessarily more severely impacted by the disease because, despite their duration of symptoms, they have retained a sufficiently high level of function (e.g., independent ambulation) to qualify for the study. Those who have had symptoms for a longer period of time may also be more likely to participate if their symptoms are milder. The eligibility criteria and bias in identifying subjects may thus have an impact on these relationships.

The assumptions underlying all statistical models will be thoroughly checked using appropriate graphical and numerical methods. In the face of nonlinearity or non-normality, appropriate remedial measures (e.g., variable transformation) will be attempted. If outliers or influential cases are detected, the accuracy of the data or special circumstances surrounding the cases (e.g., the use of aids such as a cane or leg bracing to improve function) will be investigated. If no errors are found, the analyses may be repeated after removing these cases to evaluate their impact on the results; however, the final analyses will include these data points.

Analytical plans to handle dropouts

Reasons for drop out will be sought, documented, and evaluated by the investigators. We will compare data for those who drop out with those who complete the study. If the reasons or mechanisms for drop out pertain to the study outcomes, the analysis will be done separately for subjects who complete the study and for subjects who drop out.

8.1.2. Aims 2 and 3

Analysis

Changes over time from baseline to 12 months of the outcome COA measures will be analyzed using a longitudinal model approach. This longitudinal model approach allows the examination of patterns of change in COA; to detect how these changes relate to covariates such as age, sex, race/ethnicity; and how continuous covariates such as BMI affect these changes. The model imputes missing values and includes measurements made at various time intervals as well as time-varying covariates. The model can be expressed as: $y_{ijk} = \mu + \alpha_i + \beta_j + \gamma_{ik} + \delta_{ij} x_{ijk} + \varepsilon_{ijk}$,where y_{ijk} is the dependent variable, i.e., serial data of COA; i denotes the variables, i.e., each COA; j denotes the subject; and k denotes the time, baseline and 12 months; x_{ijk} represents the covariates, and ε_{ijk} is an error term. γ_{ik} reflects the value of the dependent variable when a significant difference occurs between the subjects with, for example, male or female gender. Using the model, we will estimate the changes over time in each

COA, and the timing when the effects of, for example, gender significantly affects the COAs. If the variables are not normally distributed, generalized estimation equations will be employed.[46]

Responsiveness to change over time and minimal clinically important changes (MCICs). In the absence of an intervention known to have a beneficial effect in LGMD, responsiveness of the outcome measures to change over 12 months will be assessed. This is reasonable under the assumption that measurable progression occurs in LGMD over a period of 1 years. Paired t-tests will be used to test the null hypothesis of zero mean change at 12 months for each measure. Various statistics can be used for quantifying responsiveness, and the effect size and standardized response mean have been recommended for this purpose. The effect size is defined as the mean change divided by the standard deviation of the baseline value. The standardized response mean is defined as the mean change divided by the standard deviation of the changes from baseline. The bootstrap resampling technique will be used to perform formal statistical comparisons among the different outcome measures in terms of these two measures of responsiveness. With this technique, one takes a random sample with replacement of the participants, including their outcomes (bootstrap sample). With this bootstrap sample, the difference in, say, effect size between any two outcome measures is recorded. The process is then repeated a large number of times, with the difference in effect size between the COAs recorded each time; the histogram of these differences in effect size over all bootstrap samples approximates the sampling distribution of the differences in effect size between the COAs. The mean of this approximate sampling distribution (bootstrap distribution) and a 95% confidence interval (obtained using the 2.5th and 97.5th percentiles of the bootstrap distribution) summarizes the results. If the confidence interval does not contain the value of zero, the conclusion is that there is a significant difference in average effect size between the COAs.

Anchor-based and distribution-based methods will be used to determine the MCICs on the COAs and the PROs. Mean responses on the COAs will be described for each of the categories of the domain delta questionnaire (e.g., unchanged, a little better, a lot better, etc.). Receiver operating characteristic (ROC) curve methods will be used to select a cut-off for the 12-month changes in the COAs that is best at minimizing misclassification error, i.e., best distinguishes those who indicate that they are at least “a little better” on the domain-delta questionnaire and those who indicate otherwise. The 12-month changes in the COAs that correspond to effect sizes ranging from 0.30 to 0.50 standard deviation units will also be described and compared to the MCIC identified by ROC curve methods. Anchor-based and distribution-based methods are known to have strengths and limitations, and examination of the results derived by both methods will be useful in reaching consensus on recommendations in this regard for future trials in LGMD.

Although there is much variability in disease progression in LGMD, little is known about factors that might account for some of this variability. Identification of such factors may help in the design of future clinical trials. For example, important predictors of outcome could be used as stratification variables in the randomization plan and as covariates in the statistical analysis of the primary outcome variable, which would improve the precision of the estimated treatment effect. The baseline variables of primary interest include the COAs, age, gender, age at symptom onset, years since symptom onset, and mutation class. A multiple regression model will be constructed, and competing models will be evaluated using a best-subsets regression technique, in conjunction with Akaike information criterion (AIC) and the Bayesian information criterion (BIC). This information will be combined with clinical judgment to arrive at a final model. Appropriate model checking will be performed, as described above. Regression trees use recursive partitioning to partition the sample into different subsets that have different levels of mean change in the COAs. A strength of these methods is that a cross-

validation procedure is available for checking the final tree, which can be pruned back to avoid over-fitting.

8.1.3. Aim 4

Analysis

Exploratory telemedicine outcome assessment. A similar approach to reliability will be taken to that described for aim 1 above. Performance on the telemedicine PUL 2.0 and TUG will be compared between baseline and telemedicine visit 1, and between month 6- and 6-month telemedicine visits. In addition, the responsiveness to LGMD progression as described above for aim 2 will be used to compare the responsiveness on the PUL and TUG between telemedicine visits and in-person encounters.

