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CONTRACTING ORGANIZATION:

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13. SUPPLEMENTARY NOTES

14. ABSTRACT (approximately 200 words) The Cooperative International Neuromuscular Research Group (CINRG) is a consortium of medical and scientific investigators and centers focused on improving quality of life of neuromuscular disease (NMD) patients by cooperatively conducting clinical research studies in NMD. The CINRG coordinating center (CC) is an infrastructure to support the network in conducting study protocols, standardizing clinical trial methodology, data collection and quality assurance, and performing data analyses. In this award period the electronic database capture system was revamped and implemented for two studies in Duchenne Muscular Dystrophy (DMD). CINRG's public website has been revamped. One measurement clinical trial was completed, one large observational study is in follow-up and two studies are in active recruitment. New subcommittees were formed; three new sites were added to the network. Eleven presentations were given at national and international scientific and parent advocacy groups. Connections with DMD external groups were strengthened and formalized. With a strong ability to assess which outcomes are more sensitive and reliable to measure clinical change, as this CINRG CC supports, therapeutic approaches can be assessed and either adopted or abandoned quickly. This infrastructure support yields better overall results in research for improving care in DMD in the largest network of institutions for this disease worldwide.

15. SUBJECT TERMS
Duchenne Muscular Dystrophy, CINRG, CQMS, coordinating center, electronic data capture

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INTRODUCTION

Duchenne muscular dystrophy (DMD) is a rare disease occurring in 1 of 3500 live born males worldwide. The Cooperative International Neuromuscular Research Group (CINRG) is a consortium of medical and scientific investigators from academic and research centers sharing a common goal of improving the quality of life of neuromuscular disease patients by cooperative planning, implementation, analysis and reporting of controlled clinical studies and of other research for neuromuscular disease. In order to support CINRG in its efforts to perform the highest quality of research, a coordinating center (CC) is required to coordinate efforts and protocols, standardize methods of clinical trial treatment administration and assessments, as well as data collection and quality assurance, and analyses of data. The goal of this project is to provide the CINRG clinical research network with an infrastructure for operational support to conduct its studies, database and data management support for collection of data from CINRG studies, specific support in training clinical evaluators (CEs) for muscle strength and biostatistical support for study design, assessment of feasibility and analysis of study results, as well as supporting new grant submissions. The CINRG CC will provide a centralized administrative and technical infrastructure to meet the complex needs of the program that is supportive of CINRG's scientific agenda.

RESEARCH ACCOMPLISHMENTS DETAILED SUMMARY

A. Revamp of the Electronic Data Capture (EDC)

In Year 1 CINRG proposed to revamp the electronic data capture (EDC) system using Akaza Research, LLC to implement OpenClinica. OpenClinica is an open source database management system which is 21 CFR Part 11 compliant. Akaza hosts the servers, and provided end user support for one year while the CC learned the system.

Shortly after the start of this award, an OpenClinica trainer from Akaza Research conducted a 3-day Intensive End User Training session at the CINRG CC in Washington DC. Six CINRG CC members attended the training: the Database Manager (DBM), Biostatistician, Operations Manager, Regulatory specialist, and two additional CINRG members. This training included instruction on the basic general flow of the system, how to create and manage new studies, sites and users and how to export data sets. The largest portion of the training concentrated on case report forms (CRF) design based on OpenClinica's Excel spreadsheet template. This template is where the text for each item/question is entered, the format of the values/answer, the answer options, etc. During Year 1 the DBM and Biostatistician also attended an advanced training session separately. This session concentrated on how to create advanced CRFs and write validation checks in an XML template. The validation checks allow the data team to write queries on data within the same CRF or across separate CRFs, in addition to range definitions within the Excel template.

In the first year, the CINRG CC used end user support from Akaza to answer any questions the group had. In addition to now having some experience with the software, the CINRG CC team is now connected to OpenClinica's large, very active, users group which is available to answer questions that any user asks. The user's groups proved helpful as a resource in designing CRFs, question on the best way to utilize the system and providing help reading the data into statistical software.

In this funding period, three studies (Evaluation of Limb Girdle muscular dystrophy, Cardiac Outcome Measures in Children with Muscular Dystrophy, and Comparative Study of Clinical Endpoints in DMD: HHM vs. CQM) have been set up in OpenClinica. The first study served as a test and learning tool of the software, while the data was still collected first on paper CRFs. This includes first designing, developing and testing twenty five CRFs. The next step was to write and test basic data queries (both within and across forms) for these studies in OpenClinica. Paper source documentation for each CRF was then developed to match the OpenClinica data entry screens for the sites to collect the data at the time of the actual study visit. Once CRFs are developed each study must also be established in OpenClinica assigning the proper CRFs, sites and users for each study. A fourth study, CoQ10 Lisinopril, is in the process of CRF development and testing. Appendix I provides the CRFs as they appear to the web user

for these first 3 studies. In situations where an essentially equivalent CRF was used for more than one study, only the first developed is shown.

The Data management team has been writing manuals associated with OpenClinica including: data entry, how to add a study in OpenClinica and how to update a version of a CRF.

Before a site user could start entering data, the DBM trained each user on system navigation, data entry and correction in OpenClinica. Twenty-two users from nine sites have been trained during six training sessions via online teleconferencing. Data has been entered for all three studies set up with very little questions or problems. Once data is entered into OpenClinica the data team must export the data into SAS to clean, summarize or analyze.

Two challenges have arisen that the data team is working through. First, exporting the dataset into SAS has proved difficult, but is a known challenge within the OpenClinica interface. The DBM has been researching how to solve this challenge and is currently using a short-term method which allows the team to read the data. However, this will continue to be researched with the goal of finding a more permanent method. It is also expected that Akaza Research, LLC, will resolve this limitation in an update of the software. Once the data are in SAS the data team writes more advanced data queries to continue to clean the data.

The second challenge is that there are currently separate databases housing the OpenClinica data and the CQMs data, and they are only combined separately by the data team. This is planned to be included in the CQMS revamp to create a single database and more efficient system.

B. Revamp of the CINRG Quantitative Measurement System (CQMS)

This task has not been completed within the first year of the award. While we did not complete the revamp of the CQMS in this funding period, we made forward movement in refining the process for a more efficient revamp in the next funding period. We received a quote from a well recommended bio-engineering company to work on revamping the CQMS system but the quote did not provide adequate technical detail. There were several concerns with the quote. As requested by CINRG, C-Motion updated their proposed scope or work, tasks, deliverables and associated costs, but remaining concerns with this proposal included:

- With the accomplishment of the first task and the work on OpenClinica, this needs to be leveraged into accomplishing this task. In other words, currently data from the evaluation of muscle strength tests, pulmonary function tests, anthropometrics and goniometry, and timed function tests are all uploaded/entered into the CQMS system and then uploaded into a database hosted by an off-site provider. The vendor of revamping the CQMS system needs to be able to integrate the information collected into OpenClinica, so that all database information is in one database.
- There was a lack of clarity about how much information from the load cell testing actually is expected to be stored.
- There was a lack of clarity about the audio-visual interactive component revamping
- The quote was higher financially than the original quote and lacked specificity in terms of assessing the relationship between tasks and costs within the quote.

Due to these concerns, the CINRG CC assessed that a more advantageous route would be to create a request for proposal (RFP) to better identify and explain the technical and functional needs and b) elicit additional proposals that would be more in line with our budget.

We have started drafting the RFP and during this process we have realized several areas where we needed to increase our technical language to ensure our needs are received. We received input from our internal software engineer and IT department to provide better technical language for this RFP and the components of this RFP were subsequently broken down to include both functional technical requirements in: study development, registration, calibration, testing, documentation, installation, support,

maintenance and updates, training, proof of concept. We are continuing to obtain guidance and input from engineering staff to better refine the technical requirements of this RFP prior to circulating this document for service bids.

We currently work with MicroProcessor Designs, the original manufacturer of the CQMS equipment for ongoing service and replacement parts of the current system. We considered working with Microprocessor Designs as the vendor for revamping and contacted them to take a first step in this process by working to negotiate a contract for service (which currently does not exist). However, these efforts were met with difficulties surrounding contract negotiations for services and product warranty, which ultimately led to no contract being signed..We continue to work with this vendor on an ongoing basis, but it is not clear whether the vendor will compete for the RFP for the revamping.

An additional consideration during this process was a protocol that was started and completed during this funding period. This protocol compared the CQMS system to another quantitative hand held device for muscle testing. Even though this study will only affect the quantitative muscle testing piece of the CQMS, this aspect is a large component of the CQMS system. We feel that the results of the study may impact the extent of modifications required. This study is currently in the data analysis phase (see below).

C. Training of new clinical evaluators on the updated CQMS software

As the training of the new CEs was dependent on the updated software development, we will be working towards this goal in the next funding period.

D. Protocols Progress Updates

In this section we have outlined the progress that Year 1 funding of infrastructure support has provided for each CINRG protocol.

a. National Initiative for Families with Duchenne (NIFD)

i. Overview

The purpose of this survey was to collect information about families of people with DMD all over the USA. The survey asked for information about the impact of DMD on the family, the needs of the family for health services, the use of those health and school support services, the overall wellness of people with DMD and attitudes toward newborn screening for DMD. A total of 237 families have participated in this study. Participants were enrolled either through the CINRG natural history study or through the NIFD study directly via a web-based survey and the CINRG CC merged the collected study data into one database.

ii. Data Management

The data management team has been applying a systematic approach to correcting data errors within the survey, section by section. In Year 1, several sections have been finalized to promote manuscript generation from this valuable cohort of families and physicians. Two data summaries have been generated from this project:

- The section *About the Diagnostic Process* was compiled for an abstract (see **Reportable Outcomes**). This abstract looks at the age and length of diagnosis and how the families learned about the disease. The abstract highlights the importance of early diagnosis and genetic counseling for families.
- The section *School* was generated for a grant submission (see **Key Accomplishments**). The section summarized responses in this section to look at how involved the school system was in helping students with DMD in school issues. The focus of the submission was on transitions of boys with DMD to adulthood.

iii. Abstract Preparation

Currently, the section that focuses on genetic diagnosis has being finalized and a dataset has been compiled to prepare an abstract (see **Reportable Outcomes**).

b. An open-label pilot study of Coenzyme Q10 in steroid-treated Duchenne muscular dystrophy

i. Overview

This was an open label pilot study of thirteen 5-10 years old corticosteroid- treated DMD patients treated with Coenzyme Q10. Patient's doses were titrated to achieve specific serum levels, as target serum levels (2.5 µg/ml) were shown to be participant and administration dependent. We conducted this pilot trial to assess if the addition of CoQ10 to a stable corticosteroid regimen could further preserve or increase muscle strength in DMD over a 6 month period. A secondary objective was to find an effective and safe dose of CoQ10 in this pediatric population. The database was locked in 2007.

ii. Statistical Analysis

In this award period the statistician conducted analyses to explore the difference between baseline vs. Month 3, Month 3 vs. end of treatment cycle and baseline vs. end of treatment cycle using both pre-post comparisons as well as linear mixed-effects models to investigate the linear trend in the total QMT scores. Of note, missing data was imputed using last observations carried forward method. The Pearson correlation coefficient was calculated to explore the correlation between QMT muscle scores with other measurements.

iii. Manuscript Preparation

These analyses were conducted during manuscript revisions. This manuscript is in draft towards resubmission (see **Key Accomplishments**).

c. Open-label pilot study of Pentoxifylline in steroid-naïve DMD

i. Overview

This open label pilot study of oral, immediate release pentoxifylline (PTX) assessed the tolerability and safety of PTX and quantitative muscle strength (QMT) in young DMD boys over twelve months of treatment. We designed the study to identify any potential effects on quantitative muscle strength that could provide us with an effect size to power a future randomized controlled trial. The database was locked in May, 2007.

ii. Statistical Analysis

Only 9 of the 17 participants who began PTX treatment were able to complete the 12 month treatment study. Five participants discontinued PTX because of adverse events. Nausea and vomiting were reported in the majority of participants (65%). The statistician conducted analyses by comparing baseline characteristics between patients who completed the study and who did not complete the study.

iii. Manuscript Preparation

These analyses were conducted for a manuscript submitted in March, 2010 which was not accepted for publication. This manuscript will be resubmitted to a different journal (see **Key Accomplishments**).

d. A randomized study of daily vs. high dose weekly prednisone therapy in DMD

i. Overview

This study, conducted at 12 CINRG centers, was designed to determine whether a high-dose weekly course (10 mg/kg over two days) of prednisone is safer than and as effective as daily dose therapy (0.75 mg/kg/day). A total of 64 participants were enrolled (32 in each treatment group) for a 12-month study treatment period. The database was locked in February, 2008. In this reporting period statistical analyses

were performed and a manuscript with study results was submitted. Based on the journal's review, revisions are currently being compiled.

ii. Statistical Analysis

Since this was an equivalence in terms of effectiveness study, equivalence limits for changes from baseline to 12 months were established to be approximately the width of one standard deviation of the baseline distribution. Safety was analyzed for differences at the 12-month point. Primary outcomes for effectiveness equivalence were overall arm and leg muscle strength as measured by the CQMS, per the protocol. All other outcomes (individual components of CQMS, pulmonary function tests, timed function tests) are considered secondary. The primary safety outcomes were anthropometrics (height, weight, BMI), behavior assessments (as rated by parents) and bone density. Analyses included standard two-sample analyses for comparison of baseline characteristics between the treatment groups as well as comparions of safety outcomes and , testing of the primary hypothesis of effectiveness equivalence. Linear mixed effect models were used to explore the BMI change over time. To comply with intention to treat analyses, a single imputation was performed for 6 (9%) patients who did not complete the study. A per protocol analysis was also performed.

iii. Manuscript Preparation

These analyses were conducted for manuscript generation, submitted in March, 2010. Journal review was conducted and returned to the investigators in July, 2010 and is currently undergoing revisions based on these suggestions (see **Key Accomplishments**).

e. A double-blinded randomized placebo controlled study of daily Pentoxifylline as a rescue treatment in DMD

i. Overview

In this study, Pentoxifylline was added as a rescue treatment to patients who were receiving steroids (prednisone, prednisolone or deflazacort) for at least 12 months in a stable dose regardless of weight change. A total of 64 participants were enrolled. The database was locked in February, 2008.

ii. Statistical Analysis

The statistician conducted two-sample comparative analyses to compare the changes from baseline to Month 12 between two treatments; the linear mixed effects model was used to explore the QMT total score change over time; the adverse events rates were compared between the two treatment groups. Of note, missing data was imputed using last observations carried forward method.

The primary outcome results for total QMT score showed that the difference between two groups is not statistically significant with p-value 0.15. The differences on most of the individual primary endpoints are not statistically significant at level 0.05. Grip score is the only significant endpoint with p-value=0.04. The grip strength measurement was stronger in Pentoxifylline group than placebo group after 12 months of treatment.

iii. Manuscript Preparation

These analyses were conducted during manuscript generation. This manuscript is currently being drafted.

f. Clinical Trial of Coenzyme Q10 and Lisinopril in muscular dystrophies

i. Overview

The objective of the proposed study is to test an angiotensin converting enzyme (ACE) inhibitor, lisinopril, and an anti-oxidant, coenzyme Q10 (CoQ10), to ameliorate the decline in cardiac muscle function that occurs in muscular dystrophies. The proposed study treatment period is 24 months per patient.

This project is primarily funded by the Department of Defense (grant W81XWH-04-1-0851). For this project the only activities to be funded by this award relate to regulatory and data management support, and are expected to occur in future award years.

ii. Protocol development & amendments

The current version of the protocol (Amendment 5, dated: November 17, 2009) implementing additional safety measures compared to the initial version, as well as providing more information about the study medications and IND exclusion notification from the FDA, has been approved by CINRG's Executive Committee, Data and Safety Monitoring Board, and the Department of Defense.

iii. Protocol progress update

The following four CINRG centers have received approval to start enrollment:

- Site 01: Children's National Medical Center in Washington, DC
- Site 03: University of Pittsburgh in Pittsburgh, PA
- Site 30: Carolina's Medical Center, Charlotte, NC
- Site 31: Children's Memorial Hospital in Chicago, IL

The initial shipment of the drug has been received and study operations manuals have been drafted. The study is registered on www.clinicaltrials.gov.

g. A longitudinal study of the relationship between impairment, activity limitation, participation and quality of life in persons with confirmed Duchenne muscular dystrophy protocol

i. Overview

There are two purposes to this study. The first purpose of this research study is to establish a large long-term assessment of people with Duchenne muscular dystrophy to better understand the current natural history of this disease, to be better able to design clinical trials based on ongoing natural history parameters. In this study, we will take a detailed look at people's physical abilities across all ages, medical problems they experience, and how they use healthcare services over a five (5) year period. We will also look at how families of people with DMD interact with their communities and at their quality of life. For the family part of our study, we will also ask parents questions about their quality of life, and about their attitudes towards different aspects of their children's diagnosis, medical care and other support. One of the first uses of this study will be to see how long-term steroid therapy affects these aspects of lives of participants with DMD.

