

**RESEARCH PARTICIPATION IN THE DUCHENNE MUSCULAR DYSTROPHY
COMMUNITY: PARENT PERCEIVED BARRIERS AND THEIR IMPACT ON
FAMILIES**

by

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ABSTRACT

Duchenne Muscular Dystrophy (DMD) is a rare, X-linked degenerative neuromuscular disorder causing severe progressive muscle loss and premature death. While research in DMD is critical to advance treatment and care it also presents many challenges and sacrifices for families who are asked to participate. These barriers and impacts families incur can affect recruitment of research participants. Poor recruitment constrains the ability to achieve and measure progress in clinical research, and consequently affects how well new therapies perform in the clinical setting. The purpose of the present study was to identify family barriers to research recruitment and participation in DMD research and to explore how these barriers impact families.

In collaboration with the Cooperative International Neuromuscular Research Group (CINRG) academic clinical research network and associated Muscular Dystrophy Association (MDA) clinics, this qualitative study included parent-centered focus groups that were conducted at five sites: Pittsburgh, PA; Washington, DC; Minneapolis, MN; Houston, TX; and Sacramento, CA. A total of eight guided focus groups attended by 28 parents of boys or young men with DMD were audio-recorded and transcribed. Qualitative thematic analysis of focus

group transcripts was conducted to identify themes. Major themes identified as perceived barriers to research participation included: 1) commitments; 2) fighting a new battle; and 3) the gamble. Parents described the familial impacts of these barriers, which included financial burdens, family sacrifices, and psychological stress.

Participating in research was shown to affect many aspects of participants' lives and additionally had an impact on the entire family. These findings highlight the need for greater support and appropriate resources to alleviate potential barriers faced by families. Genetic counselors are well suited to communicate research opportunities, address the specific needs of families, and assist with development of strategies to engage the DMD community in research. Identifying barriers of research participation and understanding how these barriers may impact families have significant public health implications which can provide information to improve research protocols, facilitate development of family resources, and influence public health policies to provide additional support to families and encourage greater research involvement.

TABLE OF CONTENTS

1.0	INTRODUCTION.....	1
2.0	RESEARCH QUESTIONS AND SPECIFIC AIMS	3
2.1	RESEARCH QUESTIONS.....	3
2.2	SPECIFIC AIMS	3
3.0	BACKGROUND AND SIGNIFICANCE	4
3.1	DUCHENNE MUSCULAR DYSTROPHY	4
3.1.1	Molecular Genetics	4
3.1.2	Inheritance.....	5
3.1.3	Clinical Course.....	5
3.2	DMD AND RARE DISEASE RESEARCH	7
3.2.1	Classification of Research	7
3.2.2	Importance of Rare Disease Research	8
3.2.2.1	Public Health Impact.....	9
3.2.2.2	Promising Treatment Strategies for DMD	10
3.2.3	Recruitment and Retention Challenges	11
3.2.3.1	Limited Patient Population	12
3.2.3.2	Diagnostic Delays and Disease Complexity	12
3.2.3.3	Study Design	13

3.2.3.4	Limited Resources.....	14
3.3	FAMILIAL PERCEPTIONS OF RESEARCH PARTICIPATION	15
3.3.1	Motivations and Perceived Benefits	16
3.3.1.1	Altruism	16
3.3.1.2	Personal Benefit.....	16
3.3.1.3	Hope.....	17
3.3.1.4	Trust and Positive Relationships	17
3.3.2	Therapeutic Misconception and Blind Optimism.....	19
3.3.3	Potential Barriers.....	21
3.3.3.1	Disease-Related Challenges.....	21
3.3.3.2	Uncertainty	23
3.3.3.3	Consent Process.....	24
3.3.3.4	Negative Experiences	25
3.4	QUALITATIVE RESEARCH.....	26
4.0	DESIGN AND METHODS	28
4.1	PERSONAL DISCLOSURE STATEMENT	28
4.2	STRATEGIES FOR ENGAGING THE DMD COMMUNITY IN RESEARCH.....	29
4.2.1	Participant Recruitment.....	29
4.2.2	Focus Groups.....	31
4.3	THEMATIC ANALYSIS.....	32
4.3.1	Familiarization with the Data	33
4.3.2	Coding.....	33

4.3.3	Theme Identification.....	35
4.3.3.1	Pawing Through the Data	36
4.3.3.2	Color-Coding and Sorting.....	36
4.3.3.3	Key Words in Context	37
4.3.4	Review of Themes	37
4.3.5	Defining Themes.....	38
4.3.6	Final Analysis	38
4.4	RELIABILITY AND VALIDITY	39
5.0	RESULTS	41
5.1	DEMOGRAPHICS.....	41
5.1.1	Parent Demographics	41
5.1.2	Demographics of Son(s) with DMD.....	44
5.2	BARRIERS OF RESEARCH PARTICIPATION	45
5.2.1	Commitments	46
5.2.2	Fighting a New Battle	48
5.2.3	The Gamble	51
5.3	IMPACT OF RESEARCH BARRIERS ON FAMILIES.....	54
5.3.1	Financial Burden.....	55
5.3.2	Family Sacrifices	57
5.3.3	Psychological Stress	58
6.0	DISCUSSION	62
6.1	BARRIERS OF RESEARCH PARTICIPATION	62
6.2	IMPACT OF RESEARCH BARRIERS ON FAMILIES.....	69

6.3	POTENTIAL IMPLICATIONS FOR GENETIC COUNSELORS	72
6.4	STUDY LIMITATIONS	73
6.5	FUTURE RESEARCH.....	75
6.6	CONCLUSIONS	78
APPENDIX A: IRB APPROVAL LETTERS.....		80
APPENDIX B: LETTERS OF SUPPORT		82
APPENDIX C: PARENT PARTICIPANT RECRUITMENT FLYER		87
APPENDIX D: PARENT PARTICIPANT CONSENT FORM.....		89
APPENDIX E: PARENT PARTICIPANT FOCUS GROUP GUIDES		94
	E1: PARENTS INVOLVED IN RESEARCH	94
	E2: PARENTS NOT INVOLVED IN RESEARCH.....	97
APPENDIX F: PARENT PARTICIPANT DEMOGRAPHIC FORM		99
BIBLIOGRAPHY.....		103

LIST OF TABLES

Table 1. Participant Demographics.....	43
Table 2. Parent Reported Demographics of Son(s) with DMD.....	45
Table 3. Prevalence of Identified Barriers	46

PREFACE

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1.0 INTRODUCTION

Duchenne muscular dystrophy (DMD) is a neuromuscular disorder resulting from mutations in the dystrophin (*DMD*) gene that encodes the dystrophin protein. The X-linked condition is the most common form of childhood muscular dystrophy, affecting 1 in 3,500 to 1 in 6,000 male births.^{1; 2} DMD leads to progressive muscle deterioration and weakness in which individuals become non-ambulatory and develop cardiac and respiratory complications, eventually resulting in death occurring in the third decade of life.^{3; 4}

Although there is no cure for this degenerative condition, research for rare diseases is critical in order to enhance knowledge of the disease natural history, establish appropriate data for future treatment advancements, expedite new interventions, and ultimately provide the best treatment options. Promising research in DMD has provided advances in treatment and care to improve the quality of life and life expectancy for individuals with DMD.⁵

While current research in DMD has offered hope, it may present many challenges and sacrifices for families when asked to participate in research.^{6; 7} For rare diseases, recruitment and retention of eligible participants is a challenge, as sample sizes tend to be small and not all participants may fulfill enrollment criteria.^{8; 9} Educational materials to connect participants with appropriate resources and research opportunities are not readily available to families. Travel and time commitments add additional challenges due to geographically dispersed participants, financial burden of transportation, and various lifestyle sacrifices.^{8; 9} Perceptions of risks and

benefits to research participation, vary between families and may raise uncertainty and fears resulting in some families declining to participate in research.^{8; 10} These barriers not only add to the financial stress of families, but can also have negative emotional impacts and undermining effects on the family, which may prohibit study enrollment and contribute to loss of research participants.^{6 8; 9}

Qualitative research has been used to explore and understand perceptions of research and barriers to research participation.^{11; 12} Qualitative research methods can be useful to health care professionals, as they allow insight into human experiences, which can identify factors and social barriers explaining attitudes and behaviors that are difficult to deduce through quantitative methods.¹¹ Thematic analysis is a widely used method in qualitative research that seeks to identify and describe patterns or themes within data. Thematic analysis allows for a rich and detailed description of data.¹²

The present study utilized qualitative thematic analyses to identify family perceptions and barriers to research participation and identified how these factors may impact families. Exploring barriers to research participation and how these barriers impact families may provide information to improve research protocols, increase research participation, and facilitate development of resources to alleviate these barriers.

2.0 RESEARCH QUESTIONS AND SPECIFIC AIMS

2.1 RESEARCH QUESTIONS

Question 1: What are the perceived barriers to research participation amongst parents of boys with DMD?

Question 2: What impacts do these barriers have on families within the DMD community?

2.2 SPECIFIC AIMS

Aim 1: Identify potential barriers to research participation within the DMD community.

Aim 2: Identify possible impacts of these potential barriers on families within the DMD community.

3.0 BACKGROUND AND SIGNIFICANCE

3.1 DUCHENNE MUSCULAR DYSTROPHY

DMD is a degenerative, neuromuscular disorder primarily affecting males. The disorder was first described in the 1860s and named after the French neurologist, Guillaume-Benjamin-Amand Duchenne.^{13; 14} DMD is the most common form of childhood muscular dystrophy, with an estimated incidence of 1 in 3,500 to 1 in 6,000 live male births.^{1; 2} In 2007, the CDC and investigators from the Muscular Dystrophy Surveillance Tracking and Research Network (MD STARnet) conducted a population-based study at four U.S. sites and estimated the prevalence of Duchenne/Becker muscular dystrophy to be 1.3 to 1.8 per 10,000 males aged 5 to 24 years.¹⁵

3.1.1 Molecular Genetics

DMD is caused by pathogenic variants in the *DMD* gene, localized to chromosomal region Xp21.2. Mutations are predominately deletions or duplications of one or more exons, but can include small deletions and point mutations. The *DMD* gene is the largest gene in the human genome spanning 2.4 Mb and encompassing 79 exons.¹⁶ The gene encodes for the protein product, dystrophin, which is an essential part of the dystrophin-glycoprotein complex that links the cytoskeleton to the extracellular matrix and provides stability and protection of muscle

structures. Absence of the dystrophin protein causes muscle membrane dysfunction leading to progressive muscle degeneration.¹⁷

3.1.2 Inheritance

DMD is inherited in an X-linked recessive manner. About 60% to 70% of all cases are inherited from a carrier female, while one in three individuals with DMD is affected as result of a *de novo* mutation.¹⁸ Carrier females have a 50% risk in each pregnancy to pass on the gene mutation. Males who inherit the mutation are affected with DMD, while females who inherit the mutation are carriers of DMD.¹⁹

3.1.3 Clinical Course

If evaluated in the newborn period, individuals with DMD present with elevated serum levels of creatine kinase (CK). However, CK evaluations are not routinely ordered during the newborn period and patients are rarely identified based on CK levels alone. Diagnosis is typically delayed and most often established between the ages of 4 and 5 years.^{20; 21; 22} The recognition of early symptoms, such as general motor delay, occur on average at age 2.5 years and are originally detected by parents or caregivers.²⁰ Symptoms progress and become more pronounced by the age of 5 years, as individuals may present with frequent falls and inability to keep up with peers. Other symptoms may include cognitive delays, articulation difficulties, speech delays, and behavioral issues.^{20; 21; 22}

DMD is characterized by skeletal muscle weakness and reduced mobility leading to loss of ambulation typically by the age of 13 years. Muscle deterioration also results in orthopedic

complications such as scoliosis and osteoporosis. The progressive course of the disorder ultimately results in premature death, most often attributable to cardiomyopathy and respiratory failure.^{3; 23} However, the administration of corticosteroid therapy has been shown to delay progression of muscle weakness, reduce risk of scoliosis, and preserve ambulation.^{24; 25} Milder allelic forms of the disorder exist such as, Becker muscular dystrophy (BMD). BMD is characterized by less severe and later onset of symptoms, but will not however, be the focus of this study.

DMD follows a progressive course with five stages of disease classification.²⁶ In stage one (presymptomatic), developmental delay is noted with absence of gait disturbance and typically no respiratory complications. In stage two (early ambulatory), symptoms may include Gowers' sign, waddling gait, toe walking, difficulties climbing stairs, and risk for respiratory problems. Stage three (late ambulatory) includes difficulties rising from the floor, increasingly labored gait, and risk for cardiac and respiratory problems. In stage four (early non-ambulatory), individuals have an increased risk to develop cardiac and respiratory complications, are able to maintain posture, may develop scoliosis, and generally able to self propel for some time. Stage five (late non-ambulatory) includes reduced upper limb function, limited ability to maintain posture, and high risk for respiratory impairment and cardiac issues. Established care guidelines provide care considerations specific to each stage of disease and provide a framework for multidisciplinary care and management.²⁶

Advancements in medical care have improved quality of life and with assisted ventilation, the average life expectancy is approximately 35 years.^{3; 27} Despite improvements in medical care, there is still no cure for this debilitating disorder. Promising research has provided

hope for development of new therapies and is essential to enhance knowledge of the disease and ultimately provide the best treatment options.

3.2 DMD AND RARE DISEASE RESEARCH

Many rare diseases, such as DMD, rely solely on research to provide treatment options. Rare diseases are often life-altering, require serious medical attention, and many result in early death. Therefore, research is crucial for developing appropriate standards of care, advancing understanding of the disease, and improving quality of life.⁵ The complexity and burden of a rare disease diagnosis, along with the relatively small number of affected individuals, host a number of challenges to recruitment and retention of research participants and ultimately complicates the development of effective treatment strategies.⁸ These issues have led to growing acceptance and public health recognition of rare diseases, including DMD.²⁸

3.2.1 Classification of Research

Research encompasses a broad spectrum of clinical studies and can be classified into two main categories: interventional studies and non-interventional studies, also known as observational studies. Both interventional and non-interventional studies play an important role in advancing treatments and improving quality of life for individuals with DMD. The designation of research in the present study will focus on research as a whole and include both interventional and non-interventional studies.