8.2.POWER CALCULATIONS AND SAMPLE SIZE

The sample size and power analysis refer to subjects who complete the study and are based upon establishing COAs that are sensitive enough to detect a clinically meaningful change. We have chosen 10%, as this would represent a change beyond that expected to occur due to chance and reflected the upper range of change in the COS study; for example, a 10% decline of the time for the 10 MW, 100-meter walk/run test, or for a 10% increase in the PUL. While the current study is underpowered to detect this change, it will serve as a pilot project to continue enrollment to the target cohort of 400 individuals.

9. QUALITY CONTROL AND QUALITY ASSURANCE

9.1. INVESTIGATOR RESPONSIBILITY

The investigator is responsible for ensuring the study is conducted according to the protocol, Code of Federal Regulations, GCP, and applicable regulatory requirements. Prior to the start of the study, there will be an in person formal site initiation meeting where focus will be directed towards training investigators, study coordinators, clinical evaluators (CE) and other relevant site staff. An overview of the study protocol, personnel qualification, data capture, GCP requirements, a review of ethics committee and site contract documentation, as well as an open discussion regarding challenges encountered in testing, comparing discrepancies, and recommendations to improve reliability or efficiency of testing will be including in this meeting. When reviewing data collection procedures, the discussion will also include identification, agreement, and documentation of data items for which the CRF will serve as the source document.

The following assessments will be administered by trained evaluators: NSAD,100m Timed test, timed 4 step, timed up and go, and pulmonary function testing. To help ensure proper and consistent test administration across evaluators/sites, all evaluators will undergo training during the investigator meeting on the proper administration of these assessments. As part of this training, clinical evaluators will also be trained to administer tests while videotaping the subject. To help ensure proper and consistent test administration over the course of the study, administration of strength and functional testing may be videotaped and reviewed for each patient at Baseline and Month 12.

When new Investigators join the study, they will be trained by webinar or by telephone conference. Additional CEs introduced to the study will be required to conduct in person training with the lead clinical evaluator. A yearly meeting will occur throughout the conduct of the study to review the protocol, review recruitment and challenges with achieving study goals, and refresh training on COAs. Our plan to ensure reliability of study procedure testing is modeled after an industry approach where a trained lead Evaluator trains site personnel to ensure consistency of technique and identify areas

requiring further training. We will schedule monthly conference calls between sites to review recruitment, enrollment, and study procedures.

9.2. PROTOCOL MODIFICATIONS

The investigator should not modify the protocol without agreement from the Study PI and Protocol Manager. Any deviations from the protocol should be documented by the investigator or designee.

10. CONFIDENTIALITY

Information collected during this study will be collected in a uniform fashion as outlined in the research plan. Participants will be asked to give permission for investigators to examine existing medical records to determine eligibility and is solely for research purposes only. All data will be de-identified and randomly coded with a unique study number.

To maintain patient privacy, all CRFs, study reports and communications will identify the patient by the assigned patient identification number. The investigator will grant clinical monitor(s) and auditor(s) and regulatory authorities' access to the patient's original medical records for verification of data gathered on the CRFs and to audit the data collection process. The patient's confidentiality will be maintained and will not be made publicly available. The patient's medical information will only be released to the extent permitted by the applicable laws and regulations.

11.PUBLICATION POLICY

The investigator(s) agrees to use this information only in conducting the study and shall not use it for any other purposes without written approval. The investigator(s) agrees not to disclose confidential information to anyone except to persons involved in the study that need such information to assist in conducting the study, and then only on like terms of confidentiality and non-use.

It is understood by the investigator(s) that the information developed from this natural history study may be used in connection with the development of study drug, and therefore may be disclosed as required to regulatory agencies.

12.PROTOCOL AMENDMENTS

In the event that the protocol needs to be modified, the study coordination center will record the changes needed for the protocol change and subsequently amend the protocol. Notification will be sent out to all participating sites once the protocol has been approved by the reviewing IRB. Protocol changes may not be implemented at any site without prior approval from the IRB

13.STUDY AUDITING AND MONITORING

13.1. MONITORING OF DATA ENTRY

The initial aspect of data monitoring will be built into the database itself, with ranges specified for numerical entries. These range restrictions often prevent common data entry errors such as transposition of a decimal place. The project manager will review the data management reports generated by the data manager and specifically query study coordinators at each site for missing data and/or data appears to be out of range with other entries.

13.2. SITE MONITORING PLAN

The monitoring visits must be conducted according to the applicable ICH and GCP guidelines to ensure protocol adherence, quality of data, compliance with regulatory requirements, and continued adequacy of the clinical sites and their facilities. When reviewing data collection procedures, the discussion will also include identification,

agreement, and documentation of data items for which the CRF will serve as the source document.

The Protocol Manager will monitor the study consistent with the demands of the study and site activity to verify that:

- Data are authentic, accurate, and complete.
- Safety and rights of subjects are being protected.
- Study is conducted in accordance with the currently approved protocol and any other study agreements, GCP, and all applicable regulatory requirements.
- The investigator agrees to allow the Protocol Manager access to all study-relevant source documents for purposes of data verification.

13.3. TIMING AND FREQUENCY

On-site monitoring at US sites will occur within 45 days of first enrollment at each site followed by bi-monthly remote monitoring. An on-site closeout monitoring visit will occur within 30 days of last enrollment. Timing and frequency may be adjusted throughout the study depending on site needs and performance.

European sites will follow the same monitoring frequency above with all monitoring visits done remotely.