This project is primarily funded by the Department of Education, which covers all patient related costs. For this project the activities covered out of this grant are site monitoring, data management and statistical analysis activities.

ii. Site Monitoring

The operations manager performed site monitoring for seven sites in 2010. Site staff are involved during the site visit and a letter of visit findings is issued to the site investigator and study staff after each visit. Visit review includes:

- Review of protocol conduct and adherence
- Source document verification, including review of informed consent documents, adverse event/serious adverse events
- Review of outstanding queries

- Regulatory document verification
- Review of strength and functional testing equipment and space
- If new staff have been added to the project, new protocol training is also conducted
- Re-training of any identified areas of inconsistency or concern

The following lists the sites with site monitoring conducted in Year 1:

- University of Pittsburgh: December, 2009
- University of Sacramento-Davis: February, 2010
- Holland Bloorview Kids Rehabilitation Hospital: February, 2010
- University of Tennessee-Memphis: April, 2010
- University of Puerto Rico: June, 2010
- Mayo Clinic: July, 2010
- University of Richmond: August, 2010

In an effort to continue to function as an efficient team for staff time and fiscal resources, three additional monitoring visits occurred that were funded by different grants as multiple studies were ongoing at these sites (listed below). These visits were performed by the project manager who performs monitoring for other studies or by the clinical evaluator manager who is involved in all protocol conduct involving strength evaluation. A sub-set of monitoring duties was performed during these combination visits to ensure site compliance and patient safety.

- Centro Clinico Nemo: June, 2010
- Queen Silvia Children's Hospital: June, 2010
- University of Sacramento-Davis: July, 2010

In this funding period, these visits have monitored over 140 patients. Overall, these samples of monitoring visits find the sites adhere to the protocol and data collection procedures and have the required regulatory documentation. The visits identify some evaluation inconsistencies that may impact data integrity for this study, as well as potential impact of testing techniques or outcome measures for future clinical trials. For example, the testing wall mount bars should be level and two sites have been noted to have shifted and been unlevel. To ensure the quality of the muscle, strength and function data collected, the equipment, housing and testing space should be monitored to ensure they adhere to the necessary minimum requirements necessary for participant testing. In some cases there were data that are present in clinical documentation but were not captured in the CRFs.

iii. Data Management

The data management team works to issue data checks to each site on an as needed basis to ensure collected data are accurate and reliable. At the beginning of this funding period, data checks were issued monthly. As we have been making great strides in cleaning the data and the number of checks have greatly reduced over the previous year period,. we now issue data checks on a quarterly basis.

In addition, the data management team has assisted in the development of an upcoming protocol amendment which includes changes to the CRFs.

iv. Statistical Analysis

The primary statistical analyses in the previous award period focused on the baseline data and the one year data. Analyses were done to summarize values at baseline for muscle strength, timed function tests, functional assessment, pulmonary function tests, and anthropometrics. Summaries of use of corticosteroids at study entry were done. The study spans an age range of 2-28 years old at entry. Results

show that a large majority of participants are on corticosteroids, with a small group, mostly younger patients, not yet on steroids, and a small group, mostly older patients, who have been on steroids but discontinued use. Comparison of the parameters listed at baseline by users versus non-users has been performed using mostly continuous parametric analyses methods. A second focus has been the one-year results, the change from study entry, and its relationship to steroid status at entry. Some of the complexities of the data, particularly timed function tests is that over time patients lose the ability to perform the tests (e.g., standing up from a supine position). The unobservable data present a challenge to analyses, which the study statisticians are working with the study leadership team at the CINRG UC Davis site to address. A separate analysis, to address a similar problem, has been performed on height data. Patients who can no longer stand, or stand without curvature, cannot have their standing height measured. A height measurement is a component in calculating the percent predicted pulmonary function test result (along with age, if <18 years old). An alternative is measuring the ulna length, and using a published formula, calculating the standing height from the ulna length. This study, with concomitant measures of standing height and ulna length for all younger patients who are capable of standing, allows reconfirming the formula based on ulna length and assessing its accuracy, based on an adequate sample size, and these analyses were performed.

v. Academic Meeting, Poster Presentations and Manuscript Preparation

See **Reportable Outcomes** section for a list of meeting and poster presentations generated from this project. This project and results of its analyses attracts considerable attention in the neuromuscular disease community, as it is reestablishing current normative data within this disease, and forms the basis for clinical trial design for all future studies.Two manuscripts are currently in draft format, listed in **Key Accomplishments.** The first draft overviews the study methods and a subset of baseline characteristics of the enrolled cohort.

h. Comparative Study of Clinical Endpoints in DMD: HHM vs. CQMS protocol

i. Overview

The aim of this clinical trial is to compare two commonly used pediatric strength testing measures: handheld myometry (HHM) and CINRG Quantitative Measurement System (CQMS), with the goal of assessing which of these two methods has a higher intra-rater and inter-rater reliability in measuring muscle strength in children with DMD. The clinical trial, all patient visits, regulatory oversight, and travel of some clinical evaluators to be a second evaluator for the reliability assessments has been funded by a grant from the Muscular Dystrophy Association. Five sites enrolled 32 participants into this complex four-period crossover, performed twice in two visits separated by 12 to 72 hours, protocol. Target accrual was met, protocol conduct is completed and is currently the data are being finalized. This award supports the data management and statistical analyses components of this study. This protocol was reviewed and approved by CINRG's Executive Committee for network participation in September, 2010.

ii. Protocol development & amendment

The original protocol was approved June 15, 2009. The final version of the protocol is Amendment 3, approved January 2010.

iii. Obtaining site approvals

Protocol and Informed Consent/Assent Templates were developed at the CINRG Coordinating Center (CC), and were distributed to the participating sites. These documents were used at all sites as templates to complete local ethics committees, either institutional review boards (IRBs) or ethics review boards (ERBs) submissions. The CC provided assistance with IRB/ERB document preparation and submissions to all participating sites' committees.

The five sites who participated in this study include:

- Children's National Medical Center, Washington, DC

- Washington University-St. Louis, St. Louis, MO
- Royal Children's Hospital, Melbourne, Australia
- Centro Clinico Nemo, Milano, Italy
- Carolina's Medical Center, Charlotte, NC

All sites obtained ethics approval between July, 2009 and June, 2010.

iv. Development of CRFs and database

This award period included generation of all protocol CRFs by the data management team (seven CRFs in total). This process involved the DBM, project manager and investigator working together to identify the study data points to be collected. Once the data points were confirmed by the study team, an Excel spreadsheet was created for each CRF based on an OpenClinica template, as described above. This spreadsheet was then uploaded into OpenClinica. This created the CRFs in the database. It further created the database itself based on the definitions in the Excel populated templates. Paper CRFs were created based on the OpenClinica form. The data management team also developed rules to create data queries in the system. This database is finalized (see **Reportable Outcomes**).

v. Protocol site initiation & monitoring

Study manuals were created as a joint effort by the project manager, the central clinical evaluator and the data management team, including: manual of operating procedures, site initiation visit operational manual, site monitoring and close-out manual.

The project manager and study principal investigator/clinical evaluator manager performed site initiation training in a single teleconference/web-based session separately for each site. Each site study initiation included training that covered protocol conduct and assessments, clinical evaluations testing, regulatory documentation, and data entry and query resolution. We had 100% attendance of active study personnel at the site initiation for all sites.

Study monitoring was performed remotely by the data management team through data queries and by the project manager through review of mailed or faxed case report forms and informed consent verification.

vi. Protocol Conduct

Five sites randomized 33 and enrolled 32 participants into the study between February and June, 2010. The non-randomized participant was unable to confirm the testing date and as a result was unable to be enrolled in the study. This study has completed all study visits and is in analysis. Thirty-two participants completed protocol conduct; however, one of these participants did not meet the inclusion/exclusion criteria, and one evaluator who evaluated one patient did not meet evaluator inclusion criteria. Therefore, 30 patients will be included in the final data analyses.Ten CEs participated in the study evaluations. The final scientific report was issued to the funding agency, Muscular Dystrophy Association, July, 2010. The study is registered on www.clinicaltrials.gov.

vii. Study Data Collection and Cleaning

Data for this study was collected using two different methods. The first method is comprised of paper CRFs collection where data are hand-written and entered into an electronic data capture system (OpenClinica). The second method is used for quantitative muscle testing data collected from the CQMS system, which is directly transferred from the testing load cell to a computer database. The data is then transferred to an electronic database through a secure internet line.

The quality and integrity of the collected study data was confirmed by verifying data entry by comparing completed CRFs to the data entered in OpenClinica. Also, additional logic checks were written and issued to sites for data entered into the OpenClinica system to confirm any value that had the potential to be a testing or collection error. Each site responded to these logic checks and, if appropriate, CRFs and OpenClinica were updated. Lastly, data was reviewed to document any protocol violations. The CRFs

were further reviewed for proper completion and documentation of any changes, review of available clinic notes to ensure any possible adverse event was appropriately reported.

i. Cardiac Outcome Measures in Children with Muscular Dystrophy protocol

Using the framework of CINRG and the Clinical and Translational Science Award (CTSA) consortium, this project will develop cardiac outcome measures that can be reliably implemented across a consortium of clinical sites devoted to the study of pharmaceutical treatments for muscular dystrophy. This study is funded through a CTSA supplement through the University of Pittsburgh. This project is currently ongoing and enrolling study participants. Although this award did not fund directly this study, the existence of the CINRG CC infrastructure enables the conduct of this study.

E. CINRG Administrative Efforts

a. CINRG Executive Committee meetings

CINRG Executive Committee (EC): The CINRG EC is responsible for, among other things, the review/approval of all protocols to be conducted by the network/utilize CINRG equipment; oversee programmatic activities of CINRG, and assess or implement recommendations from CINRG's Scientific Advisory Committee (SAC).

The CINRG operations manager coordinates the dissemination of necessary documentation and review/voting conduct of this committee. The committee has conducted six meetings, including the review/approval of 3 new CINRG network sites, review/approval of 3 new protocols, review of the newly released CINRG public website, and continued oversight of CINRG activities and conduct. In Year 1, two CINRG protocols were finalized and received CINRG EC approval (see **Protocol Progress Updates**), one non-CINRG protocol and one grant submission (bulleted below). No protocols were rejected. The CINRG CC staff was involved in protocol generation and revisions to elicit the final document for protocol conduct.

Non CINRG protocol reviewed: A randomized, double-blinded, placebo-controlled, dose-escalation study to evaluate the safety, tolerability, pharmacokinetics and pharmacodynamics of ACE-031 (ActRIIB-IgG1) in patients with DMD. This protocol was reviewed and approved in February, 2010 for CQMS utilization at the participation CINRG sites.

Review of Potential Grant submissions: Treatment of early cardiac systolic dysfunction in Duchenne muscular dystrophy with lisinopril or Losartan: a prospective, randomized, blinded, crossover trial. This proposed study was submitted for review by the Treat-NMD therapeutics committee (TACT). This committee provides reviews and insights, but is not representative of any available funding. Its comments were helpful in assessing future directions for this proposed study.

b. CINRG annual investigator meeting

The CINRG CC organized and conducted an Investigator meeting in November, 2009 which included a review of the scientific and business function of CINRG. This meeting is intended to be attended by at least one of the CINRG site staff fulfilling the roles of investigator, coordinator, or CE. We had a very positive turn-out with 77 site attendees and more than thirty stakeholder or public attendees. During this three day meeting, the following was presented and/or conducted (see Appendix C for the meeting agenda):

- One and a half day session attended by CINRG CE: This training was conducted to provided re-certification to all previously trained CE, and included a review of the techniques and positioning for the CQMS, including equipment upkeep; review of current and future protocol testing measures, including new CE testing measures for Facioscapulohumeral muscular dystrophy

(FSHD) patients as well as training on the 6 minute walk test; and troubleshooting techniques related to the CQMS software.

- One CE from each CINRG site attended the annual re-training and certification training conducted during the November Investigator Meeting. In addition, five new CEs were certified to perform CINRG testing from existing three CINRG sites both nationally and internationally. Finally, two new site CEs were trained by the CINRG clinical evaluator manager. This was a cost and time saving measures, as the staff were already traveling to DC for the investigator meeting.

- One half day workshop session attended by all CINRG site staff: This included an introduction from all participating CINRG network sites on their local practice and population, operational direction for new protocol submission, data requests updates on all current studies, and publication guidance.

- One full day session attended by CINRG site staff and public: This included an overview of programs in translational and clinical research, CINRG study updates, translation research, exon skipping updates, and basic science updates.

- One half day meeting of the SAC: This was a closed session, only attended by SAC members, CINRG Medical, Scientific, Statistics and Data Management Directors and the Publication Subcommittee Chair.

The meeting planning and implementation was a team effort by all CC personnel, and consisted of addressing issues of meeting locations (at CNMC and off site), site personnel travel arrangement, agenda and materials dissemination, as well as all training and presentation materials necessary to ensure success.

c. CINRG clinical evaluator recertification and new training

In addition to the recertification that is conducted at the CINRG Investigator Meeting (see **CINRG Annual Investigator Meeting** above), current CINRG policy requires all certified CEs must have annual recertification of the use and function of testing instruments and procedures to ensure all tests performed in a standardized fashion. Additionally, all CEs are required to test at least one participant every quarter.

Currently, 22 CINRG sites have active certified CE and performing evaluations on a regular basis, with two new CINRG sites pending training.

There are two challenges regarding CE training and recertification:

- Training: As outcome measures in DMD are critically evaluated and standardized throughout the DMD scientific community, we need to be able to stay current with new test measures and evaluation techniques. To accomplish this, we need to find effective and creative avenues utilizing technology to train and implement new test measures in an efficient manner if the need arises for new projects that are initiated in the interim between the annual CINRG Investigator meetings.

- Re-certification: We need to re-assess whether reliability testing should be required by all CEs on an annual basis or less frequently. The reliability testing requires site staff to recruit a participant with a neuromuscular disease and perform all CQMS measures, which is a burdensome task for both the site staff and families.

d. CINRG network communication

We maintain communication with all CINRG network staff to ensure an open flow of communication between the CINRG Coordinating Center and the network sites, using newsletters and teleconferences that are conducted throughout the year. The Operations Manager compiles CINRG network newsletters

which are issued twice a year to all CINRG network staff. These network newsletters include general network updates: new institutional or staff additions to the network team, CINRG sub-committee progress and milestones, an overview of academic presentations, and protocol updates. In addition, the newsletter is then edited into a public friendly version and posted on the CINRG public website.

We conduct teleconferences based on the staff research role of investigator, coordinator and evaluator. The first teleconference is led by the Medical Director and provides an overview of network progress, including academic presentations of study data as well as meeting attendance where the CINRG network is highlighted, updates on pending manuscripts from CINRG study data, and current and upcoming protocol updates. Over the last year, three teleconferences have been conducted. We consistently have at least one site investigator call in from at least 70% of the sites, which is an accomplishment given that the network encompasses a 17 hour time zone.

Second, we also conduct teleconferences with all site clinical coordinators and clinical evaluators where we review CINRG network updates such as new sites or subcommittees. However, this call differs greatly from the investigator call in that it also includes any testing updates or problem areas identified during DMD protocols that warrant re-training or technique adjustments. We include challenges and problem solving of protocol conduct or data collection issues, and include an open forum where all site staff can ask testing or protocol specific questions. These teleconferences are led by the operations manager and clinical evaluator manager and are offered over two days (differing times) to provide an opportunity for all site staff to attend across time zones. Over the two days, we have an average 90% turn-out of site attendance. We did not convene the coordinators and evaluators in fall, 2010 as the CINRG Investigator meeting was conducted in November, 2009 and training and updates occurred during the meeting. Two calls have been conducted in 2010.

e. Collaborating with other DMD research entities

The CINRG CC has made a concerted effort to continue collaborative efforts with other DMD research groups in the world-wide community. The principal investigator participated in the first Treat-NMD Advisory Committee for Therapeutics (TACT) established to conduct drug review and evaluation for proposed future clinical trials. Three protocols were evaluated at the meeting, one of which is described above and the PI did not participate in that evaluation due to conflict of interest (see Subsection a. Executive Committee).

One of the CINRG operations managers attended two meetings in this funding period. The *Third Annual Patient Registry Curator Training* included attendees from more than 90 participants from 23 countries, and over 30 countries worldwide are now part of the TREAT-NMD global registries initiative for DMD. Participants at the meeting received training in correct annotation of the genetic diagnosis and discussed the registry dataset. During this meeting, the operations manager was voted to be a member of the Treat-NMD Global Database Oversight Committee, which is the body responsible for the ethical governance of the registry, and this committee met to discuss important questions relating to the way patients are recruited for trials through the registries.

A CINRG operations manager also attended the *Parent Project Muscular Dystrophy's 2010 Annual Connect Conference* where she represented CINRG and its DMD research program. For the first time the Annual Connect meeting held a parallel meeting: Connect Conference – the Duchenne Therapeutic Development Meeting. This meeting included 40 distinguished scientific speakers, representatives of eight biotech companies, and is the most comprehensive Duchenne-specific, scientific meeting in the U.S. At this meeting CINRG was able to distribute two flyers. The first flyer contained general information about CINRG and the CINRG network. The second flyer was a three-fold brochure describing the DMD research studies that are open for enrollment through the CINRG network. This meeting attendance was an outstanding way for CINRG to collaborate and network with families and DMD researchers.