Interventional studies seek to evaluate the safety and efficacy of a specific intervention. Interventions may include drugs, devices, medical procedures, and/or behavioral interventions such as changes to lifestyle and diet. Some studies may compare new interventions to placebos or current medical approaches in order to measure the impacts of a treatment or preventive measure on the disease.²⁹ The Food and Drug Administration (FDA) categorize interventional studies for drug development into different research phases based on the characteristics of the study. Studies can range from phase I trials, which assess initial safety of a drug within a small population to phase III trials, which include larger randomized controlled studies to further confirm safety and efficacy before FDA approval of the drug.²⁹

Non-interventional studies, also known as observational studies, seek to assess health outcomes of a specific disease or medical intervention in a naturalistic setting consistent with the current standards of care and typically within a large population. Participants are not assigned to an intervention as part of the study protocol, but may be assessed in a similar fashion as what is applied in standard clinical practice. Non-interventional studies may provide insight to influence treatment methods and may include, but is not limited to, surveys, questionnaires, interviews, and natural history studies.²⁹ Natural history studies are conducted to increase disease knowledge and better characterize the disease course. These studies are beneficial to evaluate outcome measures that can be used in interventional trials.³⁰

3.2.2 Importance of Rare Disease Research

Research is required in order to provide treatment to individuals within the rare disease community.²⁸ Research provides knowledge regarding the diagnosis, natural history, treatment, and prevention of a particular disease. The devastating nature of DMD, unmet medical needs,

and urgency for new therapeutic strategies, highlight the significance of ongoing research. As there is currently no cure for DMD, novel treatment strategies including exon skipping, cell therapy, and gene replacement hold potential to improve quality of life in individuals with DMD.⁵

3.2.2.1 Public Health Impact

The FDA defines a rare disease as a disease or condition affecting less than 200,000 people in the United States. Prior to the Orphan Drug Act of 1983, research and development of treatments for rare diseases had been neglected. The law was passed by US Congress to facilitate the development of drugs and treatment for rare diseases. The Department of Health and Human Services National Commission on Orphan Diseases in 1989, heard testimonies from patients, families, physicians, and researchers who raised awareness about the challenges of rare diseases and highlighted public health issues. Stakeholders emphasized barriers to rare disease research including limited disease knowledge and lack of effective treatments to satisfy the unique needs of the rare disease population.²⁸

Lack of disease knowledge is one of the greatest barriers to the diagnosis, treatment, and prevention of rare diseases. Research is designed to enhance medical knowledge of a disease in effort to assist with the diagnosis, identify disease risk factors, evaluate current interventions, prevent development and/or recurrence of a condition, explore methods for improving quality of life and supportive care, and ultimately establish effective treatments. Without knowledge of a disease, designing and implementing treatment strategies become a challenge.²⁸ Research, such as natural history studies, aim to gather data regarding disease progression and response to treatments and therapies across a lifespan. Natural history studies, along with other non-interventional studies, provide useful information to enhance overall knowledge of the disease

progression, identify genetic variability, assist with design of future studies, develop new clinical trials, and establish clinical endpoints.^{30; 31}

Rare diseases present many challenges to the medical community, but over the years, have gained public health recognition to support research efforts.^{28; 32} However, most rare diseases, including DMD, lack effective treatment options due to various disease-related challenges. The development of treatments for rare diseases is a complex, lengthy, and an expensive process, which limit approved treatment options available to patients.³³ As a result, many patients and physicians have resorted to the use of non-FDA approved drugs or drugs approved by the FDA for other conditions, not specific to their diagnosis.²⁸ Most rare diseases, including DMD, are serious, life-threatening conditions typically affecting vulnerable populations. The devastating nature of such rare diseases, highlight the urgency for effective treatment options and assessment of the safety and efficacy of new therapeutic strategies, as research is crucial to the understanding, development, and approval of effective treatments.^{28; 32}

3.2.2.2 Promising Treatment Strategies for DMD

For a disease in which there is ultimately no treatment, research provides the greatest hope for families within the DMD community. As the standard of care for treatment of DMD is essentially limited to the use of steroids to preserve ambulation, novel treatment approaches currently undergoing research, including exon skipping, cell therapy, and gene replacement have shown promise.⁵

A major advancement in DMD research has utilized the strategy of exon skipping. As DMD occurs as a result of a frame-shift mutation in one or more exons of the dystrophin gene, exon skipping omits specific exons in effort to restore the reading frame. The drug used in this approach has shown the greatest potential to become clinically approved for individuals with

specific exon deletions.³⁴ Another approach to treatment that is currently underdoing research is cell therapy. Due to the recurrent breakdown of muscle fibers associated with DMD, cell therapy aims to replace the loss of muscle fibers through delivery of normal myogenic cells or pluripotent stem cells.³⁵ Gene replacement is another promising therapeutic approach and in theory, would provide long-term treatment benefits. The goal of gene replacement is ideally to replace the defective dystrophin gene with synthetic counterparts to facilitate functioning of the gene.^{34; 36}

Although there remain many challenges to overcome with these research approaches and much research is still required before these treatment strategies become clinically available, it is hypothesized that these approaches will have a major impact on the future of DMD and the quality of life for individuals affected with this disease.⁵

3.2.3 Recruitment and Retention Challenges

Recruitment and retention of eligible participants is a challenge for most rare disease researchers. Ability to achieve and measure progress in clinical research is constrained by these recruitment challenges and low levels of participation.^{8; 9} Given the small number of affected individuals, diagnostic complexities, inconvenient trial designs, and limited access to resources, timely and adequate recruitment is difficult to achieve.³⁷ Maintaining recruitment numbers can help provide smooth transitions through various phases of clinical trials and assist with advancements in development and application of new therapeutic strategies into the clinical setting. However, various challenges to study recruitment and retention hinder the progress for development of effective treatments and add to barriers already faced by researchers and families.^{8; 9}

3.2.3.1 Limited Patient Population

As with any rare disease, DMD affects a relatively small number of individuals and is further limited by its pattern of inheritance to males, which present challenges to satisfying study enrollment goals. Given the small pool of eligible participants, researchers find themselves competing to recruit the same study population.³⁷ ClinicalTrials.gov is a web-based resource that provides access to research studies for a variety of conditions. All government-funded research is required to be posted on ClinicalTrials.gov. Additionally, many industry groups or pharmaceutical companies may post their research studies, but are not required to do so. Therefore, not all studies will be listed in this resource, but it does serve as a central repository for most research studies. As of March 2015, there are approximately 25 studies in the United States openly recruiting DMD patients and/or families, which would require over 3,200 participants to fulfill recruitment needs. Most research in DMD desires younger study participants at an early disease stage. Strict criteria typically exclude most non-ambulatory individuals with DMD and those at a critical stage of the disease, where hopes of treatment and advancing quality of life are diminished.⁶ Of the 25 studies openly recruiting DMD patients and/or families, only 11 studies are recruiting non-ambulatory and/or older patients. Therefore, recruitment of eligible participants is a struggle for many researchers in DMD studies as well as patients and families in the DMD community that wish to participate.

3.2.3.2 Diagnostic Delays and Disease Complexity

Despite availability of diagnostic testing, including molecular genetic testing, there is still a delay in recognition of early signs and symptoms of DMD.²⁰ Lack of disease awareness by families and health care providers may result in a diagnostic odyssey leading to a delay in diagnosis or in some cases, no diagnosis at all. Obtaining an accurate and timely diagnosis is

essential to provide appropriate care and discussion of research opportunities.³⁸ Most research studies require diagnostic testing to confirm a DMD diagnosis in order to meet eligibility criteria. This holds especially true to interventions that are mutation-specific, such as exon-skipping studies. Delays in the diagnosis may consequently delay research participation, as research may not be discussed with health care providers until patients are at an advance stage of the disease process and therefore, narrowing research opportunities for which a patient is eligible for.³³

As there is currently no cure for DMD, the diagnosis alone can be quite burdensome and complex to manage. DMD is a disabling disease that severely impairs muscle function, significantly limits physical abilities, and shortens life expectancy, which make continuous involvement in research studies a difficult task for families. Travel to research centers may become an overwhelming barrier to participation, due to physical impairments associated with DMD. Therefore, diagnostic delays and disease complexity pose challenges for not only recruitment but retention of study participants as well.³⁹

3.2.3.3 Study Design

A randomized controlled trial is a well-adopted study design used for most clinical trials. The study design randomly assigns participants to either a placebo (or non-interventional therapy) or to an experimental drug (or interventional therapy). However, for a disease in which there are limited effective treatment options, many potential participants are opposed the concept of randomization and reluctant to enroll in placebo-controlled studies.³⁷

Once participants have been recruited for a study, retention of study participants is an essential element to study success and completion. Study visits for DMD are often time consuming and require frequent research visits in which participants may undergo multiple

testing procedures. Therefore, if study protocols do not include strategies to relieve stress associated with study participation, then families are more likely to drop out of the study.⁸

3.2.3.4 Limited Resources

In a disease population, such as DMD, where effective treatments are scarce, development and coordination of resources are imperative to meet the unique needs of the DMD community. Collaboration between stakeholders is needed to enhance access to resources including research funding, educational materials, and partnership with support organizations and patient registries. However, satisfying the unique needs of the rare disease population has presented challenges due to competitive funding, lack of clinical resources, and fragmentation of resources and support organizations.²⁸

Access to resources needs to be considered when designing and implementing a research study in order to ensure successful recruitment and completion of the study. Although the Orphan Drug Act increased industry attention to rare diseases, research is still in competition with common diseases, which makes obtaining research funding even more challenging to the rare disease population.³⁷ Additionally, lack of clinical resources and educational materials for both families and clinical staff become a hindrance to the recruitment process. Geographic dispersion of study participants requires appropriate funding and multiple research centers in order to carry out study protocol and fulfill enrollment needs.⁸

Research studies in the DMD population can be expensive and rigorous, requiring collaboration between multiple parties including investigators, physicians, and patient families. Many active support organizations and patient registries are available in the DMD community but a lack of coordination between these entities presents additional challenges to recruitment.⁴⁰

Clinic providers, including genetic counselors, play a significant role in recruitment and retention of research participants by communicating research opportunities to patients and their families.⁸ Organizations and institutions with minimal infrastructure may not be equipped to facilitate an appropriate level of communication between researchers and families and therefore, fail to identify eligible participants and connect families to research opportunities.

3.3 FAMILIAL PERCEPTIONS OF RESEARCH PARTICIPATION

Understanding family perceptions of research participation can help clarify the rationale behind families electing or declining to participate in research. Interestingly, studies have found that what physicians identify as likely important factors to families were not reported as important factors by families themselves.⁴¹ This disconnect emphasizes the need to better understand family perspectives in order to bridge this gap and assist with recruitment efforts.

Studies have been conducted to identify family perspectives, motives, barriers, and impacts of research participation within various disease populations, most prevalently within the cancer population.⁴² Studies within the DMD community have explored barriers and family impacts associated with the disease diagnosis; however, studies have not focused specifically on research participation within the DMD community. Although one can hypothesize familial perceptions and expectations of research may overlap across varying disease populations, parents of children diagnosed with a progressively fatal disease, such as DMD, may face different challenges compared to children with cancer or other disease diagnoses.⁴³ These differing circumstances further highlight the significance of the present study to identify barriers and family impacts of research participation that is unique to the DMD community.

3.3.1 Motivations and Perceived Benefits

3.3.1.1 Altruism

Altruism has been cited in several cancer-related studies and in some DMD studies as a major motivation for research participation.^{6; 41; 44} It has been speculated that participants in genetic-related research may be more willing to participate primarily because research may benefit future generations and/or family members. Studies report participants are more likely to be altruistic when research involves little effort or limited risks and when the personal benefits are similar to that for others.⁴⁴ Another reported possibility, which may be the case for the DMD community, is that participants are more willing to be altruistic when there are no therapeutic options available, even in cases that may be associated with high risks.⁴¹ Studies have shown that research participants felt it is their obligation to help future generations and those within the disease community.^{6; 44}

3.3.1.2 Personal Benefit

Studies related to DMD and other diseases have identified personal benefit as a motivator of research participation. Although the perception of personal benefit is variable and subjective to the individual, some studies have reported specific benefits including, health improvements, increased medical attention, improved knowledge of disease, and promotion of self-sufficient care.^{6; 41; 45}

In a study, which described expectations and experiences of parents involved in a DMD clinical trial, all parents expected some form of direct benefit, which was reported as their primary motivation for enrolling in research studies.⁶ The majority of parents hoped for health improvements, such as improving quality of life, slowing disease progression, and improving

strength, endurance, and cognitive function.⁶ Another study, assessed perceptions of research participants for other diseases, including cancer, had similar findings.⁴¹ The study also found that participants felt they received more medical attention during the research process than during routine medical visits. Participants felt research in the rare disease population was the only option to obtain access to new therapies and in some cases receive free healthcare and diagnostic testing that would otherwise, not have been covered by insurance.⁴¹ However, as financial compensation was a contributing factor for participants, it is generally not the primary motivation for research participation. Participants additionally reported that the increased medical attention from the research team allowed them the opportunity to learn more about the disease and allowed participants to become more self-sufficient in their care.⁴¹

3.3.1.3 Hope

Following a diagnosis, some parents have been instructed by their physicians to just take their sons home and love them, which may destroy any vestige of hope for these families. In many disease communities, including DMD, hope provides psychological benefits and serves as a means of coping with this life-limiting disease.⁴³ To some families, research represents the possibility of a cure and having an opportunity to participate in an endeavor, which may prolong life and allow hope to be maintained in families. Therefore, some families turn to research as a source of hope and may be more accepting of risks associated with research participation in a quest for a cure.⁶

3.3.1.4 Trust and Positive Relationships

Building trust and establishing positive relationships with the research team has been highly valued by participants and their families.⁶ Studies have shown that research participants are more

likely to remain in studies when connected with a caring, respectful, and responsive research team. Additionally, individuals who had a positive research experience are also more likely to remain in the study and participate in future studies.⁴¹ A common contributing factor to a positive research experience was development of close relationships with the research team. A study that looked at expectations and experiences of parents involved in research for DMD, found these relationships were significantly important when participants felt threatened and overpowered by consequences of the disease.⁶ One study found that many families felt they received more attention and care during the research process than during routine medical care. These families perceived research participation as an opportunity to develop a closer relationship with their physicians and gain additional access to medical care.⁴¹

Additionally, establishing positive relationships with the healthcare team resulted in greater trust in healthcare providers. Studies conducted within the DMD community have shown that families rely on their physician to educate them about research opportunities for which their child may be eligible for and provide guidance to the family in the decision making process.⁶ Healthcare providers, including genetic counselors, can play a significant role in the educational aspect of research studies and provide assistance with recruitment and retention of research participants by communicating research opportunities.⁸

Healthcare providers can also connect patients and their families to research registries. The development of patient registries, such as DuchenneConnect, has gained increasing popularity within research communities. Patient information including genetic mutation(s) and medical history is stored in a database and used to notify patients of research opportunities, assist in developing new clinical trials, and serve as a resource to clinicians and researchers by providing aggregated, de-identified data.⁴⁶ Patient contact registries provide increased access to

research opportunities and have the potential to serve as a powerful recruitment tool for research teams.⁴⁷

Additional outcomes of research involvement may include connecting families with one another, development of strong relationships among committed parents, and increased engagement within the DMD community. Although the challenges of the disease has substantial impact on families, the desire for a cure has provided motivation for many families to unite and form advocacy groups to promote and fund research within the DMD community.³²

3.3.2 Therapeutic Misconception and Blind Optimism

As previously discussed, many parents of a child diagnosed with DMD indicate hope as a motive for participating in research. However, hope may have the potential to stimulate forms of misconception linked to research.⁴³ Increased community and individual involvement with research studies and development of new therapeutic strategies may bring about heightened assumptions regarding access and participation in research. These assumptions may encourage unrealistic expectations and ultimately lead to misconceptions associated with research involvement.⁶

Increased expectations or assumptions of research involvement may result in participants misconstruing the primary purpose of research as directly benefitting, opposed to providing a contribution towards disease knowledge, regardless of potential benefits. This phenomenon has been defined in previous literature as therapeutic misconception. Some studies have suggested that research mechanisms and specific interventions may prompt therapeutic misconception.^{6; 48} This is particularly relevant to the DMD community, as mutation-specific therapies, such as exon skipping, may have heightened expectations for both families and clinicians.⁶

Studies have identified inadequate education on research expectations in which participants lack understanding of what will happen in a study. Consequently, parental expectations of research emerge from a variety of sources, including patient advocacy communities, which may inaccurately enhance expectations.^{6; 41} The progressive and fatal nature of DMD leaves many families sensitive to any hope for potential treatment options. Therefore, families may become vulnerable to exaggerated hope and underlying optimism that may present on patient organization websites, social media, parent support groups, and other resource avenues. The effect of overly optimistic advocacy of clinical trial participation within the DMD and BMD community has been described as a ‘collective therapeutic misconception.’⁴³

Unrealistic or ‘blind optimism’ is another phenomenon, which has been described in early-phase oncology studies.⁴⁹ This concept has been supported by a study, which characterized experiences of parents involved in a clinical trial for DMD and BMD.⁶ The study found participants displayed optimistic bias toward study benefits. Participants in the study were asked to differentiate between the terms expectations and hope associated with research participation. Most parents defined research expectations as what they thought would happen in the study and associated the term with feelings of confidence. However, hope was most often used as the default terminology when discussing expectations for a study. Parents defined hope as the best possible outcome and associated the term with feelings of optimism. Confusion between the terms expectation and hope may result in misconception for families and potentially suggests a dissonance between the understanding and emotional representation of a study.⁶

As all research must eventually come to an end, some parents expressed understanding of research termination, while other parents have reported feeling powerless and having a loss of hope due to what they believe as a sudden and unexpected halt of a study.⁶ Up until the traumatic

termination of a research study, most parents felt a supportive connection with the research team. Following an unsuccessful study or termination of a study, parents felt cut off in the relationship and lack of communication as to future directions and the path moving forward. These parents felt greater support should have been provided for the possibility of a study ending unexpectedly. Other parents felt better prepared as research teams provided parents with support and connection to advocacy groups.⁶ Therefore, inaccurate expectations of families encourage needs to explore participant experiences and potential barriers to research participation.