Data type	Frequency of review	Reviewer
Subject accrual (including compliance with protocol enrollment criteria)	Monthly	PI, Protocol Manager
	Semi-annually	Protocol Manager
Status of all enrolled subjects, as of date of reporting	Monthly	PI, Protocol Manager
	Semi-annually	Protocol Manager
Data entry quality control checks	Weekly	Protocol Manager
Adherence data regarding study visits	Bi-Monthly	PI, Protocol Manager
	Semi-annually	Protocol Manager
AEs and rates (including out-of-range lab values)	Monthly	PI, Protocol Manager
	Semi-annually	Safety Monitor
SAEs (unexpected and related)	Per occurrence	PI, Protocol Manager, Safety Manager
SAEs (expected or unrelated)	Per Occurrence	PI, Protocol Manager
	Annually	Safety Manager

Unanticipated Problems	Monthly	PI, Protocol Manager, Safety Manager

13.4. AUDITS AND INSPECTIONS

The investigators and clinical sites will permit trial-related monitoring, audits, IEC review, and regulatory inspections as requested by FDA or other health authorities and the sponsor or designee. In addition to CRFs, the clinical site will permit direct access to source data/documents (i.e., original medical records, laboratory reports, hospital documents, progress reports, signed ICFs, etc.). The investigator is expected to cooperate with any audit and provide assistance and documentation (including source data) as requested.

14. DATA

14.1. CASE REPORT COMPLETION

CRFs will be completed for each enrolled patient. It is the investigator's responsibility to ensure the accuracy, completeness, and timeliness of the data reported in the patient's CRF. Source documentation supporting the CRF data should indicate the patient's participation in the study and should document the dates and details of study procedures, AEs, and patient status.

Investigators will maintain copies of the CRFs at the clinical site. For patients who discontinue or terminate from the study, the CRFs will be completed as much as possible, and the reason for the discontinuation or termination clearly and concisely specified on the appropriate CRF.

14.2. DATA QUALITY

The project manager and data manager will work to ensure collection and management of CRFs at each site. This includes periodic data reports which will provide monthly enrollment, adverse event reports, and a data quality report. The data quality report will focus on data missingness. Additional responsibilities will include provision of datasets to study statisticians.

14.3. DATA HANDLING

The investigators are responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. The investigators will maintain adequate case histories of study subjects, including accurate case report forms (CRFs), and source documentation.

14.4. DATA MANAGEMENT RESPONSIBILITIES

Data collection and accurate documentation are the responsibility of the study staff under the supervision of the investigator. All source documents and laboratory reports must be reviewed by the study team and data entry staff, who will ensure that they are accurate and complete. Unanticipated problems and adverse events must be reviewed by the investigator or designee.

14.5. DATABASE PROTECTION

This study will utilize REDCap. REDCap is a web application available to all sites and access is behind the firewall through the VPN Network at Virginia Commonwealth University for additional security. The data manager will receive only coded information that is entered into the database under those identification numbers.

The database will be secured with password protection and a built-in-audit trail will be maintained that logs all user activity and all pages viewed by every user, including contextual information.

14.6. SOURCE DOCUMENT PROTECION

Source documents (consent, medical records, and case report forms) for the study are maintained in the study binder for each subject at each site. Study records are kept in secured areas, accessible only to authorized study personnel. Access to all computer-based files will be restricted at several levels. Linking codes will be kept in a secure location with access limited to select study personnel.

15.SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

15.1. INSTITUTIONAL REVIEW BOARD

The coordination site will submit this protocol, any protocol modifications, and the patient ICF to be used in this study to the appropriate IRB review and approval. A letter confirming IRB approval will be maintained in the study database and available to all coordinating sites prior to the enrollment of patients.

The reviewing IRB may also conduct a regulatory inspection of this study. Such audits/inspections can occur at any time during or after completion of the study. If an audit or inspection occurs, the investigator and institution agree to allow the auditor/inspector direct access to all relevant documents and to allocate his/her time and the time of his/her staff to the auditor/inspector to discuss findings and any relevant issues.

15.2. INFORMED CONSENT PROCESS

Subject informed consent will be obtained in writing for each subject before he or she can participate in the study. The ICF must not be altered without IRB approval.

15.3. WITHDRAWALS

Possible reasons for withdrawal may include loss of funding, completion of the study, patient noncompliance, or a concern by study staff that participation may have a harmful effect on the patient's emotional or physical health or welfare. A subject may withdraw consent in writing anytime.

15.4. RESEARCH INFORMATION IN MEDICAL RECORDS

Research may be included in the subject's medical record (e.g. indication of study participation) and is dependent on recruiting site standard operating procedures.

15.5. FUTURE USE OF STORED SPECIMENS

By participating in this study, the patient agrees that blood, urine, study data, recordings and muscle samples may be kept indefinitely. These samples will be de-identified at the study site by a code number, not by the patient's name or any other identifying information. Future research may be carried out by qualified scientists for the purpose of planning future clinical studies and trials. Each site Investigator will retain the key specific to their site

16. DATA AND SAFETY OVERSIGHT

Due to the routine risks associated with this protocol and lack of study medication or other therapeutic interventions, our proposed clinical study will not require a Data Safety and Monitoring Board.

This study will use a safety monitor, Dr. Amy Harper, to monitor for adverse events. The independent monitor is a board-certified physician with knowledge of LGMD. In addition to the site PI, the safety monitor will review all study procedures, and adverse events throughout the study. Reporting of serious adverse events will comply with FDA and IRB requirements.

17. RETENTION OF RECORDS

The investigator will maintain all study records according to ICH GCP and applicable regulatory requirements. Records will be retained for at least 2 years after formal closure, or according to applicable regulatory requirements. If the investigator withdraws from the responsibility of keeping the study records, custody must be transferred to a person willing to accept the responsibility. The sponsor must be notified in writing of a custodial change such as long term storage or transfer of PI to new facility when records will accompany PI.

