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# CLINICAL TRIAL HARMONIZATION GUIDANCES



# TABLE OF CONTENTS

Clinical Trials Harmonization Guidances Introduction	3
Protocol Development Guidance for Duchenne Clinical Trial Study Sponsors	5
Informed Consent Guidance for Duchenne Clinical Trial Study Sponsors	12
Travel Guidance for Duchenne Clinical Trial Study Sponsors	16
Commitment to Non-ambulatory Duchenne Community	20
Communications Guidance for Duchenne Clinical Trial Study Sponsors	25
Optimizing Contract Research Organization (CRO) Engagement	29
Clinical Trial Welcome Packets	31
Welcome Packet Introduction	31
Clinical Trial Patients and Caregivers Bill of Rights	32
The Informed Consent Process	34
Frequently Asked Questions	36
Advocacy Organization Contact Information	37
The Importance of Reporting Adverse Events	39
Trial Participation and Coordination of Care with the Patient's Neuromuscular Specialist	40
Social Media Use During Clinical Trial Participation	42
Welcome Letter Example	43

# CLINICAL TRIAL HARMONIZATION GUIDANCES

The **PPMD Duchenne Drug Development Roundtable (DDDR)** is an informal group of stakeholders representing industry and relevant stakeholders that has the goals of accelerating the development of meaningful treatments for Duchenne muscular dystrophy through open discussion to minimize duplication and to pool resources in the precompetitive space.

In 2017 and 2018, the DDDR convened a series of small meetings each focused on specific topics areas that were identified as critical priorities by the DDDR Steering Committee and through discussions with DDDR membership. The goal of the series was to identify opportunities to optimize regulatory learnings and explore innovations that could be applied to the Duchenne therapy development space. From those meetings, the **Clinical Trial Harmonization Working Group** was formed as a collaboration between DDDR members and other key stakeholders in the Duchenne drug development ecosystem. The **Clinical Trial Harmonization Working Group** includes representation from sponsors, CROs, advocacy organizations, and clinical sites, managed by Parent Project Muscular Dystrophy (PPMD), working together to harmonize clinical trial processes in Duchenne. A key role of this group is to provide tools, templates and guidance to encourage and facilitate quality, efficiency and consistency across Duchenne clinical trials. A key deliverable of this working group was to create a series of clinical trial harmonization guidance documents to aid in the development of trials and provide more consistency with Duchenne trial planning and process considerations.

## **The guidance includes:**

- Protocol Development & Review
- Consenting/Assenting Processes
- Travel Guidance for Duchenne Clinical Trial Sponsors
- Non-Ambulatory Community Commitment
- Best Practices in Communications
- Formal Engagement of CROs
- Clinical Trial Welcome Packets

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# PROTOCOL DEVELOPMENT GUIDANCE FOR DUCHENNE CLINICAL TRIAL STUDY SPONSORS

## Clinical Trial Harmonization Working Group

The Clinical Trial Harmonization Working Group represents sponsors, CROs, advocacy organizations, and sites supported by Parent Project Muscular Dystrophy (PPMD) working together to harmonize clinical trial processes in Duchenne. A key role of this group is to provide tools, templates and guidance to encourage and facilitate quality, efficiency and consistency across Duchenne clinical trials.

This guidance pertains to clinical trial protocol development and provides key considerations to maximize the scientific rigor and feasibility of clinical trial protocols, and to maintain high enrollment and retention rates for clinical trials in Duchenne Muscular Dystrophy (Duchenne). Reference to the [“Duchenne Muscular Dystrophy and Related Dystrophinopathies: Developing Drugs for Treatment Guidance for Industry”](#) by the FDA is strongly recommended as it provides a more comprehensive guidance to sponsors in the clinical development of drug programs for Duchenne, as well as the European Medicines Agency guidance, EMA Duchenne Guideline: EMA/CHMP/236981/2011, Corr. 11 .