The CINRG Scientific Director, Medical Director, Coordinating Center Director (PI of this award) and central clinical evaluator attended the Clinical Outcome Measures in Duchenne Muscular Dystrophy

meeting where participants from Europe and the US met in Washington DC to discuss clinical outcome measures in the context of clinical trial design for DMD. This meeting was a follow-up to the September 2009 EMEA meeting where a clear directive was given that an international consensus needs to be developed that provides guidance on age appropriate clinical outcome measures for use in clinical trials for DMD, especially as these relate to clinically meaningful events. Eight data sets including the CINRG Natural History Study dataset were presented at this meeting to explore the sensitivity, reliability and applicability of endpoints in clinical trials and relation to disease progression. The meeting demonstrated that we have a strong foundation on which to base decisions around clinical trial design in DMD. Outcome measures are reasonably well defined, making multicenter clinical trials feasible. The outcome of this meeting will lead to more cross-collaborative efforts of clinicians, researchers, academics and advocacy together with industry to better drive future clinical research design.

f. Infrastructure subcontracts

As planned, the CINRG Coordinating Center (CC) executed subcontracts with seven sites, of the existing 21 sites in the network at the time of the grant submission, and two consultant agreements, to provide support for site research related activities, including regulatory duties, attendance to CINRG meetings, conferences and training, including training of CE staff on the CQMS.

g. CQMS equipment and supplies summary

A CQMS equipment pamphlet has been created as a reference tool for CINRG members and CEs along with annual requirements for equipment checks to ensure the CQMS equipment and supplies are in good working condition. One new CINRG site has obtained all equipment and supplies with two new sites in the process of ordering the necessary components to start evaluating patients. We have started working with 7 sites to order a new computer and hardware to replace the old/broken components while the approach to revamping the CQMS is being developed.

An original piece of equipment utilized during CQMS testing is a custom made back-rest which is used to provide stability and support to the patient during testing on the hi/lo table. The company is now out of business and, as a result, we have identified a hi/lo table that may be utilized as a table and back supports. We are working to identify the standardized back supports to customize the support for people of varying sizes. One of our new sites has received and is successfully utilizing this type of set up for testing.

h. CINRG regulatory compliance assurance

The CINRG Coordinating Center (CC) has provided assistance with IRB/ERB document preparation and submissions to all participating sites for recently launched CINRG studies which include:

- Cardiac Outcome Measures In Children With Muscular Dystrophy
- Comparative Study Of Clinical Endpoint In DMD: HHM Vs. CQMS
- Clinical Trial of Coenzyme Q10 and Lisinopril in Muscular Dystrophies

The CINRG CC serves two roles for regulatory support. First, it assists the sites with the preparation of the submission documents. This includes, in particular, helping sites with the development of consent/assent documents meeting their local ethics boars approval. All informed consents and assents were reviewed by the CINRG CC to assure that they meet all elements of consent r before they were submitted to their respective IRB/ERBs. All sites received assistance until protocol and consent/assent documents received local approval. One of the challenges of this role is the fact that the consents/assents are in languages other than English at some of CINRG's international sites. The CINRG CC has been systematically working to assure the accuracy and validity of the translations and regulatory documents collected at these sites.

The second role is to assure that all regulatory documents are being collected at each site and a copy of those documents are provided to the CC. In addition to the informed consent/assent, which are study-specific, these documents include: Curriculum Vitae (signed and dated) for site principal investigator and all study personnel, a copy of current medical licensure for site principal investigator and licensed personnel, human subject training certification, and IRB/ERB statement of compliance and membership

lists. This has been a challenge since there are varying requirements among the international sites, including: content of ERB annual reporting and timelines, human subject training certification timelines and professional licenses requirements and timelines. The CINRG CC has adapted the document review and collection process accordingly.

i. New CINRG website

CINRG was committed to improving the communication both within the CINRG network and with the various external stakeholders. The CINRG website previously in existence was difficult to navigate by stakeholders, patients and families, and CINRG staff. As a result, the CINRG CC worked to revitalize this website and contracted with a new vendor on this project, including the redesign which was planned in two phases: a public section and CINRG site staff section. The public section provides a contact and communication route for the neuromuscular community and medical professionals outside the CINRG network. The public site includes 3 major sections: Learn more about Neuromuscular disorders, Find out about the CINRG network and Take action: Get Involved!. The Learn more section gives a resource to families of information about different diseases and information about different members of a healthcare team they could work with and useful links where they could learn more. The Find out about the CINRG Network section is targeted for use by healthcare professionals who may be interested in learning who CINRG is, what they do and how they may become part of the CINRG network. The third section, Take action: Get Involved! gives information about clinical trials in general and the specifics of the CINRG clinical trials and how to enroll in one. This section is useful for a family or a physician looking to refer patients to CINRG studies. The public website was released in May, 2010 and received very positive feedback.

The private section, which allows the CC to communicate with the CC through posted documents, meeting alerts, and group communication, is currently under development and is anticipated to be released by December, 2010. During this transition phase, we continue to utilize the existing vendor website to ensure continuous access to the posted information for all CINRG network members.

j. Site additions to the CINRG network

Three new sites were added to the CINRG network during Year 1. A new site submits an application to the CINRG Executive Committee (EC. All three sites who applied to join the network were reviewed and approved:

National Institute of Neuroscience, Tokyo, Japan – Site investigator: Dr. Shin'ichi Takeda:

The National Institute of Neuroscience (NIN) has its origin in 1978 when Neurological Research Center was established with the aim of elucidating the pathogenesis and etiology of psychiatric disorder, neurological disorder, and muscular diseases and for developing therapeutic means for these disorders. Currently, this clinic follows over 400 patients with neuromuscular disorders.

Current Status: This site was approved May 29, 2009 is currently in the process of setting up their CINRG CQMS testing equipment. This site is working with the CINRG CC to investigate the potential of participating in a currently enrolling CINRG protocol.

Levine Children's Hospital at Carolinas Medical Center, Charlotte, NC – Site investigator: Dr. Susan Sparks: Levine Children's Hospital is committed to patient care, research and education in children and serves as an MDA clinic. The site co-investigator (Dr. Benjamin Brooks) serves as the MDA clinic director.

Current Status: This site was approved May 20, 2009 and has received and set-up their CQMS testing equipment and received clinical evaluator training. They have participated in one completed CINRG protocol and are enrolling into a second ongoing CINRG protocol.

Children's Memorial Hospital, Chicago, IL – Site investigator: Dr. Nancy Kuntz: Children's Memorial Hospital is the region's top provider of pediatric specialty care, dedicated to the health and well-being of all children and inspired by the courage of children and families. The neuromuscular clinic and physician evaluation are utilized for all other research evaluations and assessments and both spaces fulfill CINRG space requirements.

Current Status: This site was approved February 22, 2010 and is in the process of setting up their CINRG CQMS testing equipment. This site has plans to participate in a currently enrolling CINRG protocol once their equipment is received and their new CEs are trained.

k. CINRG external and internal committees and subcommittees

CINRG CC staff has been involved in the management and administrative assistance with existing and newly formed committees and subcommittees involved with CINRG oversight and progress. The assistance provided to the operations of these committees includes managing communications to and from committees, coordinating meetings and teleconferences, and ensuring meeting minutes and/or necessary documents are drafted and circulated to the committee for review.

CINRG Scientific Advisory Board (SAC): The SAC is an existing committee whose aim is to set research priorities and offer operational recommendations to CINRG and routinely convenes during the CINRG Investigator meeting. It is composed entirely of members external to CINRG.

In Year 1, the SAC convened at this year's CINRG Investigator meeting in November, 2009 in Washington, DC. The recommendations made by this committee were reviewed by the CINRG EC.

CINRG Data and Safety Monitoring Board (DSMB): The DSMB is an existing committee whose aim is to oversee the safety of participants in CINRG studies as well as the quality and completeness of data in those studies. The DSMB meets by conference call approximately once a year if there are no CINRG clinical trials that are actively recruiting patients or providing study treatment, and all studies are observational; the committee convenes every 6 months if there are actively enrolling or treating clinical trials. In addition, the committee reviews by email new protocols, after Executive Committee approval. The committee last met by conference call in July 2009. Its next scheduled meeting is September 16, 2010. Within this award year the committee reviewed, made helpful suggestions, and approved the four protocols named above in Sections D.f, D.h, and D.i.

CINRG Publication Subcommittee (CPS): The CPS is one of the most active subcommittees, established in 2006. The CPS's goal is to assist and encourage CINRG investigators in preparation of manuscripts, abstracts, and other communication methods, and disseminate CINRG results and findings within the network, as well as to oversee data and analyses requests for other purposes, such as grant submissions.

In Year 1, the CPS has received eleven data requests, for a combination of academic meeting presentations, manuscripts and grant proposal development efforts.

CINRG Therapeutic Subcommittee (TSC): The TSC had previously been established, but had been dormant for the previous two years, prior to this award. In Year 1, the CINRG EC requested nominations to re-establish this committee, and compiled new membership based on the individual's expertise in the neuromuscular field. The committee was formed in April, 2010.

The appointed chair convened the first meeting in May, 2010 and the TSC mission was confirmed. The TSC reached a consensus that the broad role of the TSC will be to undertake an active role of brining potential agents for evaluation towards clinical trials at the CINRG network.

CINRG Outcomes Subcommittee (OSC): The TSC is a new subcommittee. The CINRG EC requested nominations for this committee, and compiled a committee based on individual's expertise in the neuromuscular field. The committee was formed in April, 2010. The appointed chair convened the first meeting in June, 2010 and the subcommittee is working to finalize a survey whose aim is to assess the

testing CEs opinion of the CQMS functionality and usability. This survey will be circulated to all network CEs.

KEY RESEARCH ACCOMPLISHMENTS

The following are key research accomplishments for the Year 1 funding period:

Manuscripts in process

- DM Escolar, C Tesi-Rocha, E Henricson, J Florence, J Mayhew, K Gorni, L Pasquali, A Pestronk, GR Martin, C Spurney, F Hu, L Nie, AM Connolly, and CINRG Investigators. CINRG Pilot trial of Coenzyme Q10 in steroid treated Duchenne Muscular Dystrophy. *In revision for journal submission.*

- A. Zimmerman, C. Tesi-Rocha, P.R. Clemens, A. Connolly, S.T. Iannaccone, N. Kuntz, R.T. Leshner, A. Arrieta, L. Hache, E. Henricson, F. Hu, J. Mayhew, and D.M. Escolar. Oral pentoxifylline is a poorly tolerated and ineffective rescue therapy for Duchenne dystrophy. *In revision for journal submission.*

- DM Escolar, LP Hache, PR Clemens, A Cnaan, C McDonald, V Viswanathan, JA Kornberg, T Bertorini, Y Nevo, T Lotze, A Pestronk, M Ryan, J. Day, A Zimmerman, A. Arrieta, E Henricson, J Mayhew, J Florence, F Hu, AM Connolly. Randomized, blinded trial of weekend versus daily prednisone in Duchenne muscular dystrophy. Submitted to Neurology March 2010. *In revision for journal resubmission.*

- E Henricson, C McDonald, RT Abresch, J Han, R Leshner, E Hoffman, D Escolar, A Cnaan, F Hu, A Zimmerman, T Duong, J Mayhew, J Florence, A Arrietta and the CINRG Investigators. A Cooperative International Neuromuscular Research Group (CINRG) Study of the Relationship Between Impairment, Activity Limitation, Participation and Quality of Life in Persons With Confirmed Dystrophinopathies: Methods and Baseline Characteristics. *Manuscript in draft form.*

Databases

Two databases were created to support three studies, including:

  - Study of Clinical Endpoints in DMD: HHM vs. CQMS protocol
  - Cardiac Outcome Measures in Children with muscular dystrophy protocol, which is combined with a sister protocol Cardiac Magnetic Resonance: A Parallel Protocol to Cardiac Outcome Measures in Children with muscular dystrophy

REPORTABLE OUTCOMES

The following bullet list includes abstracts for academic presentations and posters, and grant submissions input from the CINRG Coordinating Center as of August 13, 2010.

Manuscript

- Pegoraro, Piva, Gavassini, Cagnin, Ermani, Bello, Soraru, Lanfranchi, Angelini, Kesari, Lee, McDonald, Hoffman, and CINRG InvestigatorsIdentification of a validated genetic modifier in Duchenne muscular dystrophy (DMD): Importance as a co-variate in clinical studies. See section D.g (*in press, Neuorology).*

Abstracts

- L Hache, Feingold, DM Escolar, C McDonald, P Clemens. Comparison of Disease-Causing Mutations in Duchenne Muscular Dystrophy from the Cooperative International Neuromuscular Research Group with Two Large DMD Mutation Databases, September, 2009 (Neuromuscular Disorders, 19(8-9): 547, 2009)..

- A Cnaan, T Duong, E Henricson, RT Abresch, R Leshner, C McDonald and the CINRG Investigators (presented by J Florence). Relationship between Different Timed Tests in Duchenne Muscular Dystrophy: The CINRG experience. Poster at Treat-NMD, Brussels, November, 2009.

- T Duong, A Cnaan, RT Abresch, E Henricson, F Hu, R Leshner, C McDonald and the CINRG Investigators. (presented by J Florence) The use of ulnar length in height calculation for boys with DMD: Results from a CINRG Natural History Study. Poster at Treat-NMD, Brussels meeting, November, 2009

- L. Hache, E. Feingold, A. Grubs, D. Escolar, C. McDonald, P. Clemens. Characterization of disease-causing mutations in Duchenne muscular dystrophy patients from the Cooperative International Neuromuscular Research Group The use of ulnar length in height calculation for boys with DMD: Results from a CINRG Natural History Study Platform at the National Society of Genetic Counselors, Atlanta, GA, November , 2009.

- RT Abresch, C McDonald, E Henricson, J Han, R Leshner, D Escolar, E Hoffman, A Cnaan, A Arrieta, F Hu, A Zimmerman, T Duong, J Florence and the CINRG Investigators. Pulmonary Function Characteristics of Boys with Duchenne and Becker Muscular Dystrophy by Age Groups and Steroid Use: One-year Data from the CINRG Longitudinal Study Project. Poster at AAN, Toronto, Canada, April, 2010.

- E Henricson, C McDonald, R Abresch, J Han, R Leshner, E Hoffman, D Escolar, A Cnaan, F Hu, A Zimmerman, T Duong, J Florence, A Arrieta and the CINRG Investigators. A Cooperative International Neuromuscular Research Group (CINRG) Study of the Relationship Between Impairment, Activity Limitation, Participation and Quality of Life in Persons With Confirmed Dystrophinopathies: One Year Follow-Up of Skeletal Muscle Strength and Timed Motor Performance. Platform presentation at AAN, Toronto, Canada, April, 2010

- E Henricson, C McDonald, RT Abresch, J Han, R Leshner, E Hoffman, D Escolar, A Cnaan, F Hu, A Zimmerman, T Duong, J Mayhew, J Florence, A Arrieta and the CINRG Investigators. A Cooperative International Neuromuscular Research Group study of the relationship between impairment, activity limitation, participation and quality of life in persons with confirmed Duchenne muscular dystrophy: One year follow-up of skeletal muscle strength and timed motor performance. Poster presentation at the XII International Congress on Neuromuscular Diseases, Naples, Italy, July 2010.
- R. Ted Abresch, C McDonald, E Henricson, J Han, R Leshner, A Cnaan, A Zimmerman and the CINRG Investigators. Baseline and one-year pulmonary function data of boys with Duchenne muscular dystrophy. Presented at the XII International Congress on Neuromuscular Diseases, Naples, Italy, July 2010.

- E Henricson, C McDonald, R Abresch, J Han, R Leshner, A Cnaan, F Hu, A Zimmerman, T Duong, A Arrieta, and the CINRG Investigators. Parent proxy-reported health-related quality of life in an observational study of boys with confirmed Duchenne muscular dystrophy using the PedsQL generic core scales. Presented at the XII International Congress on Neuromuscular Diseases, Naples, Italy, July 2010.
- A Dubrovsky, J Corderi, L Mesa Effects of Chronic Exercise in Duchenne muscular dystrophy. Presented at the XII International Congress on Neuromuscular Diseases, Naples, Italy, July 2010.

- L Hache, A Arrieta, C McDonald, E Henricson, P Clemens. The Diagnostic Process in Duchenne Muscular Dystrophy Families: The CINRG Experience. Abstract for NSGC, Dallas, TX, October, 2010. See section D.c,d,e.

Grant Submissions

- Optimizing bone health in Duchenne muscular dystrophy. Submitted to NIH September 2009, not funded (PI: Clemens).

- Evaluation of CDC management guidelines for Duchenne muscular dystrophy through a five-year multinational longitudinal study. Submitted to NIDDR and funded October 2009 (PI: McDonald).

- Comparative Study of Clinical Endpoints in DMD: HHM vs CQMS. Submitted to the Board of Lady Visitors October, 2009, funded (PI: Duong).

- Wellstone Muscular Dystrophy Research Center at Children's National Medical Center. Submitted to NIH November 2009, not funded (PI: Hoffman).

- Assess Transition to Adult Roles and Independence in Duchenne Muscular Dystrophy. Submitted to MDA January, 2010, not funded (PI: Joseph).