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19. APPENDICES

APPENDIX 1. SCHEDULE OF EVENTS ARM 1

Schedule of Events Arm 1				
	Baseline Day 1	Baseline Day 2	Month 6[2]	Month 12
Informed Consent	X			
Demographics	X			
Medical and Surgical History	X			
Vital signs	X	X	X	X
Physical exam	X[3]	X[3]	X	X
100m Timed	X	X		X
10M Walk	X	X		X
Timed Up and Go (TUG)	X	X		X
4 Stair Climb	X	X		X
Hand Held Dynometry	X	X		X
Pinch and Grip	X	X		X
NSAD	X	X		X
Pregnancy Test[1]	X		X	X
Performance Upper Limb PUL 2.0	X	X		X
Concomitant Meds	X		X	X
Forced Vital Capacity	X			X
Domain Delta Questionnaire		X		X
Patient reported Measures	X[3]	X[3]		X
Urine Biomarkers	X		X	X
Blood Biomarkers	X		X	X
Prior muscle biopsy acquired (if performed)	X			
Review AE's		X	X	X

[1]Pregnancy test for women of childbearing potential only; [2]N/A TO LGMD1D cohort, [3]Assessment can be done on baseline day 1 or baseline day 2

APPENDIX 2. SCHEDULE OF EVENTS ARM 2

Schedule of Events Arm 2								
	Baseline Day 1	Baseline Day 2	Month 1 +/- 14days	Month 3 +/- 14days	Month 6 +/- 14days	Month 9 +/- 14days	Month 12 +/- 14days	Months 15,18 and 24 +/- 14days
Informed Consent	X							
Medical and Surgical History	X							
Demographic Information	X							
Vital signs	X	X		X	X		X	
Physical exam	X[3]	X[3]		X	X		X	
100m Timed[2]	X	X		X	X		X	
10M Walk[2]	X	X		X	X		X	
Timed Up and Go (TUG)	X	X		X	X		X	
4 Stair Climb	X	X		X	X		X	
Hand Held Dynometry	X	X		X	X		X	
Pinch and Grip	X	X		X	X		X	
NSAD	X	X		X	X		X	
Pregnancy Test[1]	X			X	X		X	
Performance Upper Limb PUL 2.0	X	X		X	X		X	
Concomitant Meds	X			X	X		X	
Forced Vital Capacity	X			X	X		X	
Domain Delta Questionnaire		X		X	X		X	
Patient reported Measures	X[3]	X[3]			X		X	
Urine Biomarkers	X				X		X	
Blood Biomarkers	X				X		X	
Prior muscle biopsy acquired (if performed)	X							
Telemedicine (PUL or TUG)			X		X	X	x	X[4]
Review AE's		X			X		X	

[1]Pregnancy test for women of childbearing potential only; [2] N/A to non-ambulatory patients [3] Assessment can be done on baseline day 1 or baseline day 2, [4]Will continue for 12 additional months

RESEARCH PARTICIPANT INFORMATION AND CONSENT FORM

STUDY TITLE:	**Defining Clinical Endpoints in LGMD**
STUDY DOCTOR:	Nicholas Johnson, MD
RESEARCH SITE ADDRESS:	1101 East Marshall Street, Box 980599 Richmond, Virginia 23298-0599
CONTACT PHONE NUMBER:	804-552-0014 (24 hours)
SPONSOR:	Coalition to Cure Calpain 3 Myotonic Dystrophy Foundation Sarepta Therapeutics

NOTE: In this consent form, **"you"** always refers to the research participant. If you are a parent or legal guardian, please remember that **"you"** refers to the child study participant.

About this consent form
You are being invited to participate in a research study because you have Limb Girdle Muscular Dystrophy. It is important that you carefully think about whether being in this study is right for you and your situation.

This consent form is meant to assist you in thinking about whether or not you want to be in this is a study. Please ask the study doctor or the study staff to explain any information in this consent document that is not clear to you. You may take home an unsigned copy of this consent form to think about or discuss with family or friends before making your decision.

Your participation is voluntary. You may decide not to participate in this study. If you do participate, you may withdraw from the study at any time. Your decision not to take part or to withdraw will involve no penalty or loss of benefits to which you are otherwise entitled.

Overview of the study and key information
The purpose of this study is to learn more about Limb Girdle Muscular Dystrophy and what effects it has on you during disease progression. Up to 1100 individuals will participate in this study.

There are different parts of this study that you may be eligible for. You are invited to participate in the following parts of this study:

_____ Arm 1 – for individuals with genetically or functionally confirmed mutation in ANO5 (LGMD2L), CAPN3 (LGMD2A), DYSF (LGMD 2B), or DNAJB6(LGMD1D)

_____Arm 2 – for individuals with genetically or functionally confirmed mutation in SGCA (LGMD2D), SGCB (LGMD2E), SGCD (LGMD2C); SGCG (LGMD2F)

_____ Project 3 – for all individuals with genetic confirmation of LGMD

If you participate in Arm 1, you will be asked to do the following things:

- Visit VCU for study visits 4 times (unless you are LGMD1D then you will only come 3 times) Your participation in this study will last up to 12 months.
- Have your blood drawn 3 times (Unless you are LGMD1D, then only 2 times)
- Spirometry testing 2 times
- You will be asked to give a urine sample 3 times
- Complete tasks that involve using your muscles like walking, squeezing a strength measurement tool, climbing stairs, and using your arms
- Answer questionnaires about Limb Girdle
- Give permission for the researchers to collect information from your medical records.
- Women of childbearing potential must have a negative pregnancy test. If a pregnancy test is positive at any point during this study, you will be withdrawn from the study for safety and data interpretation reasons.
- Blood samples will be collected to obtain DNA for biomarker discovery. This study will use your samples to sequence all or part of your DNA.
    - Deoxyribonucleic acid (DNA) is the "blueprint" or "recipe" that gives the body's cells instructions on how to do their jobs. Scientists can use a test called whole genome sequencing to determine the order of all or part of the molecules that make up your DNA, like reading all the letters in a book. Sequencing is usually done to look for changes in the molecules of DNA that may cause health problems.