3.3.3 Potential Barriers

DMD is a complex and life-limiting disease, which presents significant challenges to families. Families face emotional and social distress, financial burdens, and are forced to make daily sacrifices affecting employment, education, and family relationships.⁵⁰ These challenges overburden families making it difficult to participate in research. The progressive and unpredictable nature of DMD can overwhelm parents adding to fears of the unknown associated with DMD.⁵⁰ This state of apprehension, along with potentially invasive research procedures, deters many families from participating in research.⁶ Additionally, complex research protocols, lengthy informed consents, and negative experiences make recruiting and retaining research participants difficult.^{28; 41}

3.3.3.1 Disease-Related Challenges

Living with a rare disease, such as DMD, requires learning to live with a condition in which there is limited treatment and understanding by family, clinicians, researchers, and the community.²⁸ Despite many research efforts, DMD lacks effective treatments, requires numerous

medical appointments, and consequently sends many families into a diagnostic odyssey of countless tests.⁵² Psychological and social consequences due to diagnostic delays and limited access to genetic testing can result in serious health implications.⁵⁰ DMD can be difficult to manage, as there are limited treatment options and care requires a multidisciplinary team of specialists. Therefore, challenges associated with the diagnosis of DMD are complex and encompasses social, emotional, and financial costs.^{28; 51; 52 50}

A substantial amount of research has highlighted the significant emotional burden associated with a genetic condition.^{52; 53} Emotional and social costs to families can be extensive and include psychological stress, feelings of isolation, concerns of support, and social inequality. Many parents of boys with DMD live in constant fear for their sons. Parents fear a shortened lifespan, pain, injury, and unknown consequences for their sons that may occur due to this progressively fatal disease.^{52; 53} With progressive and fatal disorders, such as DMD, time can be the ultimate enemy and present many pressures that affect the decisions of parents to involve their child in research studies.⁶ One study found that many parents associated doing nothing with accepting the fate of early death and felt it their responsibility to enroll their child in research before loss of ambulation.⁸ However, other parents felt time spent in research studies eliminated opportunities for families to partake in normal life activities. Families find themselves at a constant battle with time and how best to utilize the time they have while their son is still living.⁸

This struggle combined with many societal factors, limit families' chances for normalcy. Many parents feel pressured to stay strong for the benefit of their sons and create self-imposed boundaries, which may prohibit parents to appropriately cope and/or discuss their son's diagnosis.⁵⁴ Patients and families are forced to become educated advocates and actively involved in their own care, including making household additions such as ramps, widening doorways, and

even relocating to a handicap equipped residency.⁵⁴ Family dynamics may also change and include transitions such as siblings involuntarily adopting caretaker roles or receiving inadequate attention from parents.^{51; 53; 55}

Along with emotional and social consequences, the diagnosis of DMD is accompanied by a variety of costs and substantial economic burden that families must endure. Research participants require the use of multiple healthcare resources, such as medications, various procedures, medical devices, hospital admissions, and a number of doctor visits.²⁸ These financial challenges contribute to barriers in research participation as many families suffer a loss of wages and employment opportunities. One study found parents experienced a decrease in household income and reduction or cessation of employment as a result of their son's diagnosis of DMD.⁵⁶ The study estimated the mean loss in work hours to be one day per workweek. The study estimated the corresponding household burden to be between \$58,440 and \$71,900, and the mean per patient annual direct cost was estimated to be \$28,590 for the United States, which is seven times higher than the mean per-capita health expenditure. Additionally, the total societal burden was estimated to be between \$80,120 and \$120,910 annually per patient, which increased with disease progression and the national burden of DMD in the United States was reported to be \$1,217,373,000. Addressing financial adversity can assist with full understanding of therapeutic benefits and help construct a reasonable evidence-based health policy.⁵⁶

3.3.3.2 Uncertainty

The challenges of many rare disease diagnoses present many life stressors, including living with uncertainty. This level of uncertainty relates to a number of factors that can be associated with a shortened lifespan and unpredictability of the disease. These factors contribute to the risks and fears perceived by families affected with DMD. One of the most prevalent issues associated

with rare diseases is the fear of the unknown due to limited disease knowledge and information, which leaves many families feeling isolated and potentially unwilling to participate in research.²⁸ The sheer effort of moving forward for these families becomes a challenge due to an uncertain future from both a medical and psychosocial standpoint.⁵²

Parents of boys or young men with DMD possess a desire to act within the best interest of their child. In the context of research participation, parents admitted fear of making the wrong decision regarding enrolling their son in a research study, but also acknowledged the importance of their son's autonomy when deciding to participate in research.⁶ In a rapidly progressing incurable disease, such as DMD, many parents felt greater urgency to expose their children to promising research treatments before they became nonambulatory and the window of therapeutic opportunity diminished.⁹ However, other parents had reservations for research participation due to risks involved in exposing their sons to unknown or untested substances, fear of being a guinea pig, and risking the chance of having their son receive the placebo rather than the intervention. For a disease in which lifespan is reduced, parents felt there are ethical concerns centered around placebo-controlled trials and that all families willing to participate should not be subjected to the placebo.^{9; 44}

3.3.3.3 Consent Process

Before individuals participate in research they must go through the informed consent process. This process includes an explanation of research expectations, requirements, risks and discomforts, benefits, purpose of the research, and rights to withdrawal or discontinue participation. Although the informed consent process is vital to research participation, studies have shown that participants did not fully understand the research protocol and did not recall receiving consent forms that appropriately addressed the full extent of research requirements.^{41;}

^{57; 58} Additionally, individuals were unaware of the time commitments associated with the research protocol and participation, which may be attributed to participants not listening or attending to the consent process, or may be due to the extended length and complexity of informed consent forms.⁴¹ Families preferred interacting with knowledgeable personnel during the informed consent process and appreciated simplified forms displaying clear basic language. Families also admitted to disregarding risks because they had invested their utmost trust in the institution and their healthcare providers to protect their safety and keep their best interest in mind.⁴¹ It can be hypothesized that these perceptions of the informed consent process are highly applicable to the DMD community given the disease complexity and psychological sequelae.

3.3.3.4 Negative Experiences

Positive research experiences are more likely to promote continued research participation. Similarly, negative experiences with research result in individuals terminating research participation.⁶ Studies have shown that the main factors contributing to negative research experiences include pain and discomfort associated with invasive procedures, adverse side effects related to the research intervention, demanding studies and participant inconvenience, poor study organization and appointment delays, and unprofessional study teams.^{41;59} Participants felt these factors played a significant role in determining whether they continued with current trials and/or whether they returned to participate in subsequent studies.^{41;59}

In addition, studies have found that research participants desired receipt of study outcomes and results of testing as part of research protocol.⁴¹ Providing this information made parents feel valued and that their participation contributed to the disease community. Participants expressed some disappointment when research information was not shared. The

level of disappointment may play a role as to which research studies individuals elect to pursue and whether they decide to enroll in future studies.⁴¹

3.4 QUALITATIVE RESEARCH

Qualitative research is a form of research which encompasses methodologies from a variety of disciplines that can be used to study and understand phenomena and the perceptions that influence human behaviors. Qualitative research methods can be useful to health care professionals, as they allow insight into human experiences, which can identify factors and social barriers and explain attitudes and behaviors that are difficult to deduce through quantitative methods of data analysis.^{11; 12} DMD is a complex disease resulting in burdensome medical and psychosocial sequelae. Therefore, relying solely on quantitative methods does not provide full understanding of the psychosocial elements and interpretation of the particular subject matter associated with DMD. Information concluded from qualitative research has been utilized in cancer and some rare disease populations to assist with recruitment efforts and study design of future research.^{8; 42} Qualitative research plays a pivotal role in ensuring that advancements in research and therapeutic methods are developed and executed in the best interest of families.¹¹

There are many approaches to qualitative research and a number of methods, which can be implemented to characterize the data. Thematic analysis is an analytic method in qualitative research that seeks to identify and describe patterns or themes within data. This method has been widely used in a variety of disciplines to identify quantitative patterns, experiences, meanings, and realities of a particular subject matter.⁶⁰ A coding system is generally developed and utilized to describe, organize, and analyze information obtained from qualitative studies. It allows for

flexibility in theoretical framework and provides detailed description of the data. Therefore, thematic analysis is a useful qualitative methodology to identify perceived barriers to research participation and interpret the impacts on families. Characterization of this information can help direct research strategies, improve research protocols, and assist with recruitment efforts.¹²

4.0 DESIGN AND METHODS

This project was developed from an approved and funded research study, “Strategies for Engaging the Duchenne Muscular Dystrophy (DMD) Community in Research.” The study was designed and organized to additionally serve as a Master’s thesis project. This project will focus specifically on the barriers to research participation and the familial impacts elicited solely from the parent-centered focus groups.

4.1 PERSONAL DISCLOSURE STATEMENT

As one of the project researchers and author of the present study, I wish to disclose my personal experiences and relationship to DMD that may bring personal bias to the study. My training and experiences with DMD enhance my knowledge, awareness, and sensitivity to the topics discussed in the current study. Serving as a genetic counselor and advocate within the DMD community, I am drawn toward the families and the medical, psychosocial, and familial implications associated with this devastating disease. My role as a genetic counselor allows me the opportunity to interact with patients and their families in the DMD community and additionally be involved in the recruitment for research participants. The dual role as both a clinician and researcher in the present study may present additional bias to interpretation and understanding of the data. As the study presents perspectives solely from parents of boys/young

men with DMD, I recognize the importance to set aside my bias and experiences to better understand perspectives of the parent participants. My personal bias may shape the interpretation and understanding of the data; however, reliability and validity of the data were checked in a number of ways that will be addressed in section 4.4, Reliability and Validity.

4.2 STRATEGIES FOR ENGAGING THE DMD COMMUNITY IN RESEARCH

“Strategies for Engaging the DMD Community in Research” is a study funded by the Foundation to Eradicate Duchenne (FED). The study aimed to understand barriers to engaging the DMD community in research and to develop strategies to assist with recruitment efforts through parent-centered and researcher/clinician-centered focus groups. The study was reviewed and approved by the University of Pittsburgh’s Institutional Review Board (IRB) on March 5, 2014 and was renewed for data analysis on February 5, 2015 (Appendix A). For purposes of this project, design and methods for researcher/clinician-centered focus groups will not be discussed.

4.2.1 Participant Recruitment

Participants were recruited in collaboration with the Cooperative International Neuromuscular Research Group (CINRG) and associated Muscular Dystrophy Association (MDA) clinics. CINRG serves as an academic clinical network for research studies in neuromuscular diseases with a main focus on DMD and BMD. CINRG is an international collaborative group with over 24 neuromuscular referral centers that each individually care for over 100 DMD patients or more. MDA is a nonprofit organization that funds research, provides comprehensive care and

support to families, and serves as an advocate for the neuromuscular disease community. MDA maintains roughly 200 specialized clinics within the United States and Puerto Rico, which consist of a multidisciplinary healthcare team of specialists dedicated to providing care and support resources to patients and their families.

Five CINRG sites with associated MDA clinics were selected to geographically represent varying patient populations throughout the United States and included the following sites: Pittsburgh, PA; Washington, DC; Minneapolis, MN; Houston, TX; and Sacramento, CA. Each participating CINRG/MDA clinical site agreed to participate and provided a letter of support to demonstrate willingness to contribute recruitment assistance, facility access for focus group sessions, and additional guidance to research investigators (Appendix B). The study recruited parents of boys and young men diagnosed with DMD for parent-centered focus groups. Both families who were currently or had previously been involved in research and families who had never been involved in research in DMD were asked to participate.

An IRB approved recruitment flyer was created and emailed to each clinic/research team to be distributed to families (Appendix C). Flyers were posted and/or handed out at clinic visits and some centers utilized site-specific patient registries to contact families directly. The recruitment flyer was also shared by MDA representatives and other parent advocates by word of mouth, email, and social media. Parents interested in participating were asked to contact the principal investigator and/or the study coordinator regarding additional information and to confirm their son(s) had a diagnosis of DMD. Additionally, participants were emailed a copy of the consent form in advance to review (Appendix D). The study's lead investigator obtained informed consent from each participant prior to commencing the focus group sessions.

4.2.2 Focus Groups

Focus groups were selected as the most appropriate method to encourage exchange of participant thoughts and experiences, permit researcher and participant interaction, capture comprehensive and multidimensional responses, account for diverse patterns of participant attitudes and motives, and provide the most rapid and efficient collection of data.⁶¹ Focus group guides were developed by study investigators to facilitate conversation amongst participants and to maintain organization of the focus group sessions (Appendix E). Focus groups were completed at all five participating clinical sites and were conducted between July and October 2014. Three study investigators traveled to each site and coordinated focus groups sessions with assistance from the associated CINRG/MDA clinic team. For participant convenience, focus groups were mainly held in conference meeting rooms at centrally located hotels that were in close proximity to the clinic site. Participants received a complementary meal served prior to the initiation of each focus group, received remuneration of \$25 for participation, and also received travel reimbursement up to \$60. Childcare was provided to make participation more convenient for parents and allowed the opportunity for parents to discuss their children without them present during the focus group sessions. Children received a complementary meal and were supervised in a separate room by either genetic counseling students, MDA representatives, or a volunteer from the associated CINRG/MDA clinic team.

Each focus group session was limited to no more than six parents of boys or young men with DMD in effort to ensure contribution of each participant and to maintain quality control of the audio transcription process. The study aimed to conduct two separate parent-centered focus groups at each site including one session for families involved in research studies and another session for families not involved in research studies. Each focus group was led by a trained

focus group moderator and lasted about 90 to 120 minutes. The study investigators took field notes during each focus group and debriefing sessions were held after each focus group. Theoretical saturation was achieved through eight in-depth focus groups conducted with a total of 28 parent participants.

Following each focus group session, participants were asked to complete a demographic form to depict socio-demographic factors and to provide a clinical depiction of their son(s) (Appendix F). All focus groups were audio recorded and professionally transcribed by Landmark Associates, Inc. A professional transcriptionist transcribed the audiotapes from focus groups verbatim into Microsoft Word documents. Following review of the written documents, personal identifiers were removed and audio recordings were disposed of in accordance with IRB protocol in effort to protect participant confidentiality.

4.3 THEMATIC ANALYSIS

Thematic analysis is a method used to encode qualitative information, which seeks to identify and describe patterns or themes within qualitative research data. Thematic analysis was determined as the most suitable method for data analysis given its flexibility and usefulness to characterize patterns of meaning across different theoretical frameworks, and provide a representative account of the dataset and responses to focus group questions. Although thematic analysis is a widely used analytical method, its methodology is open to researcher interpretation and allows for a variety of approaches.¹²

Themes and patterns are typically identified in two primary ways through either a deductive or inductive approach. Deductive thematic analysis is a theory-driven approach in

which themes are derived from preconceptions or a pre-existing framework. This type of approach tends to focus on pre-determined aspects designated prior to data analysis and is generally less descriptive of the data overall.⁶² Inductive thematic analysis is a data-driven approach in which themes are strongly linked to the data and not forced to fit within a pre-existing framework.⁶⁰ This approach has been well documented within the literature and was selected as the most appropriate approach for the present study in that it allowed unexpected themes to emerge. In this approach, participants were permitted to freely tell their stories, which could potentially uncover themes that would not have been determined prior to the study.