- Effectiveness of different methods of Achilles tendon management for boys with DMD. Submitted to the American Physical Therapy Association August, 2010 (PI: Duong). *Review pending.*

- Center of Research Translation of systemic Exon-Skipping in muscular dystrophy. Submitted to NIH June 2010 (PIs: Hoffman/Clemens). *Review pending.*

- Compilation of CINRG Genetic and Clinical Data in Neuromuscular Diseases. Submitted to MDA June, 2010 (PI: Clemens). *Review pending.*

- A multicenter collaborative study on the clinical features, expression profiling and quality of life of pediatric FSHD. Submitted to FSH Society March, 2010; scientific advisory committee's comments responded to and re-reviewed August, 2010. *Response to reviewers pending.*

CONCLUSION

In the first year of this award for infrastructure support for CINRG's Coordinating Center, a complete revamping of the electronic database capture occurred and the new approach has been implemented for two new studies in Duchenne Muscular Dystrophy, one of which already concluded the data collection phase successfully. The public website has been completely revamped. One small measurement clinical trial was started and completed and a larger therapeutic clinical trial has been started. Organizationally, new subcommittees were formed, and activities of previous committees and subcommittees either maintained or expanded. Three new sites were added to the network. Several CINRG sites have been monitored, per a regular schedule, for data quality assurance, regulatory compliance and compliance with physical structure testing requirements for the clinical evaluator's assessment. There has been renewed energy in bringing some older studies forward towards publications, and there have been several presentations of CINRG data at national and international scientific and parent advocacy groups. Connections with external groups whose focus is neuromuscular disease were strengthened and formalized. Overall, this first year of award promoted new energy and accomplishments in numerous areas and growth is ongoing.

With a strong ability to assess which outcomes are more sensitive and reliable to measure clinical change (based on all observational studies reported above and supported by this award), therapeutic approaches can be assessed and either adopted or abandoned more quickly and with a higher degree of confidence. Monitoring the quality of the network and accountability towards the various organizational bodies involved in CINRG internally and externally promotes better data and results for ongoing as well as future research. This infrastructure support yields better overall results in research for improving care in Duchenne muscular dystrophy in the largest network of institutions for this disease worldwide.

REFERENCES

As this is the first year of this award, all publications pertinent to this annual report are either in press, in revision, in draft form, or being developed.

CINRG Manuscript, Poster and Presentation Abstracts from August 2009 to August 2010

Manuscript

1) Neurology: Manuscript in Press

Title: SPP1 genotype is a determinant of disease severity in Duchenne muscular dystrophy

Authors: Pegoraro, Hoffman, Piva, Gavassini, Cagnin, Ermani, Bello, Soraru, Pacchioni, Bonifati, Lanfranchi, Angelini, Kesari, Lee, Gordish-Dressman, Devaney, McDonald, and the Cooperative International Neuromuscular Research Group.

Abstract: Objective: Duchenne muscular dystrophy (DMD) is the most common single gene lethal disorder. Substantial patient-patient variability in disease onset and progression and response to glucocorticoids is seen, suggesting genetic and/or environmental modifiers.

Methods: Two DMD cohorts were used as test and validation groups to define genetic modifiers: a Padova longitudinal cohort (n=106), and the CINRG cross-sectional natural history cohort (n=156). SNPs to be genotyped were selected from mRNA profiling in severe vs. mild DMD patients, GWAS in metabolism, and polymorphisms influencing muscle phenotypes in normal volunteers were studied.

Results: Strong effect on both disease progression and response to glucocorticoids were observed with polymorphism rs28357094 in the gene promoter of SPP1 (osteopontin). The G allele (dominant model; 35% of subjects) was associated with rapid progression and lower responsiveness to glucocorticoid (Padova cohort log rank $p = 0.003$; CINRG cohort $p = 0.0003$). Conclusions: Osteopontin genotype is a genetic modifier of disease severity in Duchenne dystrophy. Inclusion of genotype data as a covariate or in inclusion criteria in DMD clinical trials would reduce inter-subject variance, and increase sensitivity of the trials, particularly in older subjects.

Abstracts

1) World Muscle Society (September 9th – 12th, 2009, Geneva, Switzerland) Poster

Title: Comparison of Disease-Causing Mutations in Duchenne Muscular Dystrophy from the Cooperative International Neuromuscular Research Group with Two Large DMD Mutation Databases

Authors: Hache, Feingold, Escolar, McDonald, Clemens

Acknowledgments: CINRG Investigators, UMD-DMD, Leiden, and DuchenneConnect

Abstract: **Objectives**: Multiple dystrophin mutation types cause Duchenne muscular dystrophy (DMD). The recent development of DMD patient registries accentuates the need for global harmonization of mutation data collection. More consistent characterization of disease-causing mutations would enhance analyses of the distribution of such mutations from around the world. We investigated the mutations reported in DMD patients studied by the large international academic research group, the Cooperative International Neuromuscular Research Group (CINRG). We compared the types of mutations in the CINRG cohort to those reported in two large mutation databases, Leiden DMD mutation database and the French UMD-DMD. **Methods**: Diagnostic, strength, and medical history data were retrospectively reviewed for 374 DMD patients from 20 CINRG centers worldwide. The frequency of each type of mutation found in the CINRG data was compared with similar information abstracted from the Leiden and UMDDMD mutation databases. The distribution of DMD-causing lesions in the CINRG data was also compared to data from the DuchenneConnect patient registry. **Results**: Of the 294 (78.6%) CINRG participants that had DNA testing, the majority had large deletions (72%), followed by no mutations identified (13%), point mutations (8%), large duplications (5%), and small deletions (2%). The distribution of dystrophin mutations within the CINRG database is similar to the two large published databases and the patient registry despite the dissimilar ways that these databases were created. The CINRG data is drawn solely from subjects entered into clinical trials. Furthermore, CINRG data may be susceptible to regional variations in dystrophin mutation type. Regional patterns in the CINRG data set will be presented. **Conclusions**: Harmonization of mutation data collection for DMD studies will benefit clinical trials and ultimately enhance pairing of eligible patients to specific molecular-based treatments.

2) Treat-NMD: "Bringing down the Barriers - Translational Medicine in Inherited Neuromuscular Diseases" (November 17th – 19th, 2009, Brussels, Belgium) Poster

Title: Relationship between Different Timed Tests in Duchenne Muscular Dystrophy: The CINRG experience
Authors: Cnaan, Duong, Henricson, Abresch, Leshner, McDonald and the CINRG Investigators (Florence)
Acknowledgments: CINRG Investigators
Abstract: Timed tests of mobility are measures that have been used as objective measures and surrogate markers in boys with Duchenne Muscular Dystrophy (DMD). The tests include the time to walk 10 meters, time to climb four steps, and time to rise from a supine to standing position. These tests have proven highly reliable and may be administered even in the face of substantial limb girdle and axial muscle weakness. If these tests correlate well with functional measures and are good predictors to life altering events, such as loss of ambulation, they can serve as excellent surrogate markers for clinical trials. In a DMD natural history study conducted by the CINRG network (n=348, ages 2-28), we have evaluated over 200 patients for at least one year (4 quarterly measurements). While the fact that the disease progresses with age is clearly established, the variability in these measurements within ages, how they relate to each other, and how they change over time is not well-established. Our results show the increasing variability through mid to late teen years. With long-term follow-up we will be able to establish whether this variability corresponds to variability of age of loss of ambulation. Although the results from the tests are clearly correlated with each other, each timed test explains only approximately one-third of the variability of the other test; thus, these tests may represent different features of the impact of the disease and may have different predictive ability with regard to life-altering events.

3) Treat-NMD: "Bringing down the Barriers - Translational Medicine in Inherited Neuromuscular Diseases" (November 17th – 19th, 2009, Brussels, Belgium) Poster
Title: The use of ulnar length in height calculation for boys with DMD: Results from a CINRG Natural History Study
Authors: Duong, Cnaan, Abresch, Henricson, Hu, Leshner, McDonald and the CINRG Investigators (presented by Florence)
Acknowledgments: CINRG Investigators
Abstract: Height measurements are essential in monitoring growth and nutrition, as well as determining normal ranges and percent of predicted values for pulmonary function tests (PFTs). In boys with Duchenne Muscular Dystrophy (DMD) for whom respiratory complications are a leading cause of mortality and morbidity, PFTs are particularly important, and help describe the extent of disease. Therefore, PFTs may serve as an excellent surrogate marker and outcome of treatment efficacy. However, it is difficult to obtain accurate standing height measurements in DMD patients due to decreased mobility, lower extremity contractures, poor posture, and muscle weakness. In this study, we examined whether standing height and ulnar length calculated height measures could be used interchangeably to accurately assess height in boys with DMD. We obtained data from the Cooperative International Neuromuscular Research Group (CINRG) Natural History study on DMD (n=347). Ulnar length measurements (using a Rosscraft segmometer) and standing height (using a stadiometer) were obtained in 187 participants at study entry. Standardized measurement techniques were certified through ongoing CINRG reliability training. The height prediction equation was based on ulnar length and age using the linear regression provided by Gauld, 2004. Analysis of correlation coefficients between standing height measures and calculated height showed a correlation coefficient of 0.96. We conclude that ulnar length measures used for calculated height maybe used as an alternative for standing height in DMD patients. Further analyses seek to identify factors contributing to inaccuracy in either measurement method as well as steroidal effects on ulnar bone growth.

4) National Society of Genetic Counselors (November 13th – 15th , 2009, Atlanta, GA) Platform
Title: Characterization of disease-causing mutations in Duchenne muscular dystrophy patients from the Cooperative International Neuromuscular Research Group The use of ulnar length in height calculation for boys with DMD: Results from a CINRG Natural History Study
Authors: Hache, Feingold, Grubs, Escolar, McDonald, Clemens
Acknowledgments: CINRG Investigators, UMD-DMD, Leiden, and DuchenneConnect
Abstract: **Purpose**: Duchenne muscular dystrophy (DMD) is a progressive, degenerative muscle disease caused by mutations in the dystrophin gene. The recent development of DMD patient registries

accentuates the need for global harmonization of mutation data collection and highlights the importance of counseling families with regards to their specific mutations. This study characterizes the mutations reported in patients with DMD by a large international academic research group. The study compares the types of mutations in the CINRG cohort to those reported: in the literature, in two large mutation databases (Leiden DMD mutation database and the French UMD-DMD), and to those reported in the DuchenneConnect patient registry. **Methods**: Diagnostic, strength, and medical history data were retrospectively reviewed for 374 DMD patients from 20 centers of the Cooperative International Neuromuscular Research Group (CINRG). The frequency of each type of mutation found in the CINRG data was compared with similar information abstracted from the Leiden and UMD-DMD mutation databases as well as data from the DuchenneConnect patient registry. The distribution of mutations was correlated against strength measurements in order to identify any genotype-phenotype patterns. **Results**: Of the 294 (78.6%) CINRG participants that had DNA testing, the majority had large deletions (72%), followed by no mutations identified (13%), point mutations (8%), large duplications (5%), and small deletions (2%). The distribution of dystrophin mutations within the CINRG database is similar to the two large published databases and the patient registry despite the dissimilar ways that these databases were created. Genotype-phenotype patterns will be presented. **Conclusions**: The multi-center clinical trials group enrolled subjects with a similar spectrum of disease-causing mutations as two large published databases and a patient registry. Harmonization of mutation data collection for DMD studies will benefit clinical trials, raise awareness of genetic counseling, and ultimately enhance pairing of eligible patients to specific molecular-based treatments.

5) American Academy of Neurology (April 10th – 17th, 2010, Toronto, Ontario, Canada) Poster
Title: Pulmonary Function Characteristics of Boys with Duchenne and Becker Muscular Dystrophy by Age Groups and Steroid Use: One-year Data from the CINRG Longitudinal Study Project
Authors: Abresch, McDonald, Henricson, Han, Leshner, Escolar, Hoffman, Cnaan, Arrieta, Hu, Zimmerman, Duong, Florence and the CINRG Investigators.
Acknowledgments:
Abstract: This study describes the pulmonary function test (PFT) results of 205 patients, ages 7-28 years, with severe dystrophinopathies from 20-centers of the Cooperative International Neuromuscular Research Group at baseline and 12 months. PFTs included forced vital capacity (FVC), percent predicted forced vital capacity (%FVC), forced expiratory volume in 1 second (FEV_1), percent predicted FEV_1 (%FEV_1), peak expiratory flow rate (PEFR), percent predicted PEFR (%PEFR), maximum inspiratory pressure (MIP) percent predicted MIP (%MIP), maximum expiratory pressure (MEP), and percent predicted MEP (%MEP). Significance was accepted at $p<0.05$. In the 7-12 year age group the FVC, FEV1, and PEFR (mean change = 0.12l± 0.2, 0.1l± 0.2, 0.18 l/s±12.4, respectively; n=97) and the MIP and MEP (3.2 cmH_20±13.3 and 4.4 cmH_20±11.4, n=116) increased significantly over one year, while there was a significant decline in %FVC and %FEV_1 (-3.2%±10.8, -4.0%±12.4; n=97). In the 13-18 year age groups there was a significant one-year decline in the FVC (-0.06l±0.2), %FVC (-5.4%±5.8), FEV_1 (-0.05l±0.2), %FEV_1 (-5.1%±6.5), and %PEFR (-4.5%±10.2; n=61). In the ≥19 year age group there was a significant one-year decline in FVC,%FVC, FEV_1,%FEV_1 (-0.04±0.6, 1.0%±10.5, -0.07l±0.4 and -2.0%±9.7, respectively; n=25), as well as the MIP and %MIP (-3.9cmH_20±8.5 and -3.2%±7.2; n=28). Pulmonary function testing reflects growth-associated changes in patients with severe dystrophinopathies in the 7-12 year age-group and disease-related one-year PFT declines in the 7-12, 13-18 and ≥19 year age-groups.

6) American Academy of Neurology (April 10th – 17th, 2010, Toronto, Ontario, Canada) Platform
Title: A Cooperative International Neuromuscular Research Group (CINRG) Study of the Relationship Between Impairment, Activity Limitation, Participation and Quality of Life in Persons With Confirmed Dystrophinopathies: One Year Follow-Up of Skeletal Muscle Strength and Timed Motor Performance.
Authors: Henricson, McDonald, Abresch, Han, Leshner, Hoffman, Escolar, Cnaan, Hu, Zimmerman, Duong, Florence, Arrieta and the CINRG Investigators.
Acknowledgments:
Abstract: **Objective**: We tested 12-month change in skeletal muscle strength and timed motor function in ambulatory and transitioning males with severe dystrophinopathies aged 4-28 years. **Methods**: We enrolled 255 participants from 20 participating centers of the Cooperative International Neuromuscular

Research Group. Participants underwent MRC manual muscle tests (MMT), quantitative muscle tests (QMT) of hand grip and extremity flexion/extension, and timed function tests (TFT) at baseline and months 3, 6, 9, 12. 15% were glucocorticoids. **Results**: Over a year, children <7 years decreased time to climb 4 steps by 1.83+/-4.4s (p<0.0001 N=56) and increased QMT grip strength by 2.96+/-2.5 lbs (p<0.0001 N=37) and knee flexors by 1.18+/-2.6 lbs (p<0.04 N=37). Children aged 7-12 years increased time to run/walk 10m by 1.38+/-1.8s (p<0.0001 N=65), time to climb 4 stairs by 2.47+/-4.9s (p<0.0001 N=65) and time to stand from supine by 3.42+/-6.1s (p<0.0001 N=65). Children aged 13-18 years decreased QMT elbow extensor strength by 1.23+/-1.1 lbs (p<0.001 N=61) and elbow flexor strength by 0.98+/-1.3 lbs (p<0.01 N=61) and decreased MMT score by 0.32+/-0.4 points (p<0.01 N=61). Adults aged >18 years who were testable decreased QMT grip strength by 0.6+/-0.9 lbs (p<0.02 N=31). **Conclusions**: Over a 12-month period, children aged <7 years showed changes in TFT and QMT testing consistent with growth. Children aged 7-12 years showed changes in TFTs consistent with disease-related deficits. Children aged 13-18 showed disease-related impairment in QMT and MMT.

7) XII International Congress on Neuromuscular Diseases (July 17th -22nd, 2010, Naples, Italy) Poster

Title: A Cooperative International Neuromuscular Research Group study of the relationship between impairment, activity limitation, participation and quality of life in persons with confirmed Duchenne muscular dystrophy: One year follow-up of skeletal muscle strength and timed motor performance.
Authors: E Henricson, C McDonald, RT Abresch, J Han, R Leshner, E Hoffman, D Escolar, A Cnaan, F Hu, A Zimmerman, T Duong, J Mayhew, J Florence, A Arrieta and the CINRG Investigators
Acknowledgments: CINRG Investigators
Abstract: **Objective**: We tested 12-month change in skeletal muscle strength and timed motor function in ambulatory and transitioning males with severe dystrophinopathies aged 4-28 years. **Methods**: We enrolled 255 participants from 20 participating centers of the Cooperative International Neuromuscular Research Group. Participants underwent MRC manual muscle tests (MMT), quantitative muscle tests (QMT) of hand grip and extremity flexion/extension, and timed function tests (TFT) at baseline and months 3, 6, 9, 12. 15% were glucocorticoids. **Results**: Over a year, children <7 years decreased time to climb 4 steps by 1.83+/-4.4s (p<0.0001 N=56) and increased QMT grip strength by 2.96+/-2.5 lbs (p<0.0001 N=37) and knee flexors by 1.18+/-2.6 lbs (p<0.04 N=37). Children aged 7-12 years increased time to run/walk 10m by 1.38+/-1.8s (p<0.0001 N=65), time to climb 4 stairs by 2.47+/-4.9s (p<0.0001 N=65) and time to stand from supine by 3.42+/-6.1s (p<0.0001 N=65). Children aged 13-18 years decreased QMT elbow extensor strength by 1.23+/-1.1 lbs (p<0.001 N=61) and elbow flexor strength by 0.98+/-1.3 lbs (p<0.01 N=61) and decreased MMT score by 0.32+/-0.4 points (p<0.01 N=61). Adults aged >18 years who were testable decreased QMT grip strength by 0.6+/-0.9 lbs (p<0.02 N=31). **Conclusions**: Over a 12-month period, children aged <7 years showed changes in TFT and QMT testing consistent with growth. Children aged 7-12 years showed changes in TFTs consistent with disease-related deficits. Children aged 13-18 showed disease-related impairment in QMT and MMT testing. Adults aged >18 showed disease related decreases in QMT grip strength measures. This data provides information necessary to perform power analyses for clinical trials.