If you participate in Arm 2, you will be asked to do the following things:

- Visit VCU for study visits 5 times
- You will have a telemedicine visit 8 times with a Clinical Evaluator by Zoom that will be done at home to measure your strength. A box will be mailed to your home that contains items to complete physical therapy assessments on your own. You will time yourself, record the information and mail the box back to the study doctor free of charge. Have your blood drawn 3 times

- You will be asked to give a urine sample 3 times
- Spirometry testing 2 times
- Complete tasks that involve using your muscles like walking, squeezing a measurement tool, climbing stairs, and using your arms
- Answer questionnaires about Limb Girdle
- Give permission for the researchers to collect information from your medical records.
- Women of childbearing potential must have a negative pregnancy test. If a pregnancy test is positive at any point during this study, you will be withdrawn from the study for safety and data interpretation reasons.
- Blood samples will be collected to obtain DNA for biomarker discovery. This study will use your samples to sequence all or part of your DNA.
    - Deoxyribonucleic acid (DNA) is the "blueprint" or "recipe" that gives the body's cells instructions on how to do their jobs. Scientists can use a test called whole genome sequencing to determine the order of all or part of the molecules that make up your DNA, like reading all the letters in a book. Sequencing is usually done to look for changes in the molecules of DNA that may cause health problems.

If you participate in Project 3, you will be asked to do the following things:

- Complete a 1-2 hour survey about LGMD and how it affects you. You may complete the survey at this visit, or take it home and return it in the mail to the address listed below. If you chose to return it in the mail, a self-addressed stamped envelope will be provided to you.

There are both risks and benefits of participating in research studies. Below are some of the key risks to being part of this study. Additional information is located in the "Risks" section of this consent form.

Most Common Risks and Discomforts	**Benefits to You and Others**
Risks for Arm 1 and Arm 2 • Blood draws may cause pain, bleeding, and/or bruising. You may faint and could develop an infection at the site where blood is drawn. • Mild to moderate physical activity may cause sore or pulled muscles, physical discomfort, and/or accidental injuries such as falling. • Physical discomfort such as increased heart rate, chest pain, shortness of	• There are no direct benefits you can expect to receive as a result of participating in this study. Your participation in this study will help us and other researchers learn more about Limb Girdle Muscular Dystrophy.

breath, headache, nausea, and/or fatigue. **Risks for Arm 1, Arm 2 and Project 3** • The study questionnaires ask personal questions that are sensitive in nature and may make you feel uncomfortable. • Participating in a research study comes with a chance of a loss of confidentiality.	

Please read, or have someone read to you, the rest of this document. If there is anything you don't understand, be sure to ask the study staff.

Why is this study being done?
Limb Girdle Muscular Dystrophy (LGMD) is one of the four most common muscular dystrophies. The purpose of this study to learn more about Limb Girdle Muscular Dystrophy by measuring how your muscles change over time. This information will help plan future studies and drug development for people with LGMD.

What will happen if I participate in Project 3?
If you/your child choose to participate in this study, you will be asked complete a survey about LGMD and how it affects you. The survey will ask you questions about yourself and about different symptoms you may experience.

You may complete the survey now, or take it home and return it in the mail to the address listed below. If you chose to return it in the mail, a self-addressed stamped envelope will be provided to you.

Brittney Holmberg GRASP LGMD
VCU Sanger Hall
1101 East Marshall Street; Box 980599
Richmond, Virginia 23298-0599

What will happen if I participate in Arm 1?
You will come to the clinic 4 times unless you are in the LGMD1D cohort then you will only come 3 times. Your first study visit (baseline visit)will take place over 2 days. The second study visit will take place six months after the baseline visit and will take place over 1 day unless you are in the LGMD1D cohort, then you will not have a study visit. The third and final study visit will take place over 1 day twelve months after the baseline visit.

The following tests, procedures, and assessments will be carried out during each study

visit:

Baseline Day 1:

- Review of the study procedures/consent review: Upon arrival at the clinic, the information in this consent form will be reviewed with you in detail. You will be provided with an opportunity to ask any additional questions you may have prior to starting the study procedures scheduled for the day.
- You will have a brief physical exam by a study physician. Height, weight, and vital signs will be recorded. You will be asked about your demographics, contact information, symptoms, medical history, and medications. Your medical records, obtained with your written permission, will be reviewed.
- Pregnancy Test (for women of childbearing potential only)
- Spirometry, measuring respiratory function by blowing into a tube, will be performed.
- Your muscle strength will be tested by our clinical evaluator. You will walk and/or run for 100 meters. You will be videotaped during this assessment. You will also be asked to use a hand held squeezing tool to measure upper muscle strength.
- You will be asked to complete a series of questionnaires to find out how Limb Girdle impacts your daily activities. These include: the Domain Delta Questionnaire, the DASH questionnaire, the ACTIVLIM questionnaire, and PROMIS questionnaires.
- You will be asked to provide a urine sample and a blood sample. These samples will be put in a biorepository bank and will be used for future research.
- We will ask for your consent to allow the researchers in this study to contact your physician so that we can access your frozen muscle tissue that was taken to diagnose your disease.

Baseline Day 2:

- We will evaluate your muscle strength again.
- You will have your vital signs taken
- You may need to finish the questionnaires from Day 1
- We will ask you if you have had any problems or concerns since your last visit.

Month 6: (LGMD1D excluded)

- You will have a brief physical exam by a study physician. Height, weight, and vital signs will be recorded.
- Pregnancy Test (for women of childbearing potential only)
- You will be asked to provide a urine sample and a blood sample.
- We will ask if you have had any problems or concerns since your last visit.