Braun and Clarke proposed a step-by-step process for thematic analysis. These steps were used in the present study and outlined below.¹²

4.3.1 Familiarization with the Data

In order to become familiar with the dataset, all transcripts were read through at least twice before the coding process. Meticulous reading and re-reading of the transcripts allowed the researcher(s) to become immersed with the content of the data. Preliminary notes were taken in order to search for meaning and patterns across the dataset, and permitted the researcher(s) to collect ideas for potential codes.¹²

4.3.2 Coding

After familiarization with the data, the next step involved the coding process to generate an initial list of reoccurring patterns and description of the data. Coding is a part of the analytic process that describes and organizes meaningful data as it relates to the phenomena and/or

research questions.⁶³ A code is defined as a label that describes the data and can further be categorized into themes. As the present study utilized inductive thematic analysis, coding was dependent on data-driven themes and encouraged the researcher(s) to remain open to all possible interpretations across the dataset.

Researchers may select to manually code the data or use a software program. Software programs are typically used for coding large amounts of data. For the present study, manual coding was selected as the best method given the dataset was easily manageable and additional training would be required in order to utilize a software program. Braun and Clarke suggested ‘no data set is without contradiction’ and data may be uncoded or coded multiple times. Therefore, data was coded inclusively and included as many potential themes and patterns as possible.¹² Boyatzi proposed that a good code should have five main elements: 1) a label, 2) a definition or characteristic establishing the theme, 3) a description to assist with flagging the theme, 4) a list of qualifications to identify the theme, and 5) a set of positive and negative examples to eliminate possible theme confusion.⁶⁰ These elements were utilized to complete line-by-line coding to identify important components, which captured the qualitative richness of the data.⁶⁴ Participants would occasionally attempt to incorporate multiple components into a single conversation segment, jump between a variety of topics, and/or lose their train of thought. Therefore, line-by-line coding ensured that all aspects of the data were considered and minimized exclusion of important components.

A variety of approaches may be used in the coding process to ensure validity and appropriate coding.⁶⁴ Data was coded initially through a memo writing process in which notes were taken directly onto printed transcripts in order to document the researcher’s thoughts regarding possible patterns and themes. Transcripts were then highlighted and color-coded in

Microsoft Word to further indicate and distinguish potential patterns before being synthesized into themes. The memo writing, highlighting, and color-coding approach was performed as part of the coding process and continued throughout the identification of themes.

4.3.3 Theme Identification

Theme identification is an interpretative analytic process in which themes are developed from generated codes and patterns among codes.⁶⁰ A theme seeks to capture an important element of the data related to the specific research questions and represents meaning within the dataset. A theme can be identified as a direct observation or as an underlying phenomenon of the data.¹² In the present study, themes were generated inductively and strongly linked to the original dataset. The flexibility of thematic analysis allowed for a variety of approaches to determine themes. However, development of an organized system to categorize potential themes and maintaining consistency in identifying themes was important to ensure the data was interpreted within the appropriate framework.⁶⁰ Potential themes were initially noted throughout the coding process. Relationships between the codes and preliminary themes were considered and additionally noted in the dataset. Codes and patterns among codes were grouped into potential themes and subthemes based on the context. Codes were organized into preliminary themes, with some being classified into multiple themes. Categorizing codes into themes included a process of varying methods. Utilizing a combination of methods to identify themes increased the accuracy of understanding and interpretation of the dataset.

4.3.3.1 Pawing Through the Data

One method included ‘pawing’ through the data to highlight key phrases and potential themes.⁶⁵ Specific elements within the dataset were considered when identifying themes. Repetition of a particular concept was a good indicator of a potential theme. Analogies and/or metaphors used by participants were good descriptors of their thoughts and experiences, and indicated a possible underlying theme.⁶⁶ Natural transitions of content within the dataset were markers for a new emerging theme. Making systematic comparisons across the data focused the researcher on details of the information in order to better detect themes.⁶⁷ Searching for theme-related material such as, identifying how participants perceived barriers, explained certain behaviors and motives that generated potential themes.⁶⁸

4.3.3.2 Color-Coding and Sorting

After sorting through the data, a variation of the cutting and sorting technique, described by Lincoln and Guba, was used. In the cutting and sorting technique, important quotes or expressions are cut out and sorted into theme piles. Each pile contains quotes of similar context and is representative of a particular theme.⁶⁹ The cutting and sorting method appeared applicable to the present study as it created a way to compare quotes across the different focus groups sites. In effort to be environmental friendly and limit the amount of paper used for the current project, a similar method was developed and employed.

Microsoft Word was used as a tool to highlight and pull out important quotes within the data. This technique substituted the cutting out of quotes. Highlighted quotes were then color-coded based on its context and the potential theme. For example, all quotes referencing travel were color-coded green, and all quotes referencing resources were color-coded red. This process was carried out until all quotes were color-coded. A color-code guide was created in order to

keep record of what potential theme each color represented. The quotes were then sorted based on the assigned color. This technique was similar to sorting quotes into theme piles. To the researcher's knowledge, this variation of the cutting and sorting method has not been previously published within the literature.

4.3.3.3 Key Words in Context

Word lists and key words in context is a technique evolved from the theory: 'If you want to understand what people are talking about, look closely at the words they use.'⁶⁵ In the present study, keywords and phrases were identified in effort to count their occurrence across the dataset. This method was selected as a rapidly efficient technique to identify additional themes.⁶⁵ All transcripts were merged together into one Microsoft Word document to simplify the word search process. A list of keywords and preliminary themes, documented in previous notes, were used to complete a word search to identify instances in which a particular word or phrase occurred. These quotes were then copied and sorted into similar theme piles as described in the color-coding and sorting technique. This method was used to ensure important quotes were not missed and valuable concepts were not overlooked.

4.3.4 Review of Themes

The review of themes phase allowed for expansion and revision of candidate themes. Each theme and its relevant data were reviewed and discussed amongst the research team. Potential themes were checked against the dataset to determine appropriate relation to the data. Continued review of the data permitted codes to be reorganized into different themes that may be better representative of the data context. In effort to piece together interesting aspects of the data,

connections were made between overlapping themes and deviations between the coded data were identified. Several themes that appeared to be completely separate themes collapsed into one cohesive theme, while other themes were divided to form two different themes. A few themes did not have enough supporting data and were then discarded. After the initial review and reorganization of themes, notes and thematic maps were used to help visualize connections between themes and to convey the story of the dataset.¹²

4.3.5 Defining Themes

The scope of each theme was defined and refined in order to further develop the story of each theme. To ensure no overlap between themes, consideration was given to assess the connections between the story of each theme and the overarching story portrayed by the study participants as it related to the research questions. During the refinement process, sub-themes were identified in order to provide structure to more complex themes. Identified themes were approved and agreed upon by all researchers to ensure validity and appropriateness of each theme. After themes were more clearly refined, names were assigned to represent meanings of each theme.¹²

4.3.6 Final Analysis

In the final phase of the thematic analysis, vivid extracts were selected that provided meaningful contributions in relation to the research questions and captured the essence of the dataset. Enough data extracts were selected to demonstrate the prevalence of each theme. Prevalence of an individual theme was determined at the level of each participant. Data extracts were

embedded into the analytical narrative in order to illustrate the story conveyed by the study participants.

As multiple themes were identified in the FED study, Strategies for Engaging the DMD Community in Research, one major theme titled, Barriers, was selected to be the focus of the present study. The selected theme and its associated sub-themes will be discussed in the results section.¹²

4.4 RELIABILITY AND VALIDITY

Reliability and validity are important concepts in qualitative research to assess both the objectivity and credibility of the research. Validity refers to the extent to which research findings accurately correspond to the phenomenon they intend to represent. Reliability refers the consistency and reproducibility of the research data.⁷⁰ A number of techniques can be used to substantiate reliability and validity of the data.⁶⁹ Triangulation refers to the use of two or more methods to study a phenomenon.⁷¹ Three researchers were involved with the data analysis and utilized a number of methodologies to identify potential themes. To strengthen the reliability of the research findings, the researchers held multiple meetings to discuss the data and came to a consensus on identified themes.⁷² Additionally, study information was consolidated and sent to participants for review as part of a data checking method.⁶⁹ This allowed participants to provide feedback or comments if they felt the information and presented themes were not a correct representation. Participants that responded provided positive feedback and no participants reported a disagreement with the presented information.

A Cohen's kappa was calculated as a final technique used to substantiate reliability and validity of the data. A Cohen's kappa is a statistical measure of the degree of agreement between independent researchers and assesses inter-rater reliability.⁷³ Inter-rater agreement can provide further confidence that appropriate themes have been identified. All three researchers were blinded and provided individual scores for each theme.

5.0 RESULTS

Although participants were initially recruited based on whether their family had participated in research in DMD or whether their family had never participated in research in DMD, results of the study were determined to represent collective perspectives from all parent-centered focus groups and were not separated based on status of research participation.

5.1 DEMOGRAPHICS

5.1.1 Parent Demographics

A total of eight parent-centered focus groups were conducted with a total of 28 parent participants of boys and young men with DMD (Table 1). The majority of participants were female (68%); between the ages of 30 and 55 years old (79%); and identified as Caucasian/White (82%). Most participants were from a suburban area (59%); reported a household income greater than \$100,000 (48%); and had at least a four-year college degree (50%). When asked about marital status, a majority of participants were married or in a long-term committed relationship (89%).

Most participants indicated they were the biological mother of a son(s) with DMD (54%) and had only one child with DMD (82%). However, two participants (7%) identified as the

adoptive mother of a son with DMD and two participants (7%) identified their relation to DMD as other (partner of a parent). When asked to discuss whether their family had been involved in research, the majority of participants had participated in some form of research (82%).

Table 1. Participant Demographics

Parent demographics	n (%), n=28 * n = 27
Gender	
Males	9 (32.1)
Females	19 (67.9)
Age (years)	
< 30	1 (3.6)
30 to 55	22 (78.6)
> 55	5 (17.8)
Ethnicity/Race	
Caucasian/White	23 (82.1)
African American/Black	1 (3.6)
Hispanic/Latino	2 (7.1)
Asian	1 (3.6)
Other	1 (3.6)
Location *	
Urban	5 (18.5)
Suburban	16 (59.3)
Rural	6 (22.2)
Household income *	
≤ \$50,000	6 (22.2)
\$51,000 to \$100,000	8 (29.6)
> \$100,000	13 (48.2)
Education	
High school or less	6 (21.4)
College or technical school	8 (28.6)
4-year college degree or beyond	14 (50.0)
Marital status	
Married/long-term committed relationship	25 (89.3)
Divorced/separated	3 (10.7)
Relation to DMD	
Biological father	9 (32.1)
Biological mother	15 (53.7)
Adoptive mother	2 (7.1)
Other	2 (7.1)
Number of children with DMD *	
1	23 (85.2)
> 1	4 (14.8)
Research participation	
Have participated	23 (82.1)
Have not participated	5 (17.9)

5.1.2 Demographics of Son(s) with DMD

Additional demographics were collected regarding each participant's son(s) with DMD (Table 2). As discussed previously, most participants had only one child with DMD; however, two participants each had two children with DMD. The 28 parent participants reported demographics on a total of 30 boys and young men with DMD. The majority of the participants' sons were under the age of 18 years old (87%) and required the use of a wheelchair both indoors and outdoors (43%). Reported diagnoses of other conditions, aside from DMD, consisted of learning disabilities (20%), autism (17%), developmental delays (10%), and speech disorders (7%). Other diagnosed conditions reported in only one individual each (3%), included anxiety, cardiomyopathy, type II diabetes, hypothyroidism, osteoporosis, beta thalassemia, and Gilbert syndrome.

Table 2. Parent Reported Demographics of Son(s) with DMD

Demographics of son(s) with DMD	n (%), n=30
Age (years)	
≤ 10	11 (36.7)
11 to 18	15 (50.0)
≥ 19	4 (13.3)
Physical abilities	
Walks independently for long distances (more than a football field)	6 (20.0)
Walks independently for short distances (around the house/one-block outside)	9 (30.0)
Walks independently indoors but needs wheelchair for outdoors/long distances	2 (6.7)
Uses a wheelchair indoors/outdoors	13 (43.3)
Other diagnosed conditions	
Learning disabilities	6 (20.0)
Autism	5 (16.7)
Speech disorder	2 (6.7)
Anxiety	1 (3.3)
Cardiomyopathy	1 (3.3)
Type II diabetes	1 (3.3)
Developmental delay	3 (10.0)
Hypothyroidism	1 (3.3)
Osteoporosis	1 (3.3)
Beta thalassemia	1 (3.3)
Gilbert syndrome	1 (3.3)

5.2 BARRIERS OF RESEARCH PARTICIPATION

As indicated in the focus group guides, participants were directly asked about barriers they face and their perceived limitations to participation in research in DMD. Participants discussed circumstances and components, which have previously, or may potentially, deter them from research participation. Participants also conversed about areas in DMD research that presented challenges to their families and areas in which they personally felt needed to be improved. Participants clearly articulated many barriers faced by families when asked to participate in research. For the current study, barriers and limitations to research participation were identified

and organized into the following three main sub-themes: 1) commitments; 2) fighting a new battle; and 3) the gamble. Prevalence of each sub-theme was determined at the level of each participant (Table 3). An inter-rater reliability analysis using the Kappa statistic was performed to determine consistency among raters. An almost perfect inter-rater reliability for the raters was found to be Kappa = 0.96 ($p < 0.001$), 95% CI (0.937, 0.989).

Table 3. Prevalence of Identified Barriers

Barriers	n (%), n=28
1. Commitments	26 (92.86)
2. Fighting a new battle	26 (92.86)
3. The gamble	24 (85.71)

5.2.1 Commitments

Most participants (93%) concurred that participating in DMD research is a major commitment. Research participation required commitments from all aspects of families' lives and to some, felt like a full-time job in and of itself. Participants described their experiences with research participation being a significant time commitment and consequently forced many parents to take off work. One mother stated, "*We don't always have time, because that's the main thing, when*

you do research, is to be able to have the time to take off if you're working." Many families mentioned they lived paycheck to paycheck and did not have the funds or extra time at work to take off in order to travel to research centers. One parent stated, *"...how am I supposed to engage and invest all that time, energy, and that means money, because any day that I'm not at work means I'm not earning."* The decision to participate in research left many parents concerned about risking their job and main source of family income.

Parents who were fortunate to have jobs that allowed them the opportunities to take time off work and travel to research centers, were still imposed with travel commitments. One father discussed travel concerns that were echoed by other participants, *"I feel like, financially...you're using all of your PTO, your extra time at work to travel...Time commitment."* Travel commitments are another challenge mentioned by many participants, which strained their ability to participate in research. One mother claimed, *"...when we first started the study...our biggest thing, at the time, we didn't have a vehicle, so we had to take the bus. Those long days...we had to really commit to literally going from 8:00 in the morning until 6:00 at night."* As a majority of the participants' sons required the use of a wheelchair, several families discussed the difficulties of traveling with a child with a disability. Many participants expressed their frustration of transporting a power wheelchair in both their family car and on an airplane.

Additionally, participants referenced geographical location and proximity to research centers as factors influencing their decisions to participate in research. Many participants shared the same feelings as one mother, *"I think I checked into a study at one time when he was younger and it was the travel deal. It was so far away and you had to go and be there awhile."* Participants living in rural areas or areas in which research centers are scarce, felt they needed to make a greater commitment than those living in urban or suburban areas that are more

conveniently located to research centers. One mother expressed, *“It’s the luck of the draw, where you live, as to whether or not you get to participate in a study. That’s frustrating.”*

As taking time out and traveling to participate in research imposed multiple stressors on the parents, it was also suggested that the commitments could create challenges for their sons with DMD. One mother stated:

Another area was time. As my son was younger, it was easier to get him to and from things, take him out of school, work around activities. As he’s progressed to high school and now to college, there’s just not the time to do three or four visits to taking him out of school. Where there’s a bigger impact at a high school or a college level than there is at an elementary school level. Depending on the age of the child and the extent of the study.