8) XII International Congress on Neuromuscular Diseases (July 17th -22nd, 2010, Naples, Italy) Poster

Title: Baseline and one-year pulmonary function data of boys with Duchenne muscular dystrophy.
Authors: R. Ted Abresch, C McDonald, E Henricson, J Han, R Leshner, A Cnaan, A Zimmerman and the CINRG Investigators
Acknowledgments: CINRG Investigators, grants support

This study describes the pulmonary function test (PFT) results of 205 patients, ages 7-28 years, with severe dystrophinopathies from 20-centers of the Cooperative International Neuromuscular Research Group at baseline and 12 months. PFTs included forced vital capacity (FVC), percent predicted forced vital capacity (%FVC), forced expiratory volume in 1 second (FEV_1), percent predicted FEV_1 (%FEV_1), peak expiratory flow rate (PEFR), percent predicted PEFR (%PEFR), maximum inspiratory pressure (MIP) percent predicted MIP (%MIP), maximum expiratory pressure (MEP), and percent predicted MEP (%MEP). Significance was accepted at p<0.05. In the 7-12 year age group the FVC, FEV1, and PEFR

(mean change = 0.12l± 0.2, 0.1l± 0.2, 0.18 l/s±12.4, respectively; n=97) and the MIP and MEP (3.2 cmH_20±13.3 and 4.4 cmH_20±11.4, n=116) increased significantly over one year, while there was a significant decline in %FVC and $\%FEV_1$ (-3.2%±10.8, -4.0%±12.4; n=97). In the 13-18 year age groups there was a significant one-year decline in the FVC (-0.06l±0.2), %FVC (-5.4%±5.8), FEV_1 (-0.05l±0.2), $\%FEV_1$ (-5.1%±6.5), and %PEFR (-4.5%±10.2; n=61). In the ≥19 year age group there was a significant one-year decline in FVC,%FVC, FEV_1,$\%FEV_1$ (-0.04±0.6, 1.0%±10.5, -0.07l±0.4 and -2.0%±9.7, respectively; n=25), as well as the MIP and %MIP (-3.9cmH_20±8.5 and -3.2%±7.2; n=28). Pulmonary function testing reflects growth-associated changes in patients with severe dystrophinopathies in the 7-12 year age-group.

9) XII International Congress on Neuromuscular Diseases (July 17th -22nd, 2010, Naples, Italy) Poster

Title: Parent proxy-reported health-related quality of life in an observational study of boys with confirmed Duchenne muscular dystrophy using the PedsQL generic core scales.

Authors: E Henricson, C McDonald, R Abresch, J Han, R Leshner, A Cnaan, F Hu, A Zimmerman, T Duong, A Arrieta, and the CINRG Investigators

Acknowledgments: CINRG Investigators

Abstract: **Aims**: This study compared normative PedsQL data to scores obtained from parents of patients with Duchenne muscular dystrophy (DMD) by age, ambulatory status, andglucocorticoid use. Background: PedsQL is a health-related quality of life tool that measures physical and psychosocial function in pediatric populations. It is validated in general and disease-specific scales. Normative data demonstrates that the instrument detects disease progression and effect of therapies. **Design/Methods:** Parent proxy PedsQL data were obtained from 258 parents of males with DMD aged 5-18 years enrolled in 20 centers of the Cooperative International Neuromuscular Research Group (CINRG) five-year natural history study at the baseline visit. Results: Parents of DMD boys reported mean total, physical and social function scores that were >1 SD below those reported in healthy comparison groups ($p<0.001$). Emotional and school function were lower in DMD boys ($p<0.001$). Parents of younger DMD boys reported higher total, physical, and emotional function scores relative to older DMD boys ($p<0.0001$). Parents of ambulatory DMD boys reported higher total, physical function and emotional function scores relative to nonambulatory boys ($p<0.01$). Parents of DMD boys currently on glucocorticoids reported higher physical function but not other scores relative to previously treated and treatment naive boys with DMD ($p<0.05$). **Conclusions**: Parent proxy PedsQL scores are lower in DMD compared to normative data. In boys with DMD, scores on physical and emotional function decrease with advancing age and loss of ambulatory ability. Furthermore, use of glucocorticoids leads to higher physical function scores compared to those not currently using glucocorticoids.

10) XII International Congress on Neuromuscular Diseases (July, 2010) Accepted Abstract

Title: Effects of Chronic Exercise in Duchenne muscular dystrophy

Authors: Dubrovsky, Corderi, Mesa

Acknowledgments: CINRG Network

Abstract: The effect of strength training and exercise in Duchenne dystrophy (DMD) is controversial. It is believed that resistance exercise may induce further damage to dystrophin deficient fibers. As a result, many physicians are cautious or reluctant in recommending active exercise therapy to their patients. This case study of a patient diagnosed with DMD and spastic paraparesis (SP) provides a unique opportunity to observe the effect of chronic isometric exercise in a patient in the late stages of DMD. A 10 year old boy with DMD with confirmed an out of frame 3 –7 deletion presented with severe SP since birth most notably in the lower limbs. He started using a posterior walker at the age of 4 years old. As a consequence, he opened a six year period of near continuous isometric exercise in the upper limbs with restricted lower limb activity. He developed striking muscle hypertrophy and strength in his triceps (9/10) and biceps brachialis muscles (9/10) (bilaterally). He exhibited increased strength, including the ability to lift and support his body weight with his biceps and elbows extended on his walker (manoeuvres he uses constantly while walking). Knee flexion as well as plantar flexion was weaker than regularly observed in DMD´s at the same age (2 and 3 (right and left) / 10).Knee extension remained strong (9/10) bilateral. This unique case provides new insights on the potential benefits of exercise management and the response to isometric/ resistance exercise in DMD.

11) National Society for Genetic Counselors (Meeting to be Held October, 2010) Accepted Abstract

Title: The Diagnostic Process in Duchenne Muscular Dystrophy Families: The CINRG Experience

Authors: Lauren P. Hache, MS, Adrienne Arrieta, MS, Craig McDonald, MD, Erik Henricson, MPH, and Paula R. Clemens, MD

Abstract: **Purpose**: Duchenne muscular dystrophy (DMD) is a progressive, degenerative muscle disease caused by mutations in the dystrophin gene. DMD is typically diagnosed around 5 years of age but symptoms including delayed walking, frequent falling, or toe-walking lead to suspicions of a problem even earlier. The purpose of the National Initiative for Families with Duchenne (NIFD) was to collect information about families of patients with DMD in the United States. The survey sought information about the impact of DMD on the family, provisions of health services, overall wellness of patients and attitudes toward newborn screening for DMD. **Methods**: A total of 212 surveys were completed between November 2007 and January 2009. The surveys were collected by either completing the survey electronically (45%, N= 96) or as part of a larger DMD Natural History Study (55%, N=116) conducted by the Cooperative International Neuromuscular Research Group (CINRG). This analysis presents a subset of the data on the DMD diagnostic process and the impact of the diagnosis on the family. The frequencies of each answer were analyzed. **Results**: Eighty-six percent of families that completed the survey did not report knowledge of a family history of DMD at the time of conception (N= 180/209). In 60% (N=123/203) of families, the parents were the first to raise concerns about their child; this occurred around the average age of 3. In 46% of cases, the diagnosis of DMD was not confirmed until after 5 years of age. Approximately half of families reported that they had obtained most of their knowledge of DMD through the internet. Fifty-one percent of families had another child prior to a positive diagnosis in the older sibling with DMD. **Conclusions**: Preliminary results highlight the importance of early diagnosis on family planning and genetic counseling.

Protocol Name	Case Report Form (CRF) Name	Appended (Yes/No-Duplicate)
Evaluation of Limb Girdle muscular dystrophy	Diagnosis Form	Yes
	Inclusion/Exclusion Form	Yes
	Demographics Form	Yes
	6 Minute Walk Test Form	Yes
	LGMD History Form	Yes
	Vitals and Physical and Neurological Exam Form	Yes
	Cardiology Form	Yes
	Laboratory Form	Yes
	Activity Limit Survey	Yes
	Concomitant Medication Form	Yes
	Adverse Event Form	Yes
	Follow-Up Form	Yes
Comparative Study of Clinical Endpoints in DMD: HHM vs. CQMS protocol	Diagnosis Review v1.0	No-Duplicate
	DMD Genetic Confirmation v1.0	Yes
	Inclusion/Exclusion v1.0	No-Duplicate
	Demographics v1.1	No-Duplicate
	Hand Held Myometry v1.0	Yes
	Adverse Event v1.1	No-Duplicate
Cardiac Outcome Measures in Children with muscular dystrophy & Cardiac Magnetic Resonance: A Parallel Protocol to Cardiac Outcome Measures in Children with muscular dystrophy	Cardiac Outcomes Demographics v1.1	No-Duplicate
	Diagnosis Review v1.0	No-Duplicate
	Inclusion/Exclusion v1.0	No-Duplicate
	Inclusion/Exclusion MRI v1.0	No-Duplicate
	Medication History v1.0	Yes
	Medical and Surgical Events v1.0	Yes
	Laboratory Collection v1.0	Yes
	Cardiology v1.1	Yes
	Central Cardiology Read	Yes
	Central MRI Read	Yes
	Adverse Event v1.0	No-Duplicate
**Note: "Duplicate" indicates the CRF is similar between protocols and has not been attached.*		

Evaluation of Limb Girdle Muscular Dystrophy

Subject Number: __ __ -- __ __ __	Subject Initials: __ __ __	Page 1 of 21

Diagnosis Form

Clinical Symptoms - To be completed by designated CINRG site staff

1. Has the participant been clinically diagnosed with Limb-Girdle or Becker muscular dystrophy? ☐ LGMD ☐ BMD
2. Was diagnosis made by muscle biopsy? ☐ No ☐ Yes

   If YES,

   3. Testing performed on:

☐ Subject ☐ Sibling ☐ Parent ☐ Maternal cousin ☐ Maternal uncle ☐ Other: _____

   4. Was a de-identified copy of the muscle biopsy report faxed to the CINRG genetic counselor? ☐ No ☐ Yes
5. Was diagnosis made by DNA testing? ☐ No ☐ Yes

   If YES,

   6. Testing performed on:

☐ Subject ☐ Sibling ☐ Parent ☐ Maternal cousin ☐ Maternal uncle ☐ Other: _____

   7. Was a de-identified copy of the DNA testing report faxed to the CINRG genetic counselor? ☐ No ☐ Yes
8. Age of onset of symptoms: ___ years
9. Presence of slow to moderate progression of weakness? ☐ No ☐ Yes
10. Presence of other affected family members ☐ No ☐ Yes

    If YES,

    11. Family members affected: ☐ Sibling ☐ Parent ☐ Cousin ☐ Other: _____
12. Is the participant able to walk? ☐ No ☐ Yes

    If NO,

    13. Age participant transition to a wheelchair: ___ ___ years

    If LGMD,

    14. Presence of primary involvement of the shoulder and/or pelvic girdle muscles? ☐ No ☐ Yes
    15. Presence of weakness in a typical limb-girdle pattern with the proximal muscles of the lower extremities? ☐ No ☐ Yes
    16. Presence of facial weakness? ☐ No ☐ Yes
17. Comment: _____

To be completed by the CINRG Genetic Counselor

Confirmation by Muscle Biopsy

18. Muscle biopsy performed? ☐ No (go to Q.27) ☐ Yes

If YES,

19. Date of muscle biopsy: _____ / _____ / _____
DD MMM YYYY

20. Biopsy site:
☐ Deltoid
☐ Biceps
☐ Quad
☐ EDB
☐ Other: _____

21. What testing was performed on the biopsy sample?
☐ Immunoblot
☐ Immunohistochemistry

22. If immunoblot was performed:
☐ Normal
☐ Abnormal
Protein tested:
☐ Calpain 3
☐ Dysferlin
☐ Dystrophin
☐ Dystroglycan

23. If immunohistochemistry was performed:
☐ Normal
☐ Abnormal
Protein tested:
☐ Calpain 3
☐ Dysferlin
☐ Dystrophin
☐ Dystroglycan

If immunoblot or immunohistochemistry dystrophin protein tested

24. Presence of residual dystrophin: ☐ No ☐ Yes

25. Participant confirmed by CINRG genetic counselor by muscle biopsy ☐ No ☐ Yes

If NO,

26. Additional information required: _____
_____

Confirmation by DNA Testing for Limb-Girdle

27. DNA Testing for Limb-Girdle? ☐ No (go to Q.39) ☐ Yes

If YES,

28. Date of DNA Testing: _____ / _____ / _____
DD MMM YYYY

29. What was the context of DNA testing? ☐ Research ☐ Clinical

30. What gene was tested?
☐ Dysferlin (2p12)
☐ Calpain 3 (15q15.1)
☐ Fukutin-related protein (19q13.3)

31. Sequence analysis? ☐ No ☐ Yes

32. Mutation scanning? ☐ No ☐ Yes

33. Presence of point mutation (if yes, record the base change):
☐ No point mutation

☐ A		☐ A
☐ T		☐ T
☐ C	__ __ __ __ __ Number	☐ C
☐ G		☐ G

34. Record the amino acid change:

Amino acid			Amino acid	
☐ ala	☐ arg		☐ ala	☐ arg
☐ asn	☐ asp		☐ asn	☐ asp
☐ cys	☐ gln		☐ cys	☐ gln
☐ glu	☐ gly		☐ glu	☐ gly
☐ his	☐ ile	__ __	☐ his	☐ ile
☐ leu	☐ lys	Number	☐ leu	☐ lys
☐ met	☐ phe		☐ met	☐ phe
☐ pro	☐ ser		☐ pro	☐ ser
☐ thr	☐ trp		☐ thr	☐ trp
☐ tyr	☐ val		☐ tyr	☐ val
☐ X			☐ X	

35. Was another type of mutation identified? ☐ No (go to Q.36) ☐ Yes

36. If yes, what type was identified?
☐ Deletion, specifics: _____
☐ Splice site, specifics: _____
☐ Variant of unknown significant, specifics: ___
_____

37. Participant confirmed by CINRG genetic counselor with DNA Testing? ☐ No ☐ Yes

If NO,

38. Additional information required:
_____
_____

Confirmation by DNA Testing for BMD

39. DNA Testing for BMD? ☐ No (form complete) ☐ Yes

If YES,

40. Date of DNA Testing: _____ / _____ / _____
DD MMM YYYY

41. What was the context of DNA testing? ☐ Research ☐ Clinical

42. Who was the DNA testing performed on?
☐ Subject
☐ Subject brother
☐ Subject maternal uncle

43. Method of DNA Testing:
☐ Beggs & Chamberlain PCR
☐ Other PCR
☐ Direct Sequencing Analysis
☐ Fluorescent

☐ Southern Blot
☐ MLPA
☐ MAPH
☐ Other: _____

If Other PCR,

44. List of exons: _____

45. Presence of Large deletion/duplication:
☐ No large deletion/duplication
☐ Single exon
☐ Multiple exons

46. List exons (If promoter enter P): __ __ __ __

47. Is this Large deletion/duplication in frame? ☐ No ☐ Yes

48. Presence of point mutation (if yes, record the base change):
☐ No point mutation

☐ A		☐ A
☐ T		☐ T
☐ C	__ __ __ __ __	☐ C
☐ G	Number	☐ G

49. Record the amino acid change:

Amino acid			Amino acid		
☐ ala	☐ arg		☐ ala	☐ arg	
☐ asn	☐ asp		☐ asn	☐ asp	
☐ cys	☐ gln		☐ cys	☐ gln	
☐ glu	☐ gly		☐ glu	☐ gly	
☐ his	☐ ile		☐ his	☐ ile	
☐ leu	☐ lys	__ __	☐ leu	☐ lys	
☐ met	☐ phe	Number	☐ met	☐ phe	
☐ pro	☐ ser		☐ pro	☐ ser	
☐ thr	☐ trp		☐ thr	☐ trp	
☐ tyr	☐ val		☐ tyr	☐ val	
☐ X			☐ X		

50. Presence of small lesions: insertion or deletion of base pairs (if yes, record the base change):
☐ Insertion ☐ Deletions
__ __ # of base pairs
__ __ __ __ __ to/between __ __ __ __ __

51. Does this result in a downstream amino acid change? ☐ No ☐ Yes

If YES,

52. Record the amino acid change:

Amino acid			Amino acid		
☐ ala	☐ arg		☐ ala	☐ arg	
☐ asn	☐ asp		☐ asn	☐ asp	
☐ cys	☐ gln		☐ cys	☐ gln	
☐ glu	☐ gly		☐ glu	☐ gly	
☐ his	☐ ile		☐ his	☐ ile	
☐ leu	☐ lys	__ __	☐ leu	☐ lys	
☐ met	☐ phe	Number	☐ met	☐ phe	
☐ pro	☐ ser		☐ pro	☐ ser	
☐ thr	☐ trp		☐ thr	☐ trp	
☐ tyr	☐ val		☐ tyr	☐ val	
☐ X			☐ X		

53. Participant confirmed by CINRG genetic counselor with DNA Testing? ☐ No ☐ Yes

If NO,

54. Additional information required: _____

_____

For CINRG Genetic Counselor Use Only	
Date Received by Site and Signature of Staff	
Date CRF was returned by CINRG Genetic Counselor to the CINRG Site	

Inclusion/Exclusion Form

1. Date (DD-Mmm-YYYY):	__ __ -- __ __ __ -- __ __ __ __
INCLUSION CRITERIA	
All questions must be answered YES for participant to be eligible for participation	
Instructions: *Please answer all questions that apply to the participants group.*	
2. Is the participant 18 years of age or older?	☐ Yes ☐ No
3. Is the participant able to travel to test site?	☐ Yes ☐ No
4. Has the participant received medical clearance?	☐ Yes ☐ No If yes, (DD-Mmm-YYYY) __ __ -- __ __ __ -- __ __ __ _
5. Group	☐ LGMD2i/FKRP abnormality ☐ LGMD2a/calpainopathy ☐ LGMD2b/dysferlinopathy ☐ BMD ☐ Healthy Control
LGMD / BMD	
Only answer Questions 6 for the LGMD/BMD participants	
6. Did central genetic counselor confirm diagnosis?	☐ Yes ☐ No
HEALTHY CONTROL	
Only answer Questions 7-9 for the healthy control participants	
7. Participant has no relatives affected with muscular dystrophy?	☐ Yes ☐ No
8. Participant can walk?	☐ Yes ☐ No
9. Participant has no evidence of muscle weakness?	☐ Yes ☐ No
Principal Investigator Signature: _____	

Demographics Form	
Instructions: *Please answer all questions.*	
Date of Informed consent (DD-Mmm-YYYY):	__ __ -- __ __ __ -- __ __ __ __
Gender:	☐ Male ☐ Female
Ethnicity:	☐ Hispanic ☐ Not Hispanic
Race:	☐ American Indian/Alaskan native ☐ Asian ☐ Black/African American ☐ Native Hawaiian or Pacific Islander ☐ White ☐ Other
Date of Birth (DD-Mmm-YYYY):	__ __ -- __ __ __ -- __ __ __ __

6 Minute Walk Test (6MWT) Form

BLOOD PRESSURE

If the pre 6 MWT BP is greater than 140/90 then the 6 MWT should not be done.