Month 12:

- You will have a brief physical exam by a study physician. Height, weight, and vital signs will be recorded.
- Pregnancy Test (for women of childbearing potential only)
- Spirometry, measuring respiratory function by blowing into a tube, will be performed.
- Your muscle strength will be tested by our clinical evaluator. You will walk and/or run for 100 meters. You will be videotaped during these assessments. You will also be asked to squeeze a hand-held device that will measure upper muscle strength.
- You will be asked to complete a series of questionnaires to find out how Limb Girdle impacts your and daily activities. These include: the Domain Delta Questionnaire, the DASH questionnaire, the Limb Girdle Muscular Dystrophy questionnaire, and PROMIS questionnaires.
- You will be asked to provide a urine sample and a blood sample. These samples will be put in a biorepository bank and will be used for future research.

What will happen if I participate in Arm 2?

You will come to the clinic 5 times and have 7 remote visits done at home. Your on site study visits will be as follows. Your first study visit (baseline visit) will take place over 2 days. The second study visit will take place three months after the baseline visit and will take place over 1 day. The third study visit will take place over 1 day 6 months from the baseline visit. The final study visit will take place over 1 day twelve months after the baseline visit. Your remote visits will be done at 1 month, 6 months, 9months and 12 months after baseline visit. You will continue to do remote assessments at home, every 3 months for an additional 12 months.

The following tests, procedures, and assessments will be carried out during each study visit:

Baseline Day 1:

- Review of the study procedures/consent review: Upon arrival at the clinic, the information in this consent form will be reviewed with you in detail. You will be provided with an opportunity to ask any additional questions you may have prior to starting the study procedures scheduled for the day.
- You will have a brief physical exam by a study physician. Height, weight, and vital signs will be recorded. You will be asked about your demographics, contact information, symptoms, medical history, and medications. Your medical records, obtained with your written permission, will be reviewed.

- Spirometry, measuring respiratory function by blowing into a tube, will be performed.
- Pregnancy Test (for women of childbearing potential only)
- Your muscle strength will be tested by our clinical evaluator. You will walk and/or run for 100 meters and complete a 10-meter walk test. You will be videotaped during these assessments. You will also be asked to use a hand held squeezing device to measure upper muscle strength.
- You will be asked to complete a series of questionnaires to find out how Limb Girdle impacts your daily activities. These include: The Domain Delta Questionnaire, the DASH questionnaire, questionnaire, ACTIVLI questionnaire,, and PROMIS questionnaires.
- You will be asked to provide a urine sample and a blood sample. These samples will be put in a biorepository bank and will be used for future research.
- We will ask for your consent to allow the researchers in this study to contact your physician so that we can access your frozen muscle tissue that was taken to diagnose your disease.

Baseline Day 2:

- We may evaluate your muscle strength again.
- You will have your vital signs taken
- You may need to finish the questionnaires from Day 1
- We will ask you if you have had any problems or concerns since your last visit.

Month 1 - REMOTE:

- You will have a remote visit with a Clinical Evaluator by Zoom that will be done at home to measure your strength. A box will be mailed to your home that contains items to complete physical therapy assessments on your own. You will time yourself, record the information and mail the box back to the study doctor free of charge.

Month 3:

- You will have a brief physical exam by a study physician. Height, weight, and vital signs will be recorded.
- Pregnancy Test (for women of childbearing potential only)
- Your muscle strength will be tested by our clinical evaluator. You will walk and/or run for 100 meters and complete a 10 meter walk test. You will be videotaped during these assessments. You will also be asked to use a hand held squeezing device to measure upper muscle strength.

Month 6:

- You will have a brief physical exam by a study physician. Height, weight, and vital signs will be recorded.

- Pregnancy Test (for women of childbearing potential only)
- Spirometry, measuring respiratory function by blowing into a tube, will be performed.
- Your muscle strength will be tested by our clinical evaluator. You will walk and/or run for 100 meters and complete a 10 meter walk test. You will be videotaped during these assessments. You will also be asked to use a hand held squeezing device to measure upper muscle strength.
- You will be asked to complete a series of questionnaires to find out how Limb Girdle impacts your and daily activities. These include: the Domain Delta Questionnaire, the DASH questionnaire, the Limb Girdle Muscular Dystrophy questionnaire and PROMIS questionnaires.
- You will be asked to provide a urine sample and a blood sample. These samples will be put in a biorepository bank and will be used for future research.

Month 6 – REMOTE

- You will have a remote visit that will be done at home to measure your strength.

Month 9 - REMOTE:

- You will have a remote visit that will be done at home to measure your strength.

Month 12:

- You will have a brief physical exam by a study physician. Height, weight, and vital signs will be recorded.
- Spirometry, measuring respiratory function by blowing into a tube, will be performed.
- Your muscle strength will be tested by our clinical evaluator. You will walk and/or run for 100 meters and complete a 10 meter walk test. You will be videotaped during these assessments. You will also be asked to use a hand held squeezing device to measure upper muscle strength.
- Pregnancy Test (for women of childbearing potential only)
- You will be asked to complete a series of questionnaires to find out how Limb Girdle impacts your and daily activities. These include: the Domain Delta Questionnaire, the DASH questionnaire, the Limb Girdle Muscular Dystrophy questionnaire and PROMIS questionnaires.
- You will be asked to provide a urine sample and a blood sample. These samples will be put in a biorepository bank and will be used for future research.

Months 12, 15, 18, 21, 24– REMOTE

- You will continue to have a remote visit that will be done at home to measure your strength.

What are my alternative choices?

The alternative to this study is to not participate.

What are the possible risks and discomforts?

Risks and discomforts for Arms 1 and 2:

Blood sampling/Venipuncture:
During the collection of blood samples, you may experience pain and/or bruising at the needle site. An anesthetic cream may be applied on the arm to make the area numb and reduce discomfort. Although rare, localized clot formation and infections may occur. You may also feel light-headedness and/or fainting may also happen during or shortly after having your blood drawn.

100 Meter Timed Test and 10 Meter Walk:
During these functional testing assessments, there is a potential you might fall. Two members of the study staff will follow you during the test and will help you in case you do fall.