Other parents discussed concern with research commitments limiting their sons from attending other appointments crucial to their sons’ well being. One mother discussed unexpected circumstances, which posed additional challenges, *“We’ve had circumstances...where we weren’t prepared to stay the night. We weren’t prepared to have separate visits, so we had to cancel school. We had to cancel therapy. I had to cancel his IEP meeting. Things like that make it very difficult.”*

5.2.2 Fighting a New Battle

In addition to parents feeling research required major commitments from families, a majority of participants (93%) also perceived research participation as frustrating and added another layer of stress and worry to the overwhelming emotions that participants were already experiencing with the diagnosis of DMD alone. A majority of participants felt participating in research was equivalent to fighting a new battle in DMD. One mother provided her perspective, *“I think what*

it comes down to is Duchenne families have such a large amount on their plate. The study becomes a new battle to fight. I look at Duchenne like dealing with a toddler. You have to choose your battles.” Participants discussed the daily challenges associated with DMD and how those challenges may deter them from participating in research. Many participants admitted they were overwhelmed and uneducated about DMD and that they placed all their trust in their healthcare providers to inform them of research opportunities. One mother stated, *“We're not educated on how that [research] works. We just put all of our faith and trust into our doctors and our genetic counselors that we're hooked up with. Why, you ask? Because it is so overwhelming just to live with this each day...”* Therefore, participants claimed that if they were not informed of research in clinic, then they were not seeking research opportunities for their sons. Many participants professed they were never introduced to research while in clinic, *“I can't tell you how many times I've been to clinic and not one time, I've been told about a trial. Not once, and I've been to many clinics.”* These participants felt deprived of the opportunity to participate in research and to also learn more about the research process.

Additionally, participants were not receiving appropriate resources and educational materials that they felt should be provided by the healthcare team in clinic. Participants claimed they were confused about the research process, uneducated, and did not know the appropriate questions to ask about research. One mother mentioned, *“Yeah, but if you've got a parent who's sitting there, who's totally devastated with their child, and not knowing what to do, and then not educated enough—I'm sorry. I'm not trying to say anybody's stupid. I'm just saying they're not educated to say, 'What can I do for my son?'”* Participants expressed feeling lost and did not know where and how to access resources associated with research in DMD. Finding and receiving appropriate resources became another battle for parents to fight. One mother stated, *“I*

don't know these resources, until this comes along, where we're actually sitting down. I've got about ten things that have been told to me that I was like, "Well, I didn't even know to ask." I don't know who to go to for." In addition to lack of resources, participants felt they were not receiving enough encouragement and support to participate in research. One participant stated, *"What can you do for the moms and the kids who can't, and really need to be a part of these studies to save their life and to save others? They don't have the resources and they don't have the support."*

Race/ethnicity and socioeconomic status were also mentioned by several participants as being a significant determinant of whether families received access to appropriate resources and research opportunities. One mother described challenges for non-English speaking families in her community:

... we have a lot of non-English-speaking families. They're not involved in any trials because they don't get the information correctly. They just don't get information, period. They don't have the funds to even have a computer to even know that this exists. They just don't have the resources.

One father mentioned his frustration as a Hispanic individual, *"When I go to the clinic, I see two, three, four, even nine more patients that speak nothing but Spanish. If it wasn't for [our MDA representative], that connection would be lost. As far as studies or information in Spanish, none."* Another mother discussed her first-hand experiences as a woman of color and touched on barriers in which minority groups are faced with:

The issue for research for people of color is that we're not always involved in these things. We don't always get access. We don't always get information. Most people of

color are not wealthy. They do not have the funds. You have to have education in order to be able to make informed decisions.

As most participants felt uneducated on the essence of research, participants admitted they had to educate themselves on research in DMD. Participants were overwhelmed and did not understand what research their son qualified for. The sheer complexity of research and sifting through research eligibility criteria became another battle in which parents faced. One participant stated, *“Understanding some of these other studies that are going on, it’s become very knowledge intensive. There’s confusion as to what do I qualify for? What would help my son?”* Most participants felt the study eligibility criteria are too strict and immediately prohibited their sons from participating in research. One mother described her experiences, *“Other studies, we haven’t done cuz our oldest is nonambulatory, and our youngest doesn’t take prednisone, so that cuts us out of every trial, basically...I think the criteria are too strict.”* Many participants whose sons were non-ambulatory concurred and felt a loss of hope persuading them not to participate. One mother stated, *“I think there’s probably a big drop-off once your child is no longer ambulatory, where there’s a sense of loss of hope.”* These participants felt as though they had lost the research battle and that there were no research opportunities left for their sons to participate in.

5.2.3 The Gamble

Participants expressed concern regarding perceived risks associated with research participation. A majority of participants (86%) felt that associated risks and fears placed families in a realm of the unknown in which they in essence, were taking a gamble on research and their sons. Parents described being forced to enter into a decision making process in which the benefits of research

participation must be weighed against the risks and factors that are out of the families' control. An invasive procedure involved in research was a major determining factor that many participants claimed persuaded them not to participate. One mother described her feelings:

I think some of the decision-making that we, as a family, have gone through partly has to do with how invasive the test is. There were some tests that we were—or some pilots or studies where it was gonna require them to go in and take a muscle out. As my son was progressing from walking to non-walking, we had to evaluate would this—how would this impede his healing process, his ability to continue to walk, to continue to have functionality? Would there be loss of functionality due to the invasiveness of the study that was going forward?

Although invasive procedures concerned parents, participants also mentioned how terrified their sons were of undergoing an invasive test. Many parents stated that their sons were at an age in which their opinion on research mattered and was ultimately the deciding factor as to whether their family participated in research. Several participants felt participating in research deprived their son of a “normal life.” One mother described the gamble their family faced between letting their son live a somewhat “normal life” versus having him participate in a research study that may increase his quality of life, “...it's more of a pain or an obligation or something I'll do for mom...—he sees himself as normal...when he comes and does a study, or he does something, it points out his differences. It points out his disabilities...”

Participants discussed a level of uncertainty associated with research participation. This uncertainty left many participants to question research participation and if it is really the right decision. Along with a level of uncertainty expressed by participants, came concerns for safety and unspecified side effects that may be associated with a particular research intervention.

Participants discussed many uncertainties associated with participation in research studies. One mother described her battle between weighing the risks and benefits, *“For us, we’ve contemplated the whole risk over the benefit, and what’s more important, quality or quantity for us? It’s a battle.”* Many participants discussed fear of the unknown consequences, risks, and even benefits when pursuing participation in research in DMD. One mother mentioned, *“It would scare me. I would need to know the side effects...I would need some type of information in front of me to make that educated decision to say, ‘Okay, is this worth a risk or not?’”*

When considering the benefits and risks to research participation, several participants saw an immense level of benefit to particular drug trials, such as exon-skipping trials. Therefore, many participants felt the possibility of being assigned to a placebo was too much of a gamble and elected not to pursue participation in research. One mother expressed:

They see that placebo, and they don’t want to take the chance of being on that placebo to be excluded. That’s a huge factor. I think placebo is one of the main reasons why many people just don’t do it. Why take that risk? In my opinion, I honestly think in Duchenne, since it is a rare disease, placebos should not exist...I think for Duchenne, they don’t have time. I think it’s really a waste of time.

Several participants stated they would consider enrolling their son in research if his participation would not impact his eligibility for other research opportunities. One mother attested to this viewpoint echoed by many participants, *“Let’s say it’s something that could help his strength and we know it wouldn’t impact his eligibility for [another drug trial] ...we would probably consider it.”* However, other participants felt it was too much of a gamble to risk enrolling their son in a research study at the cost of potentially becoming ineligible for another, more desirable study.

One mother claimed. *“So I guess there is one that I chose not to pursue, and the reason I chose not to pursue it is because I was holding out for the exon-skipping study.”*

The notion of “holding out” was expressed by participants in the majority of the focus group sessions. Participants felt they had received insightful knowledge regarding which research studies were perceived as most successful within the DMD community. The perceived promising studies were appealing to most families and participants admitted to declining on available research opportunities to wait for a better research opportunity. One mother stated *“...We have been told he will be in trial within a year, and probably getting this. Yes, we wanna participate but we will hold off until we get that. Because we have seen the research, and we know what it's doing. We know it will keep him alive.”* Another mother further elaborated on this notion and described the gamble that many participants may take:

I guess, too, when you hear about something in particular that you've put so much hope in and that you think has so much promise—especially like the exon skipping—you kind of put that at the top and then you filter everything else based on how it'll affect our ability to get into that or what it'll affect if that comes along. I think a lot of the gamble we take and the decisions that we make are based on what we feel the most hope for going forward.

5.3 IMPACT OF RESEARCH BARRIERS ON FAMILIES

As participants discussed barriers they faced and perceived limitations to participating in DMD research, families also alluded to these barriers having significant impacts on their families. These impacts placed additional strains on families and also appeared to play a pivotal role in the

family's decision to enroll in research studies. One mother shared an opinion echoed by many participants, “...because my son deserves—each one of my children deserve to live life in joy. I don't wanna do it [research] at a cost where it all passes by, and my family has nothing.”

Almost all participants discussed various impacts on their families as a result of participating in research studies and/or due to barriers prohibiting them from participating. One mother outlined the many aspects of families' lives that can be impacted:

We have sacrificed family vacations. We have sacrificed birthday parties. We have sacrificed my job. I had to quit my job. I want to say just in the past three weeks for different studies, we've traveled, I don't know, 2,000 miles? ...We've put a lot of miles on our car. We've had to get another new car because we put so many miles on our other car. My husband basically works just to get us through appointments, medication, and studies. Financially, it takes a toll.

Participants described financial burdens, sacrifices, and psychological stress that families endure in order to overcome barriers and limitations they face when asked to participate in research.

5.3.1 Financial Burden

Most participants agreed that participating in research posed a financial burden to families. Participants discussed the financial challenges, which limited them from participating in research. Several participants claimed they would be jeopardizing their job in order to participate in research. One mother expressed, “... we have really to weigh the pros and cons...You have to make sure that you can afford to leave for work. You may not get paid for it, for a leave. Will your job be there when you get back? One mother expressed how many families living paycheck-to-paycheck struggled just to provide for their son's disability and

having to take off work in order to participate in research was just another financial challenge placed on families. She stated:

..we needed a handicapped van, we bought a handicapped van. We needed a handicapped house, we moved to a handicapped house. We were able to do things for my son, but there are other families that don't have that...If you have a family where people are just regular people and they're dependent on every penny, and they live from paycheck to paycheck, then it's kind of hard.

Some participants greatly relied on two incomes to provide for their family. However, several participants discussed concerns for one parent having to give up his or her job in order to cover responsibilities associated with research participation.

Several participants mentioned their families had considered relocating to areas closer to research centers in order to get their son involved in research. However, participants also discussed the major financial burden associated with relocating their family. One mother described a discussion she had with her husband in relation to potentially relocating to Europe:

I mean we have thought about, "Well, what if we move to Europe and he could actually get this drug?" But then of course the financial burden came up because we can't just pick our family up and move to Europe and my husband would be able to get a job to be able to support our family. My husband had made the comment, like, "Well, I would have to stay here with our daughter and you would have to go and take [our son] for a year."

This participant alluded to an important topic discussed by other participants and the various sacrifices that families must account for when considering to enroll in a research study.

5.3.2 Family Sacrifices

The majority of participants discussed strains placed on their families when asked to participate in research in DMD. Participants reported making many sacrifices in order to take part in research studies. Participants discussed the commitments required to participate in research and how those commitments have taken away from their time spent with family. One mother expressed her thoughts, *“I’m thinking, what the heck am I doing? This is taking my valuable time, our precious short time we have together, away from my family.”* One mother explained that the research visits became their family vacation and was not something their family enjoyed:

Because really, I’d like to take a vacation to Hawaii or something with my family, rather than spend all the time—I spent the last 10, 11 years going [for research]. That’s been my biggest vacation trip. Duchenne is important, and to change the course of it, but that’s not necessarily what my family’s enjoyed.

Families considered the time they have with their son and each other, to be precious and valuable. One participant questioned, *“That’s when I start to think, ‘Why am I here? Why am I here? I should be out at the park, with my son, because how many of these days am I gonna have?’ That becomes frustrating.”* Participants described making shifts in their daily lives in order to accommodate for participating in research. These shifts in their daily lives were reported to have significant impacts on their loved ones. Many participants expressed concern for their unaffected children. One mother stated, *“...because I have two other kids. That is one of my big things. I don’t want them to feel like they’re off to a side for possibly a year while I’m just focused on [son with DMD].”* Despite the best effort of parents to not appear as though they are giving all their attention to their son with DMD, many participants admitted that siblings often felt neglected. One mother claimed:

Siblings have often felt like they're forgotten...Our son is the youngest of our three. I know, with my own children, sometimes they'll be like, "I'm right here. You never listen." It's like, "I do hear you, and I am multitasking...They feel, because you focus so much on the weakest one that they're forgotten. It's, again, striking that balance.

In addition to impacts on siblings, participants also discussed impacts and strains on their marriage and committed relationships. One mother stated, *"If you are lucky enough, fortunate enough to still be married, because many, by the way, are divorced...you're losing your better half... Are you strong enough to go do that alone with your Duchenne son? I don't know if I would be."* Though most participants were either married or in a committed relationship, several participants discussed experiences of single parents in the DMD community and the overwhelming commitments they are faced with, limiting their participation in research, *"When you're a single mom or you don't have time, you don't have money, you have other kids, you have other commitments."* Participants also mentioned consequential split parenting as a result of choosing to relocate to provide their son with more research opportunities. One mother stated, *"Then usually, it's just one of the parents that goes [to research visits] because both parents can't take time off. One has to stay with the other [children]."*

5.3.3 Psychological Stress

Many participants discussed challenges to managing study participation as a result of psychological stress associated with the many barriers to participating in research in DMD. Parents shared how they are already overwhelmed by DMD in and of itself and mentioned that research contributed to an additional layer of emotional stress and frustration. One mother stated, *"... it's our career. It's what we do. Our job is managing Duchenne. We don't ever get a break*

from it.” Participants discussed feelings of isolation associated with a new diagnosis and how families who just learned that their son has DMD may be unaware of research opportunities and where to turn to learn about them. One mother added, *“I felt like a psycho person, very emotionally distraught, because it is very frustrating with research.”*

Participants conversed about mixed feelings regarding research participation. Participants discussed the tug of war between motivations to participate in research and the many barriers discouraging their participation. One mother stated, *“It’s [research] a collaborated team effort, but it’s also an emotional rollercoaster. It is pay it forward. It’s also when’s it gonna happen, will it happen in time, and your heart breaks for others, and it breaks for your own child. It’s all of that.”* Some participants described feeling helpless and alone, particularly those parents in which cultural barriers played a role. Although all of the participants spoke English, some participants mentioned the challenges other families in the DMD community faced who did not speak English. One mother stated, *“The language barrier for the families that are in areas that they can’t communicate, and they feel exceptionally alone because there’s people they can’t even talk to, to share that.”*

Additionally, participants expressed how they wanted to help their sons as much as possible, but were constrained if their son was unable to qualify for certain research studies. One mother clearly stated, *“I don’t feel like I do enough, because sometimes we feel helpless because there’s only so much we can do as parents.”* Several participants perceived study criteria as being too strict and resulted in underlying emotional turmoil and anxiety. One mother shared her feelings regarding her sons’ inability to qualify for research studies:

It is upsetting at times to see that one-in-a-million kid who fits the criteria for whatever study, and you see them benefiting from it. That’s definitely difficult. I personally wish

that you had to be on a gag order, if you have a child in a study, that you should not be able to talk about it. Because I think for some people, especially the newly diagnosed who haven't really understood all the processes they have to go through, that could really send someone, emotionally, I think, in a place that's not good...Having two boys...neither of them qualify for anything...It is frustrating.

Along with the many frustrations regarding the barriers associated with research participation, participants also expressed increase worry and fear related to the uncertainty of research studies in DMD. Participants exchanged opinions regarding their sons undergoing invasive procedures and also being potentially exposed to experimental drugs in which the risks are unknown. One mother stated:

I'm allowing you [researchers] to take my kid and put something in his body with the hope that it will help him or someone else. Whether it's a placebo or not, I'm letting you fundamentally mess with my kid...With the chance that it's gonna hurt him when he already has a terminal disease...He's a person with a terminal illness with a short amount of time.