Pre 6 minute walk test: _____	Post 6 minute walk test: _____

If the pre 6 MWT heart rate is greater than 100 before the test then the 6 MWT should not be done.

HEART RATE

Pre 6MWT : _____ (beats per minute)	Post 6 MWT: _____ (beats per minute)

Gender: ☐ Male ☐ Female

6 MINUTE WALK INFORMATION

Was the 6 minute walk test attempted? ☐ Yes ☐ No

Reason 6 minute walk test not attempted?	
☐ Non ambulatory	☐ Participant forgot assistive device(s)
☐ BP or heart rate too high	☐ Refused
	☐ Staff error

If YES, please answer the following

Date (DD-Mmm-YYYY):	__ __ -- __ __ __ -- __ __ __ __

Total distance walked: Please remember each lap is 40 meters.

Duration of walk:	☐ 6 minutes ☐ Other
If Duration of walk is Other, specify time:	__ __ __ (minutes) __ __ __ (seconds)

Assistive Walking Devices Used:		Symptoms at end of exercise:	
☐ None	☐ Two Crutches	☐ None	☐ Joint Pain
☐ Straight Cane	☐ Standard Walker	☐ Fatigue	☐ Muscle Tightness
☐ Wide-Based Cane	☐ Rolling Walker	☐ Shortness of Breath	☐ Muscle Twitching
☐ One Crutch	☐ Other	☐ Angina	☐ Muscle Cramps
		☐ Dizziness	☐ Other

If Assistive Device is other, specify:	If Symptoms is other, specify:
_____	_____

LGMD History Form

Muscular Dystrophy history collected? ☐ No (form complete) ☐ Yes	
If the Muscular Dystrophy history collected please complete the following:	
Date (DD-Mmm-YYYY):	__ __ -- __ __ __ -- __ __ __ __
Family History of Muscular Dystrophy (check all that apply):	

☐ None	☐ Sister	☐ Paternal Grandfather	☐ Paternal Uncle
☐ Mother	☐ Maternal Grandmother	☐ Maternal Aunt	☐ Maternal 1st cousin
☐ Father	☐ Maternal Grandfather	☐ Maternal Uncle	☐ Paternal 1st cousin
☐ Brother	☐ Paternal Grandmother	☐ Maternal Uncle	☐ Other

If Family History of Muscular Dystrophy is other, specify:	_____

NEUROMUSCULAR SYMPTOM	
Developmental Delay: ☐ Yes ☐ No ☐ Unsure	Family History? ☐ Yes ☐ No ☐ Unsure
Hypotonia: ☐ Yes ☐ No ☐ Unsure	Family History? ☐ Yes ☐ No ☐ Unsure
Abnormal MRI: ☐ Yes ☐ No ☐ Unsure	Family History? ☐ Yes ☐ No ☐ Unsure
Easy Fatigability: ☐ Yes ☐ No ☐ Unsure	Family History? ☐ Yes ☐ No ☐ Unsure
Muscle Weakness: ☐ Yes ☐ No ☐ Unsure	Family History? ☐ Yes ☐ No ☐ Unsure
Cardiomyopathy: ☐ Yes ☐ No ☐ Unsure	Family History? ☐ Yes ☐ No ☐ Unsure
Heart Block: ☐ Yes ☐ No ☐ Unsure	Family History? ☐ Yes ☐ No ☐ Unsure
Muscle Cramps: ☐ Yes ☐ No ☐ Unsure	Family History? ☐ Yes ☐ No ☐ Unsure

VISCERAL SYMPTOM	
Gastrointestinal Reflux: ☐ Yes ☐ No ☐ Unsure	Family History? ☐ Yes ☐ No ☐ Unsure
Diarrhea/Constipation; ☐ Yes ☐ No ☐ Unsure	Family History? ☐ Yes ☐ No ☐ Unsure
Respiratory Involvement/Hypoventilation: ☐ Yes ☐ No ☐ Unsure	Family History? ☐ Yes ☐ No ☐ Unsure
Other: ☐ Yes ☐ No ☐ Unsure	Family History? ☐ Yes ☐ No ☐ Unsure
Specify Other: _____	

MUSCULOSKELETAL SYMPTOM	
Scoliosis: ☐ Yes ☐ No ☐ Unsure	Family History? ☐ Yes ☐ No ☐ Unsure
Achilles Tendon Contractures: ☐ Yes ☐ No ☐ Unsure	Family History? ☐ Yes ☐ No ☐ Unsure
Knee Contractures: ☐ Yes ☐ No ☐ Unsure	Family History? ☐ Yes ☐ No ☐ Unsure
Elbow Contractures: ☐ Yes ☐ No ☐ Unsure	Family History? ☐ Yes ☐ No ☐ Unsure
Neck Contractures: ☐ Yes ☐ No ☐ Unsure	Family History? ☐ Yes ☐ No ☐ Unsure
Other: ☐ Yes ☐ No ☐ Unsure	Family History? ☐ Yes ☐ No ☐ Unsure
Specify Other: _____	

GENERAL DEVELOPMENT	
Language Delay: ☐ Yes ☐ No ☐ Unsure	Family History? ☐ Yes ☐ No ☐ Unsure
Learning Disability: ☐ Yes ☐ No ☐ Unsure	Family History? ☐ Yes ☐ No ☐ Unsure
ADHD/ADD: ☐ Yes ☐ No ☐ Unsure	Family History? ☐ Yes ☐ No ☐ Unsure
Behavioral Problems: ☐ Yes ☐ No ☐ Unsure	Family History? ☐ Yes ☐ No ☐ Unsure
Other: ☐ Yes ☐ No ☐ Unsure	Family History? ☐ Yes ☐ No ☐ Unsure
Specify Other: _____	

LAB TEST RESULTS				
Elevated Transaminases: ☐ Yes ☐ No ☐ Unsure			Family History? ☐ Yes ☐ No ☐ Unsure	
Other: ☐ Yes ☐ No ☐ Unsure			Family History? ☐ Yes ☐ No ☐ Unsure	
Specify Other: _____				
Maximum CPK values (U/L):			Age: _____	
☐ <150	☐ 150-300	☐ 300-1000	☐ 1000-10000	☐ >10000
Optional Second test				
Maximum CPK values (U/L):			Age: _____	
☐ <150	☐ 150-300	☐ 300-1000	☐ 1000-10000	☐ >10000

NERVE CONDUCTION STUDY RESULTS		
☐ Not Done/Inconclusive	☐ Normal	☐ Abnormal (ie. Neuropathic Changes Present)
If Abnormal, please check all that apply below:		
Features (check all that apply):	Pattern (check all that apply):	
☐ Axonal ☐ Nemyelinating ☐ Both ☐ Not Specified	☐ Focal ☐ Peripheral ☐ Radicular ☐ Plexopathy ☐ Not Specified	
Date (DD-Mmm-YYYY):	__ __ -- __ __ __ -- __ __ __ __	

EMG STUDY RESULTS			
☐ Not Done/Inconclusive	☐ Normal	☐ Abnormal	
If Abnormal, please check all that apply below:			
Myopathic Changes:			
☐ Absent	☐ Absent	☐ Proximal	☐ Distal
Neuropathic Changes:			
☐ Absent	☐ Absent	☐ Proximal	☐ Distal
Insertional/Spontaneous Activity:			
☐ Normal	☐ Increased	☐ Decreased	
Other Features (check all that apply):			
☐ Fibrillations ☐ Fasciculations	☐ Myotonia ☐ Distal	☐ Proximal ☐ CRD	

Vitals and Physical and Neurological Exam Form					
Was the physical and neurological exam completed?	☐ No (form complete)	☐ Yes			
If YES, please complete the remaining questions. If NO, form complete.					
Date of Exam (DD-Mmm-YYYY):	__ __ -- __ __ __ -- __ __ __ __				
Temperature: __ __ __ Units:	☐ Celsius	☐ Fahrenheit			
Respiratory rate: __ __ __ (breathes/minute)					
PHYSICAL EXAM					
Skin:	☐ Normal	☐ Abnormal	☐ Not assessed		
	If abnormal, comment: _____				
Head/Neck:	☐ Normal	☐ Abnormal	☐ Not assessed		
	If abnormal, comment: _____				
Thorax/Lungs:	☐ Normal	☐ Abnormal	☐ Not assessed		
	If abnormal, comment: _____				
Cardiac/Circulatory:	☐ Normal	☐ Abnormal	☐ Not assessed		
	If abnormal, comment: _____				
Abdomen/Gastro:	☐ Normal	☐ Abnormal	☐ Not assessed		
	If abnormal, comment: _____				
Urogenital (Tanner Stages):	☐ Not assessed	☐ Abnormal			
	☐ Stage 1	☐ Stage 2	☐ Stage 3	☐ Stage 4	☐ Stage 5
	If abnormal, comment: _____				
Other significant physical findings:	☐ Normal	☐ Abnormal	☐ Not assessed		
	If abnormal, comment: _____				

NEUROLOGICAL EXAM			
Mental Status:	☐ Normal	☐ Abnormal	☐ Not assessed
	If abnormal, comment: _____		
Cranial Nerves:	☐ Normal	☐ Abnormal	☐ Not assessed
	If abnormal, comment: _____		
Coordination:	☐ Normal	☐ Abnormal	☐ Not assessed
	If abnormal, comment: _____		
Sensory:	☐ Normal	☐ Abnormal	☐ Not assessed
	If abnormal, comment: _____		
Upper Limb DT Reflex:	☐ Normal	☐ Abnormal	☐ Not assessed
	If abnormal, comment: _____		
Lower Limb DT Reflex:	☐ Normal	☐ Abnormal	☐ Not assessed
	If abnormal, comment: _____		
Other significant physical findings:	☐ Yes	☐ No	
	If yes, comment: _____		
Scoliosis:	☐ Yes	☐ No	☐ Not assessed
Contractures:	☐ Yes	☐ No	☐ Not assessed
	If yes, location:	☐ Iliotibial Band ☐ Popliteal Angle (knee) ☐ Achiles Tendon ☐ Hip flexors	☐ Finger ☐ Elbow ☐ Other
	If other, comment: _____		

MOTILITY			
Able to stand with assistance:	☐ Normal	☐ Abnormal	☐ Not assessed
Able to stand without assistance:	☐ Normal	☐ Abnormal	☐ Not assessed
Able to take steps:	☐ Normal	☐ Abnormal	☐ Not assessed
Able to lift arms overhead:	☐ Able to reach completely ☐ Able to reach head	☐ Not able ☐ Not assessed	

Cardiology Form

ECHOCARDIOGRAM

Was the echocardiogram completed?		☐ No (form complete) ☐ Yes	
If YES, answer the following questions. If No, go to ECG tab			
Date of Exam (DD-Mmm-YYYY):		__ __ -- __ __ __ -- __ __ __ __	
IVS(d):	__ __ __ (cm)	IVS(s):	__ __ __ (cm)
LVID(d):	__ __ __ (cm)	LVID(s):	__ __ __ (cm)
LVPW(d):	__ __ __ (cm)	LVPW(s):	__ __ __ (cm)
La dimension:	__ __ __ (cm)	Ao root diameter:	__ __ __ (cm)
FS:	__ __ __ (%)	EF:	__ __ __ (%)
LCFC mean:	__ __ __ (circ/s)	LV mass (C)d:	__ __ __ (g)
Mitral valve E wave vel	__ __ __ (cm/sec)	Mitral valve Ea velocity	__ __ __ (cm/sec)

ECG

Was the ECG completed?		☐ No (form complete) ☐ Yes	
If YES, answer the following questions. If No, form complete.			
Date of Exam (DD-Mmm-YYYY):		__ __ -- __ __ __ -- __ __ __ __	
Heart Rate	__ __ __ __ __ (bpm)		
PR interval	__ __ __ __ __ (ms)		
QRS interval	__ __ __ __ __ (ms)		
QTc interval	__ __ __ __ __ (ms)		
ECG Results	☐ Not available ☐ Normal ☐ Abnormal ☐ not clinically significant		
If abnormal,	☐ Abnormal Q waves	☐ Abnormal Q waves	
	☐ Resting Tachycardia	☐ Conduction defects (Right bundle branch block)	
	☐ Nonspecific ST segment changes	☐ Nonspecific ST segment changes	
	☐ Ventricular enlargement	☐ Other	
	Other, specify	_____	

Laboratory Form	
Collection Date (DD-Mmm-YYYY):	__ __ -- __ __ __ -- __ __ __ __
Sample collected for genotyping?	☐ Yes ☐ No
Was sample 1 collected?	Was sample 2 collected?
☐ Yes ☐ No	☐ Yes ☐ No
Sample 1 collection time: __ __ : __ __	Sample 2 collection time: __ __ : __ __
If sample 1 not collected, reason:	If sample 2 not collected, reason:
☐ Staff error ☐ Unable to obtain ☐ Sample lost ☐ Subject refused ☐ Other Other, specify: _____	☐ Staff error ☐ Unable to obtain ☐ Sample lost ☐ Subject refused ☐ Other Other, specify: _____
If shipping: specimens should be shipped on Monday through Thursday using FedEx overnight mail service.	
Was a sample collected and sent to Quest/ CMC lab?	☐ Yes ☐ No
If no, reason:	☐ Staff error ☐ Sample lost ☐ Other ☐ Unable to obtain ☐ Subject refused Other, specify: _____

Sample Received:	
Tube Count	
DNA Extracted	
Sample Processed:	

ACTIVLIM - Activity Limitations Measure
English version

Name:_____ Date:_____

How difficult are the following activities?		Impossible	Difficult	Easy	?
1	Putting on a T-shirt				
2	Washing one's upper body				
3	Dressing one's lower body				
4	Taking a shower				
5	Sitting on the toilet				
6	Taking a bath				
7	Walking dowstairs				
8	Stepping out of a bath tub				
9	Opening a door				
10	Walking outdoors on level ground				
11	Washing one's face				
12	Hanging up a jacket on a hatstand				
13	Wiping one's upper body				
14	Walking upstairs				

To evaluate an **adult** patient (age 16-80), please answer to the following questions.

To evaluate a **child** patient (age 6 -15), please mark the following questions with the "?"

15	Carrying a heavy load	A				
16	Getting into a car	A				
17	Standing for a long time (± 10 min)	A				
18	Walking more than 1 kilometre	A				

To evaluate a **child** patient (age 6-15), please answer to the following questions.

To evaluate an **adult** patient (age 16-80), please mark the following questions with the "?"