Functional Testing:
Muscle strength testing may cause your muscles to be sore several days after the testing. You may also experience some physical discomfort such as increased heart rate, chest pain, shortness of breath, headache, nausea, and/or fatigue.

Pulmonary Function Test:
Breathing tests may cause you to have difficulty breathing or you may feel fatigued during the test.

Genetic Risks:
If known to employers or insurance companies, the results of genetic tests might affect a person's ability to obtain a job or health or life insurance. If this information were released, it could be misused. Such misuse could be distressing, and it could cause you or your family members to have difficulty obtaining insurance coverage and/or a job.

A federal law called the Genetic Information Nondiscrimination Act (GINA) makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. However, this legal protection still may not keep someone from trying to discriminate against you in this way

Risks and discomforts for Arms 1, 2, and Project 3

Questionnaires:
Completing questionnaires about your symptoms could cause you to become tired after concentrating for a long period of time. Some questions may cause some psychological stress.

Non-Physical Risks:
Participation in research might involve some loss of privacy. There is a small risk that someone outside the research study could see and misuse information about you.

Unknown or Unforeseeable Risks
The researchers will let you know about any significant new findings (such as additional risks or discomforts) that might make you change your mind about participating in the study.

What are the costs?
There is no cost to you to participate in this study.

Will I be paid to be part of this trial?
Arm 1 - You will not be paid to take part in this study. For clarity, you will not have any rights to or be entitled to any financial or other benefits from any findings, developments, derivatives, databases, drugs, devices, biologics, products, patents, materials, designs, materials, plans, publications, or other results derived from use of your information.

Arm 2 – Travel reimbursement up to $500.00 is available to you for each study visit done at the study location, should you need.

Total payments within one calendar year that exceed $600 will require the University to annually report these payments to the IRS and you. This may require you to claim the compensation you receive for participation in this study as taxable income. VCU is required by federal law to collect your social security number. Your social security number will be kept confidential and will only be used to process payment.

What if I am injured from taking part in this research study?
If you are injured by, or become ill, from participating in this study, please contact your study doctor immediately. Medical treatment is available at the Virginia Commonwealth University Health System (VCU Health System). Your study doctor will arrange for short-term emergency care at the VCU Health System or for a referral if it is needed.

Fees for such treatment may be billed to you or to appropriate third-party insurance. Your health insurance company may or may not pay for treatment of injuries or illness as a result of your participation in this study. To help avoid research-related injury or illness, it is very important to follow all study directions.

Can I stop being in the study?
You can stop being in this research study at any time. Leaving the study will not affect your medical care, employment status, or academic standing at VCU or VCU Health.

Right of Investigator to withdraw participation
Your participation in this study may be stopped at any time by the study doctor without your consent. The reasons might include:

- the study doctor thinks it necessary for your health or safety
- you are found to not be eligible for the study
- the sponsor has stopped the study
- you have not followed study instructions
- administrative reasons require your withdrawal, including loss of funding

How will information about me be protected?
VCU and the VCU Health System have established secure research databases and computer systems to store information and to help with monitoring and oversight of research. Your information may be kept in these databases but are only accessible to individuals working on this study or authorized individuals who have access for specific research related tasks.

As part of Arm 1 and Arm 2, video recordings will be taken of you during certain assessments. We will do our best to secure your facial identity however, we cannot guarantee this. The recordings will be stored on a database at VCU and will not be available to anyone except the research staff involved on this trial. Recordings will be destroyed once the trial is complete.

Identifiable information in these databases are not released outside VCU unless stated in this consent or required by law. Although results of this research may be presented at meetings or in publications, identifiable personal information about participants will not be disclosed.

It will be noted in your protected electronic health record at VCU Health that you are in this study. Information about the study will be included in the record. This information is protected just as any of your other health records are protected.

In general, we will not give you any individual results from the study. If we find something of medical importance to you, we will inform you or your personal physician in person or in writing; although we expect that this will be a very rare occurrence. We will not tell anyone the answers you give us. However, if you tell us that someone is hurting you, or that she you might hurt herself or someone else, the law says that we must let people in authority know so they can protect you.

In the future, identifiers might be removed from the information and samples you provide in this study, and after that removal, the information/samples could be used for other research

studies by this study team or another researcher without asking you for additional consent.

Certificate of Confidentiality

To help us protect your privacy, we will apply for a Certificate of Confidentiality from the National Institutes of Health. If this certificate is obtained, it will offer the protections described here. A Certificate of Confidentiality helps the researchers keep your information private. For example, researchers can refuse to give out your information in a court case. Researchers may have to give your information if the study is audited, or if the information is required by the Food and Drug Administration (FDA).

The researchers may share information about you or your participation in the research project without your consent if we determine there is abuse or neglect; including elder and/or child or you threaten to harm yourself or others.

The researchers cannot prevent you or others, for example a member of your family, from sharing information about you or your involvement in this research. If you give an insurer, employer, or other person permission to receive research information, then the researchers may not use the Certificate to withhold that information.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Website will include a summary of the results. You can search this Web site at any time.

How will my health information be used and shared during this study?

As part of this research study, we will ask you to share identifiable health information about you with us and/or permit us to access existing information from your healthcare records. New health information may also be created from study-related tests, procedures, visits, and/or questionnaires. This type of information is considered "Protected Health Information" that is protected by federal law.