Participants talked about challenges of trying to weigh the potential of helping their son and “paying it forward” versus exposing their son to pain and invasive procedures. Participants discussed the benefits and desire to participate in research, but the worry and guilt felt by some participants weighed heavily on their decision to allow their son to participate in DMD research. One mother shared her feelings, “...that was the first study that we did and I was just more worried because they were doing a skin biopsy and just kinda felt guilty that we were inflicting pain on him to do the skin biopsy. Then, too, was worried. Will he be able to even make it through the whole MRI thing? Would it scare him?”

The level of psychological stress was not only affecting parents but according to some participants, also had an impact on their sons. One mother discussed the difference in how parents can perceive research as providing hope while their sons struggled with the emotional sequelae associated with research participation. One participant stated, *“We’re getting there, but they [boys/young men with DMD] don’t necessarily see these trials as hope, where the parents tend to look at them as hope. They tend to see it as pointing out where they’re not normal. I think for adult children that that’s an issue. On the social emotional level for them.”* Several participants described the desire for their sons with DMD to be able to relate to their peers and lead a “normal life.” Participants expressed how some boys and young men with DMD do not view research as fun and therefore, discouraged their participation. One mother stated, *“...it’s not fun for them. They don’t wanna go, they’re discouraged. They already have enough anxiety in their day-to-day activities. They just wanna feel normal and be able to relate to someone.”*

6.0 DISCUSSION

The present study utilized qualitative thematic analysis to identify parent perceived barriers to research participation and identified how those barriers may impact families in the DMD community. Participating in research was shown to affect many aspects of participants' lives and additionally had an impact on the entire family. Families expressed a desire to participate in research studies, but not at the cost of their families. As each family shares its own particular experiences and psychosocial perspectives related to research participation, a potential theory suggested from the data may be described as finding the right type of research study, for the right family, at the right time in the disease process. These findings highlight the need for greater support and appropriate resources to alleviate potential barriers faced by families. Results of the present study additionally identified a novel barrier to research participation and is one of the first studies to characterize the notion of "holding out" for a desired research study in the DMD community.

6.1 BARRIERS OF RESEARCH PARTICIPATION

Studies have been conducted to identify family perspectives, motives, barriers, and impacts of research participation within various disease populations, most prevalently within the cancer population.⁴² Although, studies have not focused specifically on barriers to research participation

within the DMD community. In the present study, three main barriers or sub-themes were identified: 1) commitments; 2) fighting a new battle; and 3) the gamble. Barriers to research participation identified in the present study were similar to those found within cancer populations. However, parents of children diagnosed with a progressively fatal disease, such as DMD, face different challenges compared to children with cancer or other disease diagnoses and therefore, additional barriers potentially unique to DMD and rare disease populations were identified.⁴³

The barrier of “commitments” described the dedication and many commitments required of families to participate in research. Most participants concurred that participating in research in DMD is an overall investment requiring a major commitment from all aspects of families’ lives. Factors that were found to influence the decision making process for families included time constraints, distance and travel to study sites, and interferences with work, home, and/or personal responsibilities. These barriers associated with the many commitments required to participate in research are similar to those that have been identified in other studies.⁴²

Additional time and effort, including costs and travel, have been described in the literature as being concerns of patients participating in research.^{74; 75} Results from the present study revealed similar findings and identified significant time commitments involved in research participation, which consequently forced many participants to take off work in order to travel to research centers. Participants mentioned they would have to use up all their vacation days at work in order to maintain the travel and time commitments involved in research participation. Therefore, the decision to participate in research left many participants concerned about jeopardizing their job and main source of family income. However, parents who were fortunate

to have jobs that allowed them the opportunities to take time off from work and travel to research centers were still imposed with travel commitments.

Participants referenced geographical location and proximity to research centers as factors influencing their decisions to participate in research. Cancer studies have also found that transportation barriers or distance to a clinical trial site is a limitation identified by many patients.⁷⁵ One study comparing barriers to clinical trial participation in rural and urban communities in South Carolina, found that there were no significant differences in willingness to participate in clinical trials, but did indicate that rural residents were more likely to lack awareness of available research opportunities and perceived access to research sites as a limitation to research participation.⁷⁴ Results from the present study suggested similar findings in that participants living in rural areas, or areas with limited research opportunities, were perceived to have a greater travel commitment than those living in urban or suburban areas that were more conveniently located to research centers. Additionally, travel to research centers may become an overwhelming barrier to participation, due to physical impairments associated with DMD.³⁹ Many DMD studies require multiple trips to research centers, which make continuous involvement in research studies a difficult task for families. Given that most participants' sons required the use of a wheelchair, a majority of the participants in the present study discussed the difficulties of traveling with a child with a disability. As many participants mentioned long hours and/or days of travel by plane, car, and bus, challenges associated with travel limited many families from participating in research. Other rare disease studies have also characterized particularly burdensome travel commitments associated with transporting a child with a disabling disease.⁸

As traveling and taking time away from work to participate in research imposed multiple strains on the parents, it was also suggested to be a commitment for their sons with DMD and required some unexpected commitments. Some studies have shown that participants struggled with understanding the full extent of their commitments associated with research participation, even when undergoing an extensive informed consent process.⁹ Some of these unexpected commitments or commitments that parents did not consider, may have a significant impact on their sons with DMD. Results of the present study revealed that some boys and young men with DMD had to miss school and were hindered from attending other doctor appointments that were crucial to their well-being. Therefore, the major commitments required of families to participate in research added to the overwhelming challenges that parents already experienced with the diagnosis of DMD alone.

In addition to the overwhelming challenges of caring for a child with DMD, frustrations and multiple complex elements associated with research participation became a new battle for families to overcome and was described by the barrier of “fight a new battle.” With progressive and life limiting disorders, such as DMD, time can be the ultimate enemy and present many pressures that affect the decisions of parents to involve their child in research studies.^{8; 39} Some studies have identified an inconvenience to everyday life, as a potential barrier to research participation in cancer clinical trials.⁷⁵ Similarly, participants in the present study discussed the daily challenges associated with DMD and how the challenges of the disease may limit them from participating in research altogether. Results showed that some participants relied on healthcare providers to inform them of research opportunities since families felt so overwhelmed. Therefore, if participants were not informed of research opportunities while in clinic, then they were unaware of research opportunities for their sons and less likely to

participate. Surprisingly, many participants were never introduced to research in the clinical setting and were forced to educate themselves on research in DMD through other means.

Additionally, cancer studies have found that barriers to research participation included patients who were not informed or not given adequate information on research studies, similar to findings outlined in the present study.⁵⁹ Some participants expressed a desire to participate in research, but mentioned they did not receive appropriate resources and educational materials to familiarize them about research opportunities. Participants admitted they did not know the appropriate questions to ask and to whom they should direct their research questions. Studies have shown that individuals are less likely to participate in research studies that they are unfamiliar with.⁷⁶ These findings are similar to those identified in the present study in which some participants claimed they were confused about the research process and sometimes felt uninformed. One study found highly educated individuals were more knowledgeable about participation in research.⁵⁹ This may be supported in the present study as most participants were well-educated and active within the DMD community, which may have contributed to a better understanding of DMD research studies.

As research is a topic new to many families, studies have shown that parents need sufficient time to ask questions, to digest information regarding research participation, and require adequate psychological support.^{77; 78} Results of the present study showed that participants had a lack of resources, and were not receiving enough encouragement and support to participate in research. Race/ethnicity and socioeconomic status were mentioned by several participants as being a significant determinant of whether families received access to appropriate resources and research opportunities. Though all participants spoke English, several participants identified with an ethnicity/race aside from Caucasian/White. As most diagnosed cases of DMD are

reported in Non-Hispanic/White individuals, racial/ethnic specific prevalence has been found to be the highest for Hispanic individuals.⁷⁹ According to the United States Census Bureau, as of July 1, 2013, 55% of the Hispanic population lived in California, Florida, and Texas. Interestingly, participants from the Houston and Sacramento focus groups sessions were most vocal about language and cultural barriers associated with research participation in DMD. Other participants discussed racial barriers limiting African American populations from gaining access and information about research opportunities in DMD. These findings highlight the urgency to address needs expressed by families experiencing cultural barriers to research participation and providing appropriate resources.

Participants additionally felt confused and did not understand what research their son qualified for. As patient registries, such as DuchenneConnect have been useful tools to notify patients of research opportunities, the utilization of registries was not consistently referenced by parents. Participants also felt study eligibility criteria were too strict and immediately limited their opportunities to participate in research. Most research in DMD desires younger study participants at an early disease stage and therefore, study eligibility criteria typically exclude most non-ambulatory individuals with DMD.⁶ As a majority of the participants' sons with DMD were non-ambulatory, most participants felt as though there were no research opportunities left for their sons to participate in and felt a loss of hope when their sons were not able to qualify for studies. However, those participants whose sons did qualify for research studies still felt participating in research was similar to taking a gamble in which families had to weigh the benefits and risks.

The barrier of “the gamble” described the perceived risks and fears associated with research participation that families must consider when deciding whether engaging in a specific

research study is worth the gamble. Weighing the benefits and risks to research participation in the DMD community has been previously described and one study found that families were more willing to accept greater risks and side effects for a disease in which there is currently no cure. However, the study also found that parents were not willing to expose their sons to infinite risks.¹⁰ One study found that factors contributing to negative research experiences, including pain and discomfort associated with invasive procedures, and adverse side effects related to the research intervention, played a significant role in determining whether families participated in research studies.⁴¹ The use of an invasive procedure in the present study was a major determining factor that persuaded some participants to not participate in research studies. Results of the present study additionally found a level of uncertainty associated with research participation regarding concerns for safety, unknown consequences, and the potential for adverse side effects or loss of functionality. Similarly, one study identified families experiencing negative emotional impacts due to stress associated with invasive procedures and disappointment related to their sons' deterioration.⁷ Participants in the present study also felt pressured to allow their sons to live a "normal life" without multiple research visits, but were conflicted with the potential of research studies to increase their sons' quality of life and provide hope.

Due to the progressive and fatal nature of DMD, families may become acutely sensitive to any possible suggestion of hope for potential treatment options. It has been documented that families may become vulnerable to exaggerated hope and therapeutic misconception as a result of high trial expectations.^{6; 41; 43} Results of the present study indicated that participants felt the possibility of being assigned to a placebo was too much of a gamble to take for a disease in which there is currently no cure and reduced life expectancy. Therefore, participants felt that placebos were a waste of time that their sons ultimately did not have to spare. Additionally,

when considering the benefits and risks to research participation, several participants saw an immense level of benefit to certain drug trials, such as exon-skipping trials. The present study highlighted a novel barrier to research participation in which participants would hold out for a more desirable research study, such as exon-skipping, than to risk their son being ineligible due to his enrollment in what they perceived to be a less promising study. Participants mentioned that the ultimate gamble regarding research in DMD is based on what will provide the most hope going forward. Participants admitted they would refrain from enrolling in a research study in order to wait for their sons' specific mutation to be included in the study criteria for a more promising study. This is the only study known by the researcher to characterize the notion of "holding out" for better research studies in the DMD community. Given the hype of promising research and active parent/advocate groups, this notion may be present in the wider DMD community and should further be explored.

6.2 IMPACT OF RESEARCH BARRIERS ON FAMILIES

Participating in DMD research can impact many aspects of families' lives. As participants discussed barriers they faced and perceived limitations to participating in research, parents also alluded to these barriers having significant impacts on their families. Challenges that families experienced when asked to participate in research required families to make many sacrifices affecting their families financially, psychologically, and structurally. Psychosocial issues experienced by families were shown to potentially affect a family's ability to fulfill the commitments required for research participation and presented as an additional barrier for

families. The impact of research barriers on families was found to play a pivotal role in a family's decision to participate in DMD research.

Families already endure a variety of costs and loss of work hours associated with the diagnosis of DMD alone.⁵⁶ Results of the present study found that research participation may present a greater loss of work hours and additional financial stress on families. Participating in research was shown to be a major commitment that forced parents to take time off work in order to travel and fulfill research requirements. Taking time off work may result in families suffering a loss of wages and consequently jeopardize their jobs. These financial challenges and additional barriers associated with research participation also resulted in psychological affects on families.

The diagnosis of DMD can have a multitude of affects on the entire family and result in many psychosocial consequences.^{28; 51; 52; 50} Managing the many commitments required to participate in research added an additional layer of emotional stress to the many challenges families already faced with the diagnosis of DMD alone. Some participants described feeling helpless, emotionally distraught, and overall uninformed about research opportunities. These emotions may be a result of families not receiving appropriate resources and support to actively engage in research opportunities. Not being able to appropriately engage in research opportunities left many participants feeling frustrated. Participants felt it their job, as parents, to do everything they can for their sons, but encountered a blockade when their sons were not qualifying for research studies. As participants admitted to "holding out" for mutation-specific research interventions, such as exon-skipping trials, families are forced to wait for the inclusion of their sons' specific mutation in order to be eligible for those studies. One study found that many parents associated doing nothing with accepting the fate of early death in DMD.⁸ In the

present study, the inability for participants' sons to qualify for research studies may be comparable to accepting the fate of early death and resulted in a lack of hope experienced by some parents.

Participants desired to have their sons participate in research as a way to "pay it forward" to future generations, but perceived certain aspects of research to include significant risks and felt an increased level of worry and guilt by allowing their sons to be exposed to a potentially invasive or harmful research intervention with uncertain consequences. Guilt has been a common emotion parents experience with the diagnosis of DMD, but to the researcher's knowledge, has not been associated with regard to their sons' participation in research studies.⁷⁹ The potential for risks associated with research participation also had emotional impacts on participants' sons. Results of the present study found many parents perceived research as providing hope, while some of their sons felt research limited them from living a "normal life." Some participants' sons perceived research participation as a constant reminder of the challenges they face and having to miss out on things they enjoy, because their days revolve around research visits.

The many psychosocial and financial implications of research participation can additionally impact family relationships. Though the many commitments required of families to participate in research allowed parents to spend more time with their sons with DMD, results showed that those commitments also took away valuable family time with other family members and added strains on their marriage and/or commitment relationships. Findings also showed that some participants felt they were neglecting their unaffected children. Unaffected siblings in the DMD community have been shown to have an increased risk for emotional problems and rebellious behavior due to feelings of jealousy, neglect, and isolation.⁸⁰ Results of the present

study highlighted similar concerns for neglect of unaffected siblings and may suggest that feelings of jealousy and isolation would intensify in unaffected siblings when families elected to participate in DMD research.

The present study focused solely on the barriers to research participation, with the purpose to highlight the impacts these barriers have on families and the need to provide support and resources to families to alleviate these barriers. Families expressed a desire to participate in research studies, but not at the cost of their families. Since each family shares its own particular experiences and psychosocial perspectives related to research participation, each family is impacted differently and has its own set of unique needs to be addressed. A potentially useful theory may be suggested from the data and can be described as finding the right type of research study, for the right family, at the right time in the disease process.

6.3 POTENTIAL IMPLICATIONS FOR GENETIC COUNSELORS

Genetic counselors may benefit from understanding barriers families face and the impacts these barriers can have on patients and their families when asked to participate in DMD-related research. Barriers and limitations to research participation can result in psychosocial sequelae impacting the entire family. Genetic counselors play a significant role in providing psychosocial support to patients and their families. Therefore, results identified in the present study may have potential implications for genetic counselors and other healthcare providers occupying a similar role.

As defined by the National Society of Genetic Counselors (NSGC), genetic counselors serve as a resource to patients and their families by helping them to understand and adapt to

medical, familial, and psychosocial implications associated with a genetic condition. Genetic counselors often play a pivotal role in communicating research opportunities to patients and their families.⁸¹ As many genetic counselors hold an additional position as a study coordinator with both clinical and research responsibilities, genetic counselors may be involved in the recruitment of research participants. Therefore, genetic counselors can make the initial introduction of research and provide resourceful tools for families to keep them up-to-date and informed on research opportunities.