19	Closing a door	C				
20	Hopping on one foot	C				
21	Putting on a backpack	C				
22	Running	C				

Order 1

Faculté de Médecine, Unité de Réadaptation et de Médecine Physique, UCL5375, Avenue Mounier 53, 1200 Bruxelles, Belgium. www.rehab-scales.org

Evaluation of Limb Girdle Muscular Dystrophy

Subject Number: __ __ -- __ __ __	Subject Initials: __ __ __	

Concomitant Medication Form

Instructions: *Please list each medication or herbal supplement in a separate row.*

Collection Date (DD-Mmm-YYYY): __ __ -- __ __ __ -- __ __ __ __

Is the participant currently taking any medications or herbal supplements? ☐ Yes ☐ No *

Medication Name	Dose	Unit		Frequency		Route		Indication	Start Date
_____	_____	☐ mg ☐ mL ☐ Tablet ☐ Capsule ☐ mcg	☐ Units ☐ mEq ☐ Puff ☐ Drop ☐ Spray	☐ Once ☐ QD ☐ BID	☐ TID ☐ PRN ☐ Other	☐ Oral ☐ IM ☐ IV ☐ Topical	☐ Inhaled ☐ Rectal ☐ Suq-Q ☐ Other	_____	_____
				Frequency, Other _____		**Route, Other** _____			
_____	_____	☐ mg ☐ mL ☐ Tablet ☐ Capsule ☐ mcg	☐ Units ☐ mEq ☐ Puff ☐ Drop ☐ Spray	☐ Once ☐ QD ☐ BID	☐ TID ☐ PRN ☐ Other	☐ Oral ☐ IM ☐ IV ☐ Topical	☐ Inhaled ☐ Rectal ☐ Suq-Q ☐ Other	_____	_____
				Frequency, Other _____		**Route, Other** _____			

Adverse Event Form

Instructions: *If adverse events experienced, please enter AE details below.*

Were any adverse events experienced? ☐ Yes ☐ No

Description	Serious adverse event?	Start date:	Stop date:	Event related to:	If other, please specify:
	☐ Yes ☐ No			☐ CQMS ☐ Blood draw ☐ Other	
	☐ Yes ☐ No			☐ CQMS ☐ Blood draw ☐ Other	
	☐ Yes ☐ No			☐ CQMS ☐ Blood draw ☐ Other	
	☐ Yes ☐ No			☐ CQMS ☐ Blood draw ☐ Other	
	☐ Yes ☐ No			☐ CQMS ☐ Blood draw ☐ Other	
	☐ Yes ☐ No			☐ CQMS ☐ Blood draw ☐ Other	
	☐ Yes ☐ No			☐ CQMS ☐ Blood draw ☐ Other	
	☐ Yes ☐ No			☐ CQMS ☐ Blood draw ☐ Other	

Follow Up Form			
Able to contact participant for follow up?	☐ Yes	☐ No	
If YES, answer the following:			
Date of Follow Up (DD-Mmm-YYYY):	__ __ -- __ __ __ -- __ __ __ __		
Did you have any adverse events?	☐ Yes	☐ No	
Can we call you in the future for a genetic survey?	☐ Yes	☐ No	☐ Control

Principal Investigator Signature Form

As the study investigator, I confirm that the informed consent was obtained from the participants in accordance with 21CFR Part 50, the rights, safety, and welfare of the participant was protected, and all study assessments and data collection were conducted per the locally approved protocol.

_____ _____

Signature Date

_____

Print Name

B/DMD Genetic Confirmation V1.0
MUSCLE BIOPSY TAB

Title: Muscle Biopsy
Subtitle: Confirmation by Muscle Biopsy for BMD/DMD
Instructions: This section should be filled by CINRG genetic counselor only

1. Muscle biopsy performed?
- ☐ Yes
- ☐ No

If Yes, please answer the following questions:

2. Date of muscle biopsy: __ __ - __ __ __ - __ __ __ __
DD - Mmm - YYYY

3. Was immunoblot performed?
- ☐ Yes
- ☐ No

If question 3 was Yes, please answer question 4 and 6.

4. Dystrophin Size:
- ☐ Absent
- ☐ Normal
- ☐ Decreased
- ☐ Not Applicable/ Not Stated

5. If size provided, amount: _____ (kb)

6. Dystrophin Amount:
- ☐ Absent
- ☐ Normal
- ☐ Decreased
- ☐ Not Applicable/ Not Stated

7. If percent provided, amount: _____ (%)

8. Was immunohistochemistry performed?
- ☐ Yes
- ☐ No

If question 8 was Yes, please answer question 9, 10 and 11.

9. Amino Terminal (ex: By4, Dys3, MAB1690) antibodies results:
- ☐ Not done
- ☐ Normal
- ☐ Mildly Reduced
- ☐ Severely Reduced
- ☐ Absent
- ☐ Unknown

10. Carboxy Terminal (ex: By8, Dys2) antibodies results:
- ☐ Not done
- ☐ Normal
- ☐ Mildly Reduced
- ☐ Severely Reduced
- ☐ Absent
- ☐ Unknown

11. Rod Domain (ex: DyS1, NAB1692) antibodies results:
- ☐ Not done
- ☐ Normal
- ☐ Mildly Reduced
- ☐ Severely Reduced
- ☐ Absent
- ☐ Unknown

Genetic Confirmation Results:

12. Based on the muscle biopsy, the genetic diagnosis is:
- ☐ DMD
- ☐ BMD

13. Participant confirmed by CINRG genetic counselor by muscle biopsy?
- ☐ Yes
- ☐ No

DNA TAB

Title: DNA Testing

Subtitle: Confirmation by DNA Testing for BMD/DMD

Instructions: This section should be filled by CINRG genetic counselor only

14. DNA Testing for the dystrophin gene was performed?
- ☐ Yes
- ☐ No

If Yes, please answer the following questions:

15. Date of DNA Testing: __ __ - __ __ __ - __ __ __ __ (DD - Mmm - YYYY)

16. Was testing performed in a clinical laboratory
- ☐ Yes
- ☐ No

17. Method of DNA Testing (check all that apply):
- ☐ Beggs & Chamberlain PCR
- ☐ Other PCR

If Other PCR, list of exons included: _____

- ☐ Direct Sequencing Analysis
- ☐ Fluorescent
- ☐ Southern Blot
- ☐ MLPA
- ☐ MAPH
- ☐ Other

If other specify: _____

Presence of large deletion/duplication:

18. Results of the deletion/ duplication testing:
- ☐ No large deletion/duplication
- ☐ Single exon deletion
- ☐ Single exon duplication
- ☐ Multiple exon deletion
- ☐ Multiple exon duplication

19. If the mutation includes the promoter, please check:
- ☐ P OR

List single exon number or the starting exon that is included in the mutation: _____ TO _____

20. What is the frameshift of the large deletion/ duplication?
- ☐ In frame
- ☐ Out of frame
- ☐ Unable to determine

If multiple exon deletion/duplication

21. Were all exons in the deletion/ duplication area tested? ☐ Yes ☐ No

22. If No, list exons that were not tested

Point mutation

23. Was a point mutation identified? ☐ Yes ☐ No

24. If Yes, record the nucleotide location:

25. Record the amino acid change:

Small mutation

26. Was a small mutation identified? ☐ Yes ☐ No

If yes, was it an insertion or deletion of base pairs? ☐ Insertion ☐ Deletion # of base pairs location

27. Does this result in a shift of the reading frame? ☐ Yes ☐ No

Variants

28. Were any variants of unknown significance identified? ☐ Yes ☐ No

Genetic Confirmation Results

29. Based on the DNA testing, the genetic diagnosis is? ☐ DMD ☐ BMD

30. Participant confirmed by CINRG genetic counselor with DNA Testing? ☐ Yes ☐ No

Hand Held Myometry V1.0

Title: Day 1

Subtitle: Day 1 Muscle Testing with HHM

Instructions: Please enter first test and second test data at Day 1

Day 1 QMT test with HHM

Please enter the CE initial and date of the test at Day 1

CE Initial: ___ ___ ___ Test Date: __ __ - __ __ __ - __ __ __ __ (DD - Mmm - YYYY)

Did the participant have medical clearance at Day 1? ☐ Yes ☐ No

First Test

Time testing started: ___ ___ : ___ ___ (hh:mm)

Knee Extensors

Right: ___ ___ . ___ Left: ___ ___ . ___

Right: ___ ___ . ___ Left: ___ ___ . ___

Knee Flexors

Right: ___ ___ . ___ Left: ___ ___ . ___

Right: ___ ___ . ___ Left: ___ ___ . ___

Elbow Flexors

Right: ___ ___ . ___ Left: ___ ___ . ___

Right: ___ ___ . ___ Left: ___ ___ . ___

Elbow Extensors

Right: ___ ___ . ___ Left: ___ ___ . ___

Right: ___ ___ . ___ Left: ___ ___ . ___

Time testing ended: ___ ___ : ___ ___ (hh:mm)

Second Test

Time testing started: ___ ___ : ___ ___ (hh:mm)

Knee Extensors

Right: ___ ___ . ___ Left: ___ ___ . ___

Right: ___ ___ . ___ Left: ___ ___ . ___

Knee Flexors

Right: ___ ___ . ___ Left: ___ ___ . ___

Right: ___ ___ . ___ Left: ___ ___ . ___

Elbow Flexors

Right: ___ ___ . ___ Left: ___ ___ . ___

Right: ___ ___ . ___ Left: ___ ___ . ___

Elbow Extensors

Right: ___ ___ . ___ Left: ___ ___ . ___

Right: ___ ___ . ___ Left: ___ ___ . ___

Time testing ended: ___ ___ : ___ ___ (hh:mm)

Title: Day 2
Subtitle: Day 2 Muscle Testing with HHM
Instructions: Please enter first test and second test data at Day 2

Day 2 QMT test with HHM
Please enter the CE initial and date of the test at Day 2

CE Initial: ___ ___ ___ Test Date: __ __ - __ __ __ - __ __ __ __
DD - Mmm - YYYY

Did the participant have medical clearance at Day 2? ☐ Yes ☐ No

First Test

Time testing started: ___ ___ : ___ ___ (hh:mm)

Knee Extensors

Right: ___ ___ . ___ Left: ___ ___ . ___
Right: ___ ___ . ___ Left: ___ ___ . ___

Knee Flexors

Right: ___ ___ . ___ Left: ___ ___ . ___
Right: ___ ___ . ___ Left: ___ ___ . ___

Elbow Flexors

Right: ___ ___ . ___ Left: ___ ___ . ___
Right: ___ ___ . ___ Left: ___ ___ . ___

Elbow Extensors

Right: ___ ___ . ___ Left: ___ ___ . ___
Right: ___ ___ . ___ Left: ___ ___ . ___

Time testing ended: ___ ___ : ___ ___ (hh:mm)

Second Test

Time testing started: ___ ___ : ___ ___ (hh:mm)

Knee Extensors

Right: ___ ___ . ___ Left: ___ ___ . ___
Right: ___ ___ . ___ Left: ___ ___ . ___

Knee Flexors

Right: ___ ___ . ___ Left: ___ ___ . ___
Right: ___ ___ . ___ Left: ___ ___ . ___

Elbow Flexors

Right: ___ ___ . ___ Left: ___ ___ . ___
Right: ___ ___ . ___ Left: ___ ___ . ___

Elbow Extensors

Right: ___ ___ . ___ Left: ___ ___ . ___
Right: ___ ___ . ___ Left: ___ ___ . ___

Time testing ended: ___ ___ : ___ ___ (hh:mm)

Cardiac Outcomes Medication History V.CTSA.1.0

Title: Collection of previous and current Cardiac Medication and CoQ10 use

Subtitle: Information on previous and current use of cardiac medications and coenzyme Q10 should be entered in this form.

Instructions: Please list each medication in a separate row. Click on the ADD button to add additional medications.

Cardiac tab

Please indicate the date the medication history was collected.

Date: ___ ___ - ___ ___ ___ - ___ ___ ___ ___ DD-Mmm-YYYY

Has the participant currently or ever taken any cardiac medication?

☐ Yes ☐ No

If Cardiac medication(s) use is confirmed, please enter details below.

Cardiac medication name	Dose	Unit	Regimen	If other, specify regimen	Total lifetime use (years)	Use ongoing?
		☐ mg ☐ mcg ☐ mL ☐ Units ☐ Tablet ☐ mEq ☐ Capsule	☐ Once ☐ TID ☐ QD ☐ PRN ☐ BID ☐ Other			☐ Yes ☐ No
		☐ mg ☐ mcg ☐ mL ☐ Units ☐ Tablet ☐ mEq ☐ Capsule	☐ Once ☐ TID ☐ QD ☐ PRN ☐ BID ☐ Other			☐ Yes ☐ No
		☐ mg ☐ mcg ☐ mL ☐ Units ☐ Tablet ☐ mEq ☐ Capsule	☐ Once ☐ TID ☐ QD ☐ PRN ☐ BID ☐ Other			☐ Yes ☐ No

Has the participant currently or ever taken any CoQ10 supplement?

- ☐ Yes
- ☐ No

If CoQ10 use is confirmed, please enter details below.

Dose (mg)	Regimen	If other, specify regimen	Total lifetime use (years)	Use ongoing?
	☐ Once ☐ TID ☐ QD ☐ PRN ☐ BID ☐ Other			☐ Yes ☐ No
	☐ Once ☐ TID ☐ QD ☐ PRN ☐ BID ☐ Other			☐ Yes ☐ No

Title: Collection of previous and current Corticosteroids use
Subtitle: Information on previous and current use of corticosteroids should be entered in this form.
Instructions: Please list each medication in a separate row. Click on the ADD button to add additional medications.

Steroids tab

Has the participant currently or ever taken any steroid medication?

☐ Yes
☐ No

If Steroid medication(s) use is confirmed, please enter details below.

Steroid medication name	Dose (mg)	Regimen	If other, specify regimen	Total lifetime use (years)	Use ongoing?
☐ Prednisone ☐ Prednisolone ☐ Deflazacort		☐ Once a day ☐ Two days a week ☐ Twice a day ☐ Ten days on/ten days off ☐ Every other day ☐ Other			☐ Yes ☐ No
☐ Prednisone ☐ Prednisolone ☐ Deflazacort		☐ Once a day ☐ Two days a week ☐ Twice a day ☐ Ten days on/ten days off ☐ Every other day ☐ Other			☐ Yes ☐ No
☐ Prednisone ☐ Prednisolone ☐ Deflazacort		☐ Once a day ☐ Two days a week ☐ Twice a day ☐ Ten days on/ten days off ☐ Every other day ☐ Other			☐ Yes ☐ No

Title: Collection of current Medications/ Supplements use
Subtitle: Information on all other current medications and supplements should be entered in this form.
Instructions: Please list each medication in a separate row. Click on the ADD button to add additional medications.

Con Meds tab

Is the participant currently on any other medication/supplement?

☐ Yes
☐ No

If currently is taking other medication please enter details below.

Medication/ Supplement name	Dose	Unit	Regimen	If other, specify regimen	Total lifetime use (years)	Indication
		☐ mg ☐ mcg ☐ Puff ☐ mL ☐ Units ☐ Drop ☐ Tablet ☐ mEq ☐ Spray ☐ Capsule	☐ Once ☐ TID ☐ QD ☐ PRN ☐ BID ☐ Other			
		☐ mg ☐ mcg ☐ Puff ☐ mL ☐ Units ☐ Drop ☐ Tablet ☐ mEq ☐ Spray ☐ Capsule	☐ Once ☐ TID ☐ QD ☐ PRN ☐ BID ☐ Other			
		☐ mg ☐ mcg ☐ Puff ☐ mL ☐ Units ☐ Drop ☐ Tablet ☐ mEq ☐ Spray ☐ Capsule	☐ Once ☐ TID ☐ QD ☐ PRN ☐ BID ☐ Other			

Con Meds tab (con't)

Medication/ Supplement name	Dose	Unit	Regimen	If other, specify regimen	Total lifetime use (years)	Indication
		☐ mg ☐ mcg ☐ Puff ☐ mL ☐ Units ☐ Drop ☐ Tablet ☐ mEq ☐ Spray ☐ Capsule	☐ Once ☐ TID ☐ QD ☐ PRN ☐ BID ☐ Other			
		☐ mg ☐ mcg ☐ Puff ☐ mL ☐ Units ☐ Drop ☐ Tablet ☐ mEq ☐ Spray ☐ Capsule	☐ Once ☐ TID ☐ QD ☐ PRN ☐ BID ☐ Other			
		☐ mg ☐ mcg ☐ Puff ☐ mL ☐ Units ☐ Drop ☐ Tablet ☐ mEq ☐ Spray ☐ Capsule	☐ Once ☐ TID ☐ QD ☐ PRN ☐ BID ☐ Other			
		☐ mg ☐ mcg ☐ Puff ☐ mL ☐ Units ☐ Drop ☐ Tablet ☐ mEq ☐ Spray ☐ Capsule	☐ Once ☐ TID ☐ QD ☐ PRN ☐ BID ☐ Other			

If additional medication/supplements are taken please copy this page to enter additional data.

Cardiac Outcomes Medical and Surgical Events V.CTSA.1.0

Title: Collection of major medical events
Subtitle: Major previous and current medical events
Instructions: Any major medical events should be listed in this form.

Medical Events tab

Please indicate the date the medical and surgical events were collected.

Date: ___ ___ - ___ ___ ___ - ___ ___ ___ ___ DD-Mmm-YYYY

Has the participant experienced any past and/or ongoing medical events?

☐ Yes
☐ No

If the participant experienced past or ongoing medical events, please list them below:

Name of event	Start date DD-Mmm-YYYY	Resolved?
	___ ___ - ___ ___ ___ - ___ ___ ___ ___	☐ Yes ☐ No
	___ ___ - ___ ___ ___ - ___ ___ ___ ___	☐ Yes ☐ No
	___ ___ - ___ ___ ___ - ___ ___ ___ ___	☐ Yes ☐ No
	___ ___ - ___ ___ ___ - ___ ___ ___ ___	☐ Yes ☐ No
	___ ___ - ___ ___ ___ - ___ ___ ___ ___	☐ Yes ☐ No

Title: Collection of surgical events
Subtitle: Previous and current surgical events
Instructions: All past surgical events should be listed in this form.