The following types of information may be used for the conduct of this research study:

- Complete Health Record
- Diagnosis
- History and physical exams
- Test results
- Video recordings
- Name, date of birth, and medical record number

Who will use or share protected health information about you?
VCU and VCU Health are required by law to protect your identifiable health information. By consenting to this study, you authorize VCU/VCU Health to use and/or share your health information for this research. The health information listed above may be used by and/or shared with the following people and groups to conduct, monitor, and oversee the research:

- Representatives of VCU and the VCU Health System
- Virginia Commonwealth University Institutional Review Board
- National Institutes of Health (NIH)
- Researchers with the Limb Girdle Muscular Dystrophy Consortium
- Muscular Dystrophy Association (MDA)
- Government/Health Agencies
- Research Collaborators
- Others as required by law

Once your health information has been disclosed to anyone outside of this study, the information may no longer be protected under this authorization.

When will this authorization (permission) to use my protected health information expire?
This research study involves the use of a Data Registry or Sample Repository and will never expire.

Statement of Privacy Rights
You may change your mind and revoke (take back) the right to use your protected health information at any time. However, even if you revoke this authorization, the researchers may still use or disclose health information they have already collected about you for this study. If you revoke this Authorization you may no longer be allowed to participate in the research study. To revoke this Authorization, you must write to the Principal Investigator:

Nicholas Johnson, MD
Virginia Commonwealth University
Sanger Hall
1101 East Marshall Street, Box 980599
Richmond, Virginia 23298-0599

Arm 1 and Arm 2: CONSENT TO CONTACT PRIMARY PHYSICIAN

By participating in this study, we would like to obtain access to your frozen muscle tissue that was taken during diagnosis to add to the repository to be available for other research studies in the future. Once your sample has been received, it will be coded so that you cannot be identified.

Please circle:

YES you may contact my physician to release frozen tissue

NO you may not contact my physician to release frozen tissue

STORAGE FOR FUTURE RESEARCH STUDIES

To advance science, it is helpful for researchers to share information. They do this by putting data or samples into one or more scientific databases (called registries or repositories), where it is stored along with information from other studies. Researchers can then study the information in other ways and combine information from many studies to learn even more about health and disease.

Data Registry at VCU

By participating in this study, we will keep the information that you provide in registry to be available for other research studies in the future. Your information will be coded so that you cannot be identified and stored at VCU by Dr. Nicholas Johnson. This information could be used for other research studies about any topic. Your information will be protected, but there is always a possibility that information could be accessed by individuals without authorization. There is no limit on the length of time we will store your information. **If you do not want your data stored in the registry, you will not be able to participate in this trial.**

Sample Repository for Arm 1 and Arm 2

By participating in this study, we will keep the samples that you provide in repository to be available for other research studies in the future. Your sample will be coded so that you cannot be identified and stored at Weil Lab at Washington University by Dr. Chris Weihl MD, PhD. These samples could be used for other research studies about any topic. Your samples will be protected, but there is always a possibility that information could be accessed by individuals without authorization. There is no limit on the length of time we will store your information/samples**. If you do not want your samples stored in the repository, you will not be able to participate in this trial.**

In the future, if you decide that you don't want to be part of one or both of these registries, you can request that your data or samples be removed and destroyed by contacting Dr. Nicholas

Johnson in writing at the address listed on page 1 of this consent form. However, information that has already been shared with other researchers will continue to be used.

When your child reaches the age 18, we will try to contact them to ask whether they want to continue to participate in this research registry. If we cannot find them, we will remove all identifying information, and continue to use their samples, genomic data and health information in research.

Who should I contact if I have questions about this study?
If you have any questions, complaints, or concerns about your participation in this research, contact:

Nicholas Johnson, MD
1101 East Marshall Street, Box 980599
Richmond, VA 23298-0599
804-552-0014

If you have general questions about your rights as a participant in this or any other research, you may contact:

Virginia Commonwealth University Office of Research
800 East Leigh Street, Suite 3000
Box 980568
Richmond, VA 23298
Telephone: (804) 827-2157

Contact this number to ask general questions, to obtain information or offer input, and to express concerns or complaints about research. You may also call this number if you cannot reach the research team or if you wish to talk to someone else. General information about participation in research studies can also be found at http://www.research.vcu.edu/irb/volunteers.htm.

Do not sign this consent form unless you have had a chance to ask questions and have received satisfactory answers to all of your questions.

You will receive a signed copy of this consent form.

STATEMENT OF CONSENT AND PARENT/LEGAL GUARDIAN PERMISSION

I have been provided with an opportunity to read this consent form carefully. All of the questions that I wish to raise concerning this study have been answered. By signing this consent form I have not waived any of the legal rights or benefits to which I otherwise would be entitled. My signature indicates that I freely consent to participate in this research study.

Signature Block for Enrolling Adult Participants	
_____ Adult Participant Name (Printed)	
_____ Adult Participant's Signature	_____ Date
_____ Name of Person Conducting Consent Discussion (Printed)	
_____ Signature of Person Conducting Consent Discussion	_____ Date
_____ Principal Investigator Signature (if different from above)	_____ Date

Signature Block for Enrolling Child Participants - Parent/Guardian Permission	
_____ Name of Child/Youth Participant	
_____ Name of First Parent/Legal Guardian (Printed) *Study team – verify that this individual is the child's parent or legal guardian.*	
_____ **Required** First Parent/Legal Guardian Signature	_____ Date
_____ **Optional** Second Parent /Legal Guardian's Signature	_____ Date
_____ Name of Person Conducting Parental Permission Discussion (Printed)	
_____ Signature of Person Conducting Parental Permission Discussion	_____ Date
_____ Principal Investigator Signature (if different from above)	_____ Date

Signature Block for Short Form Consent – Participants with Limited English Proficiency	
_____ Name of Participant (Printed)	
_____ Witness or Interpreter's Signature	_____ Date
(NOTE: The witness may be the interpreter or a family member of the LEP subject who can speak both English and the participant's language. The witness cannot be the member of the study team conducting the consent process.)	
_____ Name of Person Conducting Consent/Assent Discussion (Printed)	
_____ Signature of Person Conducting Consent/Assent Discussion	_____ Date
_____ Principal Investigator Signature (if different from above)	_____ Date