Additionally, genetic counselors serve as advocates for all patients and their families according to their specific needs. As barriers to research participation may be shared amongst families in the DMD community, barriers and limitations present in varying degrees and are unique to each family. Additionally, effects of barriers and limitations to research participation can have divergent impacts on families. Genetic counselors have the skills to tailor each session to address an individual's or family's specific needs. Therefore, genetic counselors can play a significant role in providing individualized support and resources to families interested in research opportunities in effort to mitigate barriers faced by families.

6.4 STUDY LIMITATIONS

Since this study involved in-depth focus group sessions it is possible that the study attracted parents who are more active in the DMD community, had a strong support system, and more willing to discuss their thoughts, feelings, and experiences regarding research participation. This may also reflect the challenges of the study to recruit families who had never participated in DMD research. Though families who had not been involved in research studies in DMD were

represented in the study, engaging these participants was a struggle for both the research team and the associated CINRG/MDA clinic teams assisting with recruitment of participants. As recruitment strategies were mainly carried out in a clinic setting and through shared communication via email and social media, participants not being followed in clinic and not connected within the DMD community may not have been reached and represented in the focus group sessions. Although recurrent themes were identified from conversations with parent participants, their experiences may not be universally representative of all families in the DMD community.

Additionally, available focus group dates were limited given the time commitments and restricted travel dates for the researchers. Focus groups dates were based upon the schedules of the researchers and associated CINRG/MDA clinic team members. To maximize convenience, participants were provided with at least two potential dates for focus group sessions and asked to respond with their preferred date. Attempts were made to select the most convenient date and time for the majority of participants at a particular study site. However, researchers were unable to accommodate requests by all participants and therefore, prohibited some parents from participating in the focus group sessions.

Though focus groups were selected as an appropriate research method for the study, it is recognized that this methodology has associated limitations.⁸² Efforts were made to ensure confidentiality of research participants; however, given the nature of focus group discussions, absolute confidentiality cannot be guaranteed. The relatively small number of focus group participants limited the extent of experiences shared. As the exchange of information in focus group discussions may have elicited important perspectives, it may have also hindered responses from participants with dissenting opinions and therefore, reflect greater consensus on a particular

phenomena than is warranted. Sensitive and personal topics were brought up during focus group sessions in which participants may have been reluctant to provide full disclosure of their experiences. The focus group moderator incorporated techniques to ensure each participant's opinions were shared; however, some participants may have been reluctant to share their perspectives and opinions. Additionally, as one of the project researchers and author of the present study, my personal experiences and relationship to DMD brought personal bias to the study and may have shaped the interpretation and understanding of the data.

The present study focused solely on barriers to research participation in DMD. This information may present negative connotations associated with research participation and does not provide a complete representation of all perspectives described by participants, including the many benefits and motivations to participating in research in DMD.

6.5 FUTURE RESEARCH

The present study is part of a larger research study aimed to understand barriers to engaging the DMD community in research and to develop strategies to assist with recruitment efforts. This project is important to provide insight to research strategies that may increase enrollment and participation in research studies and may support both families participating in research and clinicians involved in clinical research in DMD. As results of the present study identified many barriers and impacts families face when participating in DMD-related research, the larger study will additionally identify motivations and benefits to research participation. Assessing benefits to research participation and understanding why families elect to participate in research in DMD will not only complement the barriers faced by families, but also inform researchers and

healthcare providers on benefit-risk determinations and assist with development of strategies in which providers can better support families interested in research opportunities. The larger study also explicitly asked parents to develop a recruitment plan for research studies in DMD. This data will be beneficial in the development of recruitment strategies and resources to potentially alleviate barriers faced by families when asked to participate in research in DMD. Future research aimed at development of these strategies and incorporating participants' suggestions into the clinical research process may inform ways to maintain research benefits and minimize the associated barriers. Studies should be developed to assess implementation of these strategies into both a clinical and research setting. Additionally, as the present study only highlights the barriers and impacts associated with research participation as it relates to families, the larger study looked at the barriers to research recruitment as perceived by clinicians and researchers involved with research in DMD. This data will be significant to assess areas in which parents and clinicians/researchers identify significant gaps in research participation in DMD and areas in which they share similar viewpoints on ideas for research engagement. Future research may also benefit from exploring and understanding perspectives of boys and young men regarding participation in research in DMD.

Results of the present study identified major commitments and additional challenges placed on families, complexities and educational barriers associated with research processes, and perceived uncertainties and risks associated with research participation in DMD. Results from this study may assist with developing questionnaires and surveys to assess families' understanding of research and potentially direct researchers' and clinicians' conversation about research opportunities to meet the unique needs of the families. This information may provide a stronger foundation to further develop appropriate resources for patients and their families. As

genetic counselors play a significant role in educating families on available research opportunities, future studies may explore counseling techniques and approaches utilized by genetic counselors to introduce families to research opportunities and to help families understand and adapt to the psychological and familial implications associated with participating in research in DMD or other rare diseases.

Since many participants mentioned participating in research would add to the current challenges associated with the diagnosis of DMD, future research should aim to identify the appropriate time to introduce research studies to families. Studies could assess parents' views of when the most appropriate time to introduce research is compared to when providers' deem introducing research studies is most appropriate. Results of the present study highlighted a novel barrier to research participation expressed by some families in the DMD community as the inclination to 'hold out' for a more desirable research study. This tendency is likely be the present in the larger DMD community given the increasing publicity of potentially promising research, such as exon-skipping trials. Future research should explore this novel familial perception of research participation.

According to the National Institutes of Health (NIH), rare diseases affect 25 to 30 million individuals in the United States. Most rare diseases lack effective treatment options and present many challenges to the medical community. Recruitment of eligible participants is a challenge for most rare disease researchers, which hinders the progress for development of effective treatments and increases the barriers already faced by researchers and families.^{28; 33} As results of the present study compared to similar challenges of research participation identified and published in other diseases, these results may be applicable to barriers and limitations to research participation experienced by families in other rare disease populations.^{8; 33; 37; 41; 42} Future

research should explore perceived barriers to research participation and their impact on families in other disease populations, as similar approaches and strategies to engaging research participants may be more broadly applied.

6.6 CONCLUSIONS

This study serves as one of the few studies to explicitly identify parent-perceived barriers to research participation and the impacts these barriers have on families when engaging in research in DMD. The results demonstrated that electing to participate in research studies in DMD is a major commitment requiring planning, effort, understanding, and support from all stakeholders including family members, community members, and clinic/research team members. Participating in research was shown to affect many aspects of patients' lives and additionally had an impact on the entire family. Families should consider the commitments required and the potential psychosocial effects prior to engaging in research in DMD. Due to the overwhelming challenges shadowing many families in the DMD community, access to appropriate resources and support is essential to alleviate potential barriers faced by families. Clinic study staff, including genetic counselors, can assist families in exploring potential barriers and impacts on families. Identifying barriers of research participation and understanding how these barriers may impact families have significant public health implications which can provide information to improve research protocols, facilitate development of educational resources, and influence public health policies to provide additional support to families and encourage greater research involvement. Future research should assist in development of recruitment strategies and resources to potentially alleviate barriers faced by families when asked to participate in research

in DMD, as similar approaches and strategies to engaging research participants may be more broadly applied to other rare disease populations.

APPENDIX A: IRB APPROVAL LETTERS



University of Pittsburgh
Institutional Review Board

3500 Fifth Avenue
Pittsburgh, PA 15213
(412) 383-1480
(412) 383-1508 (fax)
<http://www.urb.pitt.edu>

Memorandum

To: Roxanna Bendixen
From: Christopher Ryan , Vice Chair
Date: 3/5/2014
IRB#: [PRO14010024](#)
Subject: Strategies for Engaging Duchenne Muscular Dystrophy (DMD) Community in Research

The University of Pittsburgh Institutional Review Board reviewed and approved the above referenced study by the expedited review procedure authorized under 45 CFR 46.110 and 21 CFR 56.110. Your research study was approved under:
45 CFR 46.110.(6) data/research
45 CFR 46.110.(7) characteristics/behaviors

The IRB has approved the advertisement that was submitted for review as written. As a reminder, any changes to the approved advertisement would require IRB approval prior to distribution.

The risk level designation is Minimal Risk.

Approval Date: 3/5/2014
Expiration Date: 3/4/2015

For studies being conducted in UPMC facilities, no clinical activities can be undertaken by investigators until they have received approval from the UPMC Fiscal Review Office.

Please note that it is the investigator's responsibility to report to the IRB any unanticipated problems involving risks to subjects or others [see 45 CFR 46.103(b)(5) and 21 CFR 56.108(b)]. Refer to the IRB Policy and Procedure Manual regarding the reporting requirements for unanticipated problems which include, but are not limited to, adverse events. If you have any questions about this process, please contact the Adverse Events Coordinator at 412-383-1480.

The protocol and consent forms, along with a brief progress report must be resubmitted at least one month prior to the renewal date noted above as required by FWA00006790 (University of Pittsburgh), FWA00006735 (University of Pittsburgh Medical Center), FWA00006000 (Children's Hospital of Pittsburgh), FWA00003567 (Magee-Womens Health Corporation), FWA00003338 (University of Pittsburgh Medical Center Cancer Institute).

Please be advised that your research study may be audited periodically by the University of Pittsburgh Research Conduct and Compliance Office.



University of Pittsburgh
Institutional Review Board

3500 Fifth Avenue
Pittsburgh, PA 15213
(412) 383-1480
(412) 383-1508 (fax)
<http://www.irb.pitt.edu>

Memorandum

To: [Roxanna Bendixen](#) , PhD
From: [IRB Office](#)
Date: 2/5/2015
IRB#: [REN15010145](#) / PRO14010024
Subject: Strategies for Engaging Duchenne Muscular Dystrophy (DMD) Community in Research

Your renewal for the above referenced research study has received expedited review and approval from the Institutional Review Board under:

45 CFR 46.110.(6)
45 CFR 46.110.(7)

Please note the following information:

Approval Date: 2/5/2015
Expiration Date: 3/4/2016

This approval is for analysis of data only.

Please note that it is the investigator's responsibility to report to the IRB any unanticipated problems involving risks to subjects or others [see 45 CFR 46.103(b)(5) and 21 CFR 56.108(b)]. Refer to the IRB Policy and Procedure Manual regarding the reporting requirements for unanticipated problems which include, but are not limited to, adverse events. If you have any questions about this process, please contact the Adverse Events Coordinator at 412-383-1480.

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Please be advised that your research study may be audited periodically by the University of Pittsburgh Research Conduct and Compliance Office.

APPENDIX B: LETTERS OF SUPPORT



January 27, 2014

Dr. Roxanna M. Bendixen, Ph.D.
Assistant Professor
Department of Occupational Therapy
University of Pittsburgh
5025 Forbes Tower
Pittsburgh, PA 15260

**RE: Support to participate in Strategies for Engaging DMD
Community in Research**

Dear Roxanna:

The Cooperative International Neuromuscular Research Group (CINRG) is a consortium of medical and scientific investigators from academic and research centers who share the common goal of wanting to positively impact the lives of neuromuscular disease patients and their families, such as families of children with Duchenne muscular dystrophy (DMD). As a CINRG site I enthusiastically offer support to participate in your project recently funded by the Foundation to Eradicate Duchenne to conduct patient-centered and research/clinician-centered focus groups to explore the challenges that exist in recruiting participants for research studies in DMD.

This letter is to demonstrate our support by participating as a site for parent and clinician-based focus groups. We are willing to provide support for recruitment, access to private facilities for focus group sessions, and guidance as necessary.

Thank you for the opportunity to assist with this important research protocol.

Sincerely,

Mathula Thangarajh, MD, PhD
Director, Neuromuscle Program
CINRG Medical Director, Children's National Medical Center,
Washington, D.C.

UNIVERSITY OF MINNESOTA

Twin Cities Campus

Paul and Sheila Wellstone Muscular Dystrophy Center

*MBB 4th Floor
Mail Code: 2641E
2101 6th Street SE
Minneapolis, MN 55455*

*Phone: 612-626-0822
Fax: 612-625-8488
<http://www.mdcenter.umn.edu>*

January 27th, 2014

Dr. Roxanna M. Bendixen, Ph.D.
Assistant Professor
Department of Occupational Therapy
University of Pittsburgh
5025 Forbes Tower
Pittsburgh, PA 15260

RE: Support to participate in Strategies for Engaging DMD Community in Research

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This letter is to demonstrate our support by participating as a site for parent and clinician-based focus groups. We are willing to provide support for recruitment, access to private facilities for focus group sessions, and guidance as necessary.

Thank you for the opportunity to assist with this important research protocol.

Sincerely,

Peter I. Karachunski, MD
Clinical Director, Paul and Sheila Wellstone MD Center



Texas Children's Hospital
www.texaschildrenshospital.org



Pediatric Neurology

January 27, 2014

Dr. Roxanna M. Bendixen, Ph.D.
Assistant Professor
Department of Occupational Therapy
University of Pittsburgh
5025 Forbes Tower
Pittsburgh, PA 15260

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This letter is to demonstrate our support by participating as a site for parent and clinician-based focus groups. We are willing to provide support for recruitment, access to private facilities for focus group sessions, and guidance as necessary.

Thank you for the opportunity to assist with this important research protocol.

Sincerely,

Tim Lotze, M.D.
Associate Professor of Pediatrics and Neurology
Director, Pediatric Neurology Residency Program
Texas Children's Hospital
Baylor College of Medicine



Department of Physical Medicine
and Rehabilitation

January 27, 2014

Dr. Roxanna M. Bendixen, Ph.D.
Assistant Professor
Department of Occupational Therapy
University of Pittsburgh
5025 Forbes Tower
Pittsburgh, PA 15260

RE: Support to participate in Strategies for Engaging DMD Community in Research

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This letter is to demonstrate our support by participating as a site for parent and clinician-based focus groups. We are willing to provide support for recruitment, access to private facilities for focus group sessions, and guidance as necessary.

Thank you for the opportunity to assist with this important research protocol.

Sincerely,

Erik Henriksen, MPH
Associate Director for Clinical Research
Department of Physical Medicine & Rehabilitation

APPENDIX C: PARENT PARTICIPANT RECRUITMENT FLYER

Seeking Participants for Duchenne Muscular Dystrophy Research Study

Strategies for Engaging the Duchenne Muscular Dystrophy Community in Research

What is the study about?

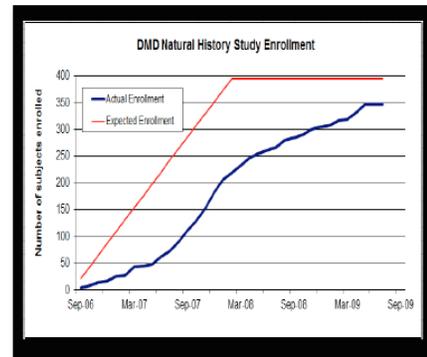
Researchers at the University of Pittsburgh, Department of Occupational Therapy, are conducting a research study to learn more about the challenges that exist in engaging and recruiting families for research in Duchenne muscular dystrophy (DMD). The purpose of this study is to conduct focus group sessions with parent(s) of boys diagnosed with DMD to learn about ways we can help to make participation in research easier. We are seeking both parents of boys with DMD who are currently or have in the past participated in research and parents of boys with DMD who have not participated in a research study.

Who can I contact for more information?

Roxanna M. Bendixen, Ph.D., OTR/L
Assistant Professor
Email: bendixen@pitt.edu
Office: 412-383-6603
Cell: 352-219-9903

Why is this study important?

Levels of participation in research studies for DMD have been lower than expected. This limits the ability of researchers to achieve and measure progress in clinical research, which can affect



how well new therapies perform in the real world. As a parent, you can help us to fully understand your feelings, and the challenges your family faces when asked to participate in DMD research with your son. The information gained in this study may help us to improve our recruitment efforts and support both clinicians involved in recruitment, and families participating in research in DMD.