Surgical Events tab

Has the participant experienced any previous surgeries? ☐ Yes ☐ No

If the participant experienced previous surgeries please list them below:

Name of surgery	**Date** DD-Mmm-YYYY
	__ __ - __ __ __ - __ __ __ __
	__ __ - __ __ __ - __ __ __ __
	__ __ - __ __ __ - __ __ __ __
	__ __ - __ __ __ - __ __ __ __
	__ __ - __ __ __ - __ __ __ __

Cardiac Outcomes Laboratory Collection V.CTSA.1.0

Title: Laboratory information
Instructions: Please enter all laboratory information

Was BNP collected? ☐ Yes ☐ No

If BNP was not collected, reason: ☐ Staff error ☐ Unable to obtain ☐ Sample lost ☐ Participant refused ☐ Other If other, specify:

If sample collected please complete the following:

Collection date: ___ ___ - ___ ___ ___ - ___ ___ ___ ___ DD-Mmm-YYYY

Collection time: ___ ___ : ___ ___ (hh:mm (24 hour clock))

BNP value: _____ (pg/mL)

Cardiac Outcomes Cardiology V.CTSA.1.2

Title: Site ECG and ECHO information
Subtitle: This form is for the site to complete.
Instructions: Please answer all ECG and ECHO questions.

Weight: _____ (kg)

Enter standing height or ulnar length (if participant cannot stand) and age.
Once the form is saved the calculated height will be calculated.

Standing Height: _____ (cm) Ulnar length: _____ (cm) Age: _____ (years)

Calculated Height: (cm)

ECG

Was the ECG completed? ☐ Yes ☐ No

Date of exam: ___ - _____ - _____
DD - Mmm - YYYY

Echocardiogram

Was the echocardiogram completed? ☐ Yes ☐ No

Date of exam: ___ - _____ - _____
DD - Mmm - YYYY

If the ECHO was done please answer the following questions. If No, the form is finished.

Positioning:
- ☐ Lateral decubitus position
- ☐ Lay flat
- ☐ Wheelchair bound - reclined
- ☐ Not able to recline

Once participant is positioned, collect Blood pressure.

Was blood pressure collected? ☐ Yes ☐ No

If no, reason:
- ☐ Staff error
- ☐ Unable to obtain
- ☐ Participant refused
- ☐ Other

Blood pressure: _____ / _____

Image quality: ☐ Excellent ☐ Good ☐ Fair ☐ Poor

Did you save images on CDs? ☐ Yes ☐ No

If no, reason:
- ☐ Staff error
- ☐ Technical problem

ECHO machine model: _____

ECHO machine brand: _____

Title: McCaffrey
Subtitle: This section is for Dr McCaffrey to complete.
Instructions: This tab is only for Dr McCaffrey to enter his data from the ECG and ECHO read.

Date ECG and ECHO read: ___ - _____ - _____
DD - Mmm - YYYY

ECG

Was the ECG done? ☐ Yes ☐ No

If yes, was it readable? ☐ Yes ☐ No

If the ECG is readable please answer the following questions.

Heart Rate: _____ (bpm)

Heart Rhythm:
- ☐ Normal
- ☐ Tachycardia
- ☐ Ventricular Fibrillation
- ☐ Ventricular Flutter
- ☐ Atrial Fibrillation
- ☐ Atrial Flutter
- ☐ Paroxysmal Supraventricular Tachycardia (PSVT)
- ☐ Wolf-Parkinson-White Syndrome
- ☐ Bradycardia
- ☐ Heart Blocks

ECG Results:
- ☐ Not available
- ☐ Normal
- ☐ Abnormal- not clinically significant
- ☐ Abnormal- clinically significant

If ECG Abnormal-clinically significant
- ☐ Abnormal Q waves
- ☐ Increased R/S ratio (V3)
- ☐ Resting Tachycardia
- ☐ Conduction defects (Right bundle branch block)
- ☐ Nonspecific ST segment changes
- ☐ Atrial enlargement
- ☐ Ventricular enlargement
- ☐ Other

Other, specify _____

Echocardiogram

Was the echocardiogram completed?	☐ Yes ☐ No	If yes, was it interpretable?	☐ Yes ☐ No

If the ECHO is interpretable please answer the following questions.

Left ventricular internal diameter (diastole):	____ . ____ (cm)	Left ventricular internal diameter (systole):	____ . ____ (cm)
Fractional shortening:	____ ____ (%)		
Ejection fraction:	____ ____ (%)		
Wall stress:	____ ____ (g/cm^2)		
Ejection time (Spectral Doppler):	____ ____ ____ (msec)	Ejection time (Tissue Doppler):	____ ____ ____ (msec)
Isovolumic Relaxation Time (IRT Spectral Doppler):	____ ____ ____ (msec)	Isovolumic Relaxation Time (IRT Tissue Doppler):	____ ____ ____ (msec)
Isovolumic Contraction Time (ICT Spectral Doppler):	____ ____ ____ (msec)	Isovolumic Contraction Time (ICT Tissue Doppler):	____ ____ ____ (msec)
Velocity of circumferential shortening (vcf):	____ ____ . ____ ____ (circ/sec)		
Velocity of circumferential shortening corrected for heart rate (vcfc):	____ ____ . ____ ____ (circ/sec)		
Myocardial performance index (Spectral Doppler):	____ ____ . ____ ____ (msec)	Myocardial performance index (Tissue Doppler):	____ ____ . ____ ____ (msec)
TDI Septal peak E' Vel:	____ ____ . ____ (cm/sec)		
TDI Lat LV peak E' Vel:	____ ____ . ____ (cm/sec)		
Mitral E wave:	____ ____ ____ (cm/sec)		
Mitral A wave:	____ ____ ____ (cm/sec)		

Title: Spurney
Subtitle: This section is for Dr Spurney to complete.
Instructions: This tab is only for Dr Spurney to enter his data from the ECG and ECHO read.

Date ECG and ECHO read: ___ - _____ - _____
DD - Mmm - YYYY

ECG

Was the ECG done? ☐ Yes ☐ No

If yes, was it readable? ☐ Yes ☐ No

If the ECG is readable please answer the following questions.

Heart Rate: _____ (bpm)

Heart Rhythm:
- ☐ Normal
- ☐ Tachycardia
- ☐ Ventricular Fibrillation
- ☐ Ventricular Flutter
- ☐ Atrial Fibrillation
- ☐ Atrial Flutter
- ☐ Paroxysmal Supraventricular Tachycardia (PSVT)
- ☐ Wolf-Parkinson-White Syndrome
- ☐ Bradycardia
- ☐ Heart Blocks

ECG Results:
- ☐ Not available
- ☐ Normal
- ☐ Abnormal- not clinically significant
- ☐ Abnormal- clinically significant

If ECG Abnormal-clinically significant
- ☐ Abnormal Q waves
- ☐ Increased R/S ratio (V3)
- ☐ Resting Tachycardia
- ☐ Conduction defects (Right bundle branch block)
- ☐ Nonspecific ST segment changes
- ☐ Atrial enlargement
- ☐ Ventricular enlargement
- ☐ Other

Other, specify _____

Echocardiogram

Was the echocardiogram completed?	☐ Yes ☐ No	If yes, was it interpretable?	☐ Yes ☐ No

If the ECHO is interpretable please answer the following questions.

Left ventricular internal diameter (diastole):	____ . ____ (cm)	Left ventricular internal diameter (systole):	____ . ____ (cm)
Fractional shortening:	____ ____ (%)		
Ejection fraction:	____ ____ (%)		
Wall stress:	____ ____ (g/cm^2)		
Ejection time (Spectral Doppler):	____ ____ ____ (msec)	Ejection time (Tissue Doppler):	____ ____ ____ (msec)
Isovolumic Relaxation Time (IRT Spectral Doppler):	____ ____ ____ (msec)	Isovolumic Relaxation Time (IRT Tissue Doppler):	____ ____ ____ (msec)
Isovolumic Contraction Time (ICT Spectral Doppler):	____ ____ ____ (msec)	Isovolumic Contraction Time (ICT Tissue Doppler):	____ ____ ____ (msec)
Velocity of circumferential shortening (vcf):	____ ____ . ____ ____ (circ/sec)		
Velocity of circumferential shortening corrected for heart rate (vcfc):	____ ____ . ____ ____ (circ/sec)		
Myocardial performance index (Spectral Doppler):	____ ____ . ____ ____ (msec)	Myocardial performance index (Tissue Doppler):	____ ____ . ____ ____ (msec)
TDI Septal peak E' Vel:	____ ____ . ____ (cm/sec)		
TDI Lat LV peak E' Vel:	____ ____ . ____ (cm/sec)		
Mitral E wave:	____ ____ ____ (cm/sec)		
Mitral A wave:	(cm/sec)		

Cardiac Outcomes MRI v1.0
Section: Measurements
To be completed by the Coordinator ONLY

Was the MRI done?

- ☐ Yes
- ☐ No
- ☐ Did not agree to MRI protocol

If the MRI was done, please answer the following:

Date: __ __ - __ __ __ - __ __ __ __
DD - Mmm - YYYY

Weight: _____ (kg)

Enter standing height or ulnar length (if participant cannot stand) and age.
Once the form is saved the calculated height will be calculated.

Standing Height: _____ (cm) Ulnar length: _____ (cm) Age: _____ (years)

Calculated Height: (cm)

Hematocrit: __ __ (%)

To be completed by the Central MRI Reader ONLY

Was the MRI readable?	☐ Yes ☐ No		
Date:	__ __ - __ __ __ - __ __ __ __ DD - Mmm - YYYY		
Mean circumferential strain:	__ __ (%)		
Lambda:	__ __ (%)	Ve:	
Global Ve maximal:	__ __ (%)	Global Ve remote:	__ __ (%)

LVEF:	__ __ (%)	Index:
LVSV:	__ __ __ (ml)	Index:
LVEDV:	__ __ __ (ml)	Index:
LVESV:	__ __ __ (ml)	Index:
LVEDD Mass:	__ __ __ (g)	Index:
LVEDS Mass:	__ __ __ (g)	Index:
LVIDD:	__ __ __ (mm)	Index:
LVISD:	__ __ __ (mm)	Index:
Fractional Shortening:	__ __ (%)	Index:
Anteroseptal:	__ __ __ (mm)	Index:
Posterolateral:	__ __ __ (mm)	Index:
Maximum:	__ __ __ (mm)	Index:
Aortic Root:	__ __ (mm)	Index:
Left atrial linear dimension:	__ __ (mm)	Index:

Mitral valve regurgitation:	☐ None	☐ Mild	☐ Moderate	☐ Severe
Aortic valve regurgitation:	☐ None	☐ Mild	☐ Moderate	☐ Severe
Tricuspid valve regurgitation:	☐ None	☐ Mild	☐ Moderate	☐ Severe

Title: Summary of Cardiac MRI Findings

LAD Territory				
LAD Territory:	Rest Function:	Viability:	Rest Perfusion:	Stress Perfusion:
1. Basal Anterior	☐ Normal ☐ Hypokinetic ☐ Akinetic ☐ Dyskinetic ☐ Anuerysmal	☐ Normal ☐ Patchy atypical ☐ Midwall atypical ☐ Subepicardial atypical ☐ 0-25% ☐ 26-50% ☐ 51-75% ☐ >75%		
2. Basal AnteroSeptal	☐ Normal ☐ Hypokinetic ☐ Akinetic ☐ Dyskinetic ☐ Anuerysmal	☐ Normal ☐ Patchy atypical ☐ Midwall atypical ☐ Subepicardial atypical ☐ 0-25% ☐ 26-50% ☐ 51-75% ☐ >75%		
7. Mid Anterior	☐ Normal ☐ Hypokinetic ☐ Akinetic ☐ Dyskinetic ☐ Anuerysmal	☐ Normal ☐ Patchy atypical ☐ Midwall atypical ☐ Subepicardial atypical ☐ 0-25% ☐ 26-50% ☐ 51-75% ☐ >75%		

LAD Territory:	Rest Function:	Viability:	Rest Perfusion:	Stress Perfusion:
8. Mid Anteroseptal	☐ Normal ☐ Hypokinetic ☐ Akinetic ☐ Dyskinetic ☐ Anuerysmal	☐ Normal ☐ Patchy atypical ☐ Midwall atypical ☐ Subepicardial atypical ☐ 0-25% ☐ 26-50% ☐ 51-75% ☐ >75%		
13. Apical Anterior	☐ Normal ☐ Hypokinetic ☐ Akinetic ☐ Dyskinetic ☐ Anuerysmal	☐ Normal ☐ Patchy atypical ☐ Midwall atypical ☐ Subepicardial atypical ☐ 0-25% ☐ 26-50% ☐ 51-75% ☐ >75%		
14. Apical Septal	☐ Normal ☐ Hypokinetic ☐ Akinetic ☐ Dyskinetic ☐ Anuerysmal	☐ Normal ☐ Patchy atypical ☐ Midwall atypical ☐ Subepicardial atypical ☐ 0-25% ☐ 26-50% ☐ 51-75% ☐ >75%		

LAD Territory:	Rest Function:	Viability:	Rest Perfusion:	Stress Perfusion:
17. Apex	☐ Normal ☐ Hypokinetic ☐ Akinetic ☐ Dyskinetic ☐ Anuerysmal	☐ Normal ☐ Patchy atypical ☐ Midwall atypical ☐ Subepicardial atypical ☐ 0-25% ☐ 26-50% ☐ 51-75% ☐ >75%		
RCA Territory				
RCA Territory:	Rest Function:	Viability:	Rest Perfusion:	Stress Perfusion:
3. Basal Inferoseptal	☐ Normal ☐ Hypokinetic ☐ Akinetic ☐ Dyskinetic ☐ Anuerysmal	☐ Normal ☐ Patchy atypical ☐ Midwall atypical ☐ Subepicardial atypical ☐ 0-25% ☐ 26-50% ☐ 51-75% ☐ >75%		
4. Basal Inferior	☐ Normal ☐ Hypokinetic ☐ Akinetic ☐ Dyskinetic ☐ Anuerysmal	☐ Normal ☐ Patchy atypical ☐ Midwall atypical ☐ Subepicardial atypical ☐ 0-25% ☐ 26-50% ☐ 51-75% ☐ >75%		

RCA Territory:	Rest Function:	Viability:	Rest Perfusion:	Stress Perfusion:
9. Mid Inferoseptal	☐ Normal ☐ Hypokinetic ☐ Akinetic ☐ Dyskinetic ☐ Anuerysmal	☐ Normal ☐ Patchy atypical ☐ Midwall atypical ☐ Subepicardial atypical ☐ 0-25% ☐ 26-50% ☐ 51-75% ☐ >75%		
10. Mid Inferior	☐ Normal ☐ Hypokinetic ☐ Akinetic ☐ Dyskinetic ☐ Anuerysmal	☐ Normal ☐ Patchy atypical ☐ Midwall atypical ☐ Subepicardial atypical ☐ 0-25% ☐ 26-50% ☐ 51-75% ☐ >75%		
15. Apical Inferior	☐ Normal ☐ Hypokinetic ☐ Akinetic ☐ Dyskinetic ☐ Anuerysmal	☐ Normal ☐ Patchy atypical ☐ Midwall atypical ☐ Subepicardial atypical ☐ 0-25% ☐ 26-50% ☐ 51-75% ☐ >75%		

Circumflex Territory				
Circumflex Territory:	Rest Function:	Viability:	Rest Perfusion:	Stress Perfusion:
5. Basal Inferolateral	☐ Normal ☐ Hypokinetic ☐ Akinetic ☐ Dyskinetic ☐ Anuerysmal	☐ Normal ☐ Patchy atypical ☐ Midwall atypical ☐ Subepicardial atypical ☐ 0-25% ☐ 26-50% ☐ 51-75% ☐ >75%		
6. Basal Anterolateral	☐ Normal ☐ Hypokinetic ☐ Akinetic ☐ Dyskinetic ☐ Anuerysmal	☐ Normal ☐ Patchy atypical ☐ Midwall atypical ☐ Subepicardial atypical ☐ 0-25% ☐ 26-50% ☐ 51-75% ☐ >75%		
11. Mid Inferolateral	☐ Normal ☐ Hypokinetic ☐ Akinetic ☐ Dyskinetic ☐ Anuerysmal	☐ Normal ☐ Patchy atypical ☐ Midwall atypical ☐ Subepicardial atypical ☐ 0-25% ☐ 26-50% ☐ 51-75% ☐ >75%		

Circumflex Territory:	Rest Function:	Viability:	Rest Perfusion:	Stress Perfusion:
12. Mid Anterolateral	☐ Normal ☐ Hypokinetic ☐ Akinetic ☐ Dyskinetic ☐ Anuerysmal	☐ Normal ☐ Patchy atypical ☐ Midwall atypical ☐ Subepicardial atypical ☐ 0-25% ☐ 26-50% ☐ 51-75% ☐ >75%		
16. Apical Lateral	☐ Normal ☐ Hypokinetic ☐ Akinetic ☐ Dyskinetic ☐ Anuerysmal	☐ Normal ☐ Patchy atypical ☐ Midwall atypical ☐ Subepicardial atypical ☐ 0-25% ☐ 26-50% ☐ 51-75% ☐ >75%		