What does the study involve?

- You will be asked to participate in a single focus group session with other parents of boys with DMD. The session will last about 90 minutes and will involve a set of questions about your thoughts and feelings toward participating in a research study.
- You may also be asked to participate in a follow-up phone interview to clarify information you gave in the focus group.
- You will receive \$25 for participation in the focus group session and will be paid for travel expenses up to \$60.

This study is funded by the Foundation to Eradicate Duchenne (FED)

APPENDIX D: PARENT PARTICIPANT CONSENT FORM



University of Pittsburgh

Parent Consent to Participate in a Research Study

Study Name: Strategies for Engaging the Duchenne Muscular Dystrophy Community in Research

Principal Investigator: Roxanna M. Bendixen, Ph.D., OTR/L
Assistant Professor
5025 Forbes Tower
412-383-6603
Email: bendixen@pitt.edu

The purpose of this research study is to conduct focus group sessions with parent(s) of boys diagnosed with Duchenne muscular dystrophy (DMD). We will ask approximately 70 parent(s) of a boy diagnosed with Duchenne muscular dystrophy (DMD) to participate in this focus group study. Since our study is focused on the challenges that parents of boys with DMD face when participating in research studies in DMD, we are seeking both parents of boys with DMD who are currently or have in the past participated in research (approximately 35 participants), and parents of boys with DMD who have not participated in a research study (approximately 35 participants). As a parent, you can help us to fully understand your feelings, and the challenges your family faces when asked to participate in DMD research with your son.

Assessment Procedures:

If you decide to participate in this study, we will ask you to participate in a focus group session one time only. The focus group session will take place at a private location. You may also be asked to participate in a follow-up phone interview to clarify information you gave us in the focus group session. The focus group session and follow-up questions will be performed by the principal investigator(s) who are trained and experienced in leading focus group sessions. Below is information about the focus group session.

- You (parent) will be asked to participate in a focus group session in person with no more than 6 other parent(s) of boys with DMD. The focus group session will take about 1-1/2 hours (90 minutes).

Page 1 of 4



University Of
Pittsburgh
Institutional Review
Board

Approval Date: 3/5/2014
Renewal Date: 3/4/2015

IRB #: PRO14010024

- We will ask you questions such as: what are your thoughts and feelings toward participating in a research study for DMD, what do you feel are the limitations to participation in research, what would help your family make the decision to participate in research, and what do you like or not like about research in DMD? We are trying to learn about the challenges that you and your family face and the ways we can help to make participation in research in DMD easier for families of boys with DMD.
- All focus group sessions will be audio (voice) recorded. We will take your audio-recorded interview and transcribe the information word-for-word directly into an encrypted desktop computer. This will help us make sure your personal information is secure. After we review the typed word-for-word transcript, we will destroy the audio (voice) recording.
- You may take as many breaks as necessary to complete the focus group session.

The possible risks and discomforts associated with this research study are minimal. You may find that some of the questions we ask the group are upsetting, or when you talk about past experiences regarding research in DMD or experiences you've had when someone has tried to recruit you to participate in research in DMD, it may bring up bad memories. Also, you will be participating in a focus group session with other parent(s) of boys with DMD. All participants will hear your discussions; some participants may say things that you do not agree with or they may not agree with you. Focus group sessions will be guided and monitored by the principal investigators of this research study, who are trained in leading and organizing focus group sessions. In addition, although confidentiality of discussions held during focus group sessions cannot be maintained within the session, all participants will be asked to maintain confidentiality of information discussed once outside of the focus group session. To reduce the likelihood of a breach of confidentiality, all researchers have been thoroughly trained to maintain your privacy. Access to your personal information will be limited to research investigators listed on this consent form.

You will not directly benefit from being in this study. We hope to learn more about the challenges faced by parents of boys with DMD regarding participation in research in DMD. You can help us to more fully understand the burdens placed on you and your son to engage in research studies.

There are no costs to you as a result of participating in this study.

You will receive a small remuneration of \$25.00 for participation in the focus group session. This remuneration will be provided to you whether you complete the focus group session or not. You will be paid for your travel expenses to attend the focus group session, up to a maximum of \$60.00. Travel related costs include all parking expenses and gas/mileage at \$0.45 per mile. Confirmation of mileage based on beginning location and parking receipts will be required for reimbursement.

To protect your privacy and maintain the confidentiality of information we obtain from you, we will keep all information about you in a secure location. Research records, including the audio taped and transcribed focus group session, will be stored in a locked file cabinet or in password-protected

Page 2 of 4

	University Of	Approval Date: 3/5/2014	IRB #: PRO14010024
	Pittsburgh	Renewal Date: 3/4/2015	
	Institutional Review		
	Board		

computer databases, and you will not be identified by name in any publication of the research results unless you sign a separate consent form giving your permission (release).

Although we will do everything in our power to protect your privacy and the confidentiality of your research records, just as with the use of your medical information for health care purposes, we cannot guarantee the confidentiality of your research records. However, **no third party**, including relatives, personal physicians or insurance companies, or other researchers **will have access to your identifiable information**, with these exceptions: In addition to the investigator(s) listed on the first page of this consent form and their research staff, authorized representatives of the University of Pittsburgh Research Conduct and Compliance Office may review your identifiable information for monitoring the appropriate conduct of this research study.

In unusual cases, the investigators may be required to release identifiable information related to your participation in this research study in response to an order from a court of law. If the investigators learn that you or someone with whom you are involved is in serious danger or potential harm, they will need to inform, as required by each State's law, the appropriate agencies.

The investigators may continue to use and disclose, for the purposes described above, identifiable information related to your participation in this research study for a minimum of seven years and for as long as it may take to complete this research study.

Your participation in this research study is completely voluntary and your decision whether or not to participate in this research, or to later withdraw your consent, will not affect your current or future medical care at a UPMC hospital or affiliated health care provider or health care insurance providers.

You may withdraw your consent for participation in this research study at any time. Any identifiable research or medical information obtained for this research study before the time you formally withdraw your consent may continue to be used and disclosed by investigators for the purposes described above. To formally withdraw your consent for participation in this research study, please contact the Principal Investigator of this research study at the address listed on the first page of this form or call the number listed.

Subjects may be withdrawn from the study without their consent if you are unable to attend the scheduled focus group session; if you are unable to complete the follow-up interview (if needed) after 4 attempts; if the investigator decides that continuing in the study would be harmful or feels that you cannot complete the study requirements safely; or if the University of Pittsburgh or other administrative body cancels the study.

If you would like additional information, you may contact the Research Office at 412-692-5551. Questions about your rights as a research participant can be answered by the Human Subject Protection Advocate at the University of Pittsburgh IRB Office: 866-212-2668.

Page 3 of 4

	University Of	Approval Date: 3/5/2014	IRB #: PRO14010024
	Pittsburgh	Renewal Date: 3/4/2015	
	Institutional Review		
	Board		

VOLUNTARY CONSENT

The above information has been explained to me and all of my current questions have been answered. I understand that I am encouraged to ask questions about any aspect of this research study during the course of this study, and that such future questions will be answered by a qualified individual or by the investigator(s) listed on the first page of this consent document. I understand that I may always request that my questions, concerns or complaints be addressed by a listed investigator.

I understand that I may contact the Human Subjects Protection Advocate of the IRB Office, University of Pittsburgh (1-866-212-2668) to discuss problems, concerns, and questions; obtain information; offer input; or discuss situations in the event that the research team is unavailable.

By signing this form, I agree to participate in this research study. A copy of this consent form will be given to me.

Participant's Signature

Date

CERTIFICATION of INFORMED CONSENT

I certify that I have explained the nature and purpose of this research study to the above-named individual(s), and I have discussed the potential benefits and possible risks of study participation. Any questions the individual(s) have about this study have been answered, and we will always be available to address future questions as they arise. I further certify that no research component of this protocol was begun until after this consent form was signed.

Printed Name of Person Obtaining Consent

Role in Research Study

Signature of Person Obtaining Consent

Date

Page 4 of 4



University Of
Pittsburgh
Institutional Review
Board

Approval Date: 3/5/2014
Renewal Date: 3/4/2015

IRB #: PRO14010024

APPENDIX E: PARENT PARTICIPANT FOCUS GROUP GUIDES

E1: PARENTS INVOLVED IN RESEARCH

Focus Group Questions – PARENTS INVOLVED IN RESEARCH

Introduction about definition of research:

Intervention studies: They determine whether experimental treatments or new ways of using known therapies are safe and effective under controlled environments (definition from clinicaltrials.gov). These include drug and device trials. They are different phases where it could be initial safety studies (phase I) to larger randomized controlled confirmation studies (phase III)

Non-intervention also called observational studies: These address health issues often in large groups of people or populations in natural settings (clinicaltrials.gov). These could include: natural history studies, surveys, questionnaires, etc.

As of Feb 2014 there were 41 studies recruiting DMD patients/families and we would need over 4,400 patients.

Opening Question (round robin)

1. Now thinking about these definitions, tell us about the types of studies you (your child) have been involved in?
2. In general, can you talk to us about what your initial thoughts and feeling are regarding research in Duchenne MD and continuing to think about all types of research?
3. Now specific to your participation, what are your (feelings) regarding *participation* in research?
4. Think back over the past years and the different research studies you have participated in or heard of?
 - a. What was the reason you decided to participate in the study?
 - b. What helped you or allowed you to participate?
 - c. If you heard of a study and decided not to participate, what was the reason?
(What were your perceived limitations to participate? Probe about transportation, time constraints, incentives, psychological factors, fears about the risks, lack of understanding of the existing available studies, etc.)
 - d. What do you think would have changed your mind about participating (what needs to be improved)?
5. We are now putting you in charge of developing a recruitment plan. How would you write up this plan and what elements would you make sure are included that would engage families?
For example you get the opportunity to work with the healthcare team to develop a new study that would help answer your most burning questions about DMD. You now have to develop a plan to reach the patients and family in your community to tell them about the study and how they can join and participate. What does this plan look like?

6. What are your thoughts about health care providers attempting to recruit you/your son for participation in research?
Please talk about whether there was a particular time when a healthcare provider “oversold” a study? Was there a particular time when a healthcare provider really engaged you in a study?

Ending Questions

7. If you could change anything about how research is done in the Duchenne community, what would you do?
8. If you could give advice to other Duchenne families, what advice would you give?
9. Is there anything further you would like to talk about or discuss that we did not ask you regarding recruitment for studies in DMD?

E2: PARENTS NOT INVOLVED IN RESEARCH

Focus Group Questions – PARENTS NOT INVOLVED IN RESEARCH

Introduction about definition of research:

Intervention studies: They determine whether experimental treatments or new ways of using known therapies are safe and effective under controlled environments (definition from clinicaltrials.gov). These include drug and device trials. They are different phases where it could be initial safety studies (phase I) to larger randomized controlled confirmation studies (phase III)

Non-intervention also called observational studies: These address health issues often in large groups of people or populations in natural settings (clinicaltrials.gov). These could include: natural history studies, surveys, questionnaires, etc.

As of Feb 2014 there were 41 studies recruiting DMD patients/families and we would need over 4,400 patients.

Opening Question (round robin)

1. Can you talk to us about your initial thoughts/feelings regarding research in ~~Duchenne~~ MD?
 - a. *Have you wanted to participate but have not been able to? Why?*
2. Think back over the past years and the different research studies you have heard of or were invited to participate in.
 - a. How did your healthcare providers/clinicians talk with you about a research study?
 - b. Did they try to recruit you? If so, how did they try to recruit you?
 - c. What are your thoughts about health care providers attempting to recruit you/your son for participation in research?
 - d. Can you tell me an effective way to receive information about a research study?
Please talk about whether there was a particular time when a healthcare provider "oversold" a study? Was there a particular time when a healthcare provider really engaged you in a study?
 - e. What was the reason you decided not to participate?
What are your perceived limitations to participate? Probe about transportation, time constraints, incentives, psychological factors, fears about the risks, lack of understanding of the existing available studies, etc.
3. What would have helped that might have allowed you to participate or would have changed your mind about participating (what needs to be improved)?

4. We are now putting you in charge of developing a recruitment plan. How would you write up this plan and what elements would you make sure are included that would engage families?
For example you get the opportunity to work with the healthcare team to develop a new study that would help answer your most burning questions about DMD. You now have to develop a plan to reach the patients and family in our community to tell them about the study and how they can join and participate. What does this plan look like?

Ending Questions

5. If you could change anything about how research is done in the ~~Duchenne~~ community, what would you do?
6. Is there anything further you would like to talk about or discuss that we did not ask you regarding recruitment for studies in DMD?

APPENDIX F: PARENT PARTICIPANT DEMOGRAPHIC FORM

Parent Participant Form

Date:	Time:	Location:
Demographics Section		
What is your age?	<input type="radio"/> Less than 30 years old <input type="radio"/> 30 years – 35 years old <input type="radio"/> 36 years – 40 years old <input type="radio"/> 41 years – 45 years old <input type="radio"/> 46 years – 50 years old <input type="radio"/> 51 years – 55 years old <input type="radio"/> 55 years – 60 years old <input type="radio"/> Greater than 61 years old	
What is your marital status?	<input type="radio"/> Single <input type="radio"/> Married or long-term committed relationship <input type="radio"/> Divorced or separated <input type="radio"/> Widowed	
Your gender	<input type="radio"/> Female <input type="radio"/> Male	
What racial group best describes you? (select all that apply)	<input type="radio"/> American Indian or Alaska Native <input type="radio"/> Asian <input type="radio"/> Black or African American <input type="radio"/> Native Hawaiian or other Pacific Islander <input type="radio"/> Hispanic or Latino <input type="radio"/> White <input type="radio"/> Other _____	
What is the highest level of education you have completed?	<input type="radio"/> Less than some High School <input type="radio"/> Some High School <input type="radio"/> High school or GED <input type="radio"/> Some College but no degree <input type="radio"/> Technical School <input type="radio"/> Associate's Degree (2 year college degree) <input type="radio"/> 4-year College Degree (e.g., BA, BS) <input type="radio"/> Some Graduate School but no degree <input type="radio"/> Graduate or Professional Degree (MBA, MS, MD, PhD)	
Where do you live?	<input type="radio"/> Urban <input type="radio"/> Suburban <input type="radio"/> Rural	

Family Income per year?	<input type="radio"/> \$25,000 or less <input type="radio"/> \$26,000 to \$50,000 <input type="radio"/> \$51,000 to \$75,000 <input type="radio"/> \$76,000 to 100,000 <input type="radio"/> \$101, 000 to \$125,000 <input type="radio"/> Greater than \$125,000 <input type="radio"/> Decline
What is true about you? I am the _____ of the person with DMD.	<input type="radio"/> Biological Father <input type="radio"/> Biological Mother <input type="radio"/> Adoptive Father <input type="radio"/> Adoptive Mother <input type="radio"/> Grandfather (who is guardian) <input type="radio"/> Grandmother (who is guardian) <input type="radio"/> Other _____
Do you have more than one child with DMD?	<input type="radio"/> Yes <input type="radio"/> No
About Your Son	
How old is your son?	_____
Has your son been diagnosed with another condition(s)? If so, please state the diagnosis/es:	<input type="radio"/> Medical: _____ <input type="radio"/> Mental Health: _____ <input type="radio"/> Learning Disability: _____ <input type="radio"/> Other: _____
Choose the option that best describes your son's physical abilities today.	<input type="radio"/> Walks independently for long distances <input type="radio"/> <input type="radio"/> More than a football field <input type="radio"/> Walks independently for short distances <input type="radio"/> <input type="radio"/> Around the house/one-block outside <input type="radio"/> Walks independently indoors but needs a wheelchair for outdoors or long distances <input type="radio"/> Uses a wheelchair indoors/outdoors

Evaluation Section	
<p>Do you have any other thoughts on strategies for engaging the DMD community in research that were not covered during the focus group?</p> <p>Anything else you want to tell us?</p>	

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