### **The working group discerned three key domains for Duchenne protocol development guidance:**

1. **Selection of appropriate outcomes** to designate as key study endpoints which directly relate to the intervention (drug, device, etc.) mode of action, are scientifically valid, are feasible for the study population, and are included in the analysis plan.
2. **Protocols should take proper considerations of potential risks and benefits** according to the population studies and be designed to address common sources of family burden, including visit schedule and duration, and patient pain and distress.
3. Key portions of the protocol should be **reviewed and/or developed with at least one Duchenne provider** (MD/ARNP/PT/OT) and **at least one parent or patient representative** prior to releasing the final version of the protocol.
4. Sponsors should provide opportunities for research participation **for all patients who are representative** of likely future consumers or recipients of their investigational products.

This guidance is divided into the following broad categories:

1. Outcome Measure and Endpoint Selection
2. Risk/Benefit and Reduction of Family Burden
3. Community Partnership
4. Special Populations

## Outcome Measure and Endpoint Selection

Past Duchenne trials have utilized a variety of different outcome measures, administered using different methods, in widely variable study schedules. The design of a study protocol and the choice of outcome measures will always first be driven by the mechanism of the proposed treatment. While different outcome measures will continue to be used in this area, there is an opportunity to reduce variability across studies and sites in how the measures are used, and to improve the quality and consistency of study data.

In a rare disease population, each trial poses the opportunity to explore new outcome measures which may reveal important findings to drive future discovery. At the same time, each additional outcome measure presents an increase in visit time, study complexity, and opportunity for error. The sponsor's protocol development team should strive to balance the need for focused assessment of possible clinical changes with the opportunities to add additional measurements which may only be tenuously related to the expected mechanism of drug action. We offer several guidelines below which may be helpful for sponsors developing new trials.

### **We recommend that sponsors choose outcome measures which:**

- Assess the most important aspects of the outcome of interest.
- Relate to the objective endpoint that can capture the spectrum of the possible intervention effect.
- Have been validated for the study population in published academic manuscripts.
- Are listed as outcomes in a specific hypothesis in the analysis plan, and for which the study is powered to detect a clinically relevant difference.
- Will be administered in a manner consistent with published validation studies.
- If exploratory in nature, are administered to a subset of study participants who “opt in” to an additional sub-study rather than as a part of the required study events in the main protocol.

## Risks/Benefit and Reduction of Family Burden

While families of children with Duchenne often accept greater risks when participating in clinical trials, protocols should properly address the risks and benefits of the intervention on the specific circumstances of the study patient population. Participating in clinical trials confers an additional burden on the family with Duchenne. The practical and emotional impacts of attending study visits, missing school or work, and witnessing or experiencing painful or distressing procedures are real effects on families who participate in clinical trials. Families caring for a child with Duchenne experience emotional, practical, and financial impacts of having a child with a disability, and then experience added burdens resulting from agreeing to participate in a clinical trial.

While each child is different, there are known and expected needs according to a child's functional level and age that can be incorporated into the study protocol. By addressing these needs up front, variability in how the study is conducted at each site will be reduced and the quality of the study data will be improved. We recommend that sponsors consider the factors below as they design their study protocols, and make adjustments where possible to reduce the risks and burden of participating in trials.

### **Pain and Distress**

- The pain and distress of activities listed on the schedule of events should be acknowledged. Where possible for all children (strongly recommended for children younger than 7 years), painful or distressing procedures should not be done in the same room as non-distressing events. Consider using a procedure room or splitting the schedule to allow the child to have non-invasive procedures done separately from invasive procedures.
- Separation from parents is itself distressing for young children. If needed, time should be allowed in the study schedule of events for the separation to be done in a humane way.
- Sponsors should include in their protocols measures to avoid pain and distress, including numbing creams or sprays, distraction, child life support, and reduction in the number of painful procedures (e.g.: number of peripheral blood draws in a single visit, etc.).

### **Scheduling and Logistics**

- Sponsors should list time estimates, including required rest times, in the schedule of events table. Time estimates would allow sponsors to monitor how long a given visit will take, and would allow sites to plan appropriately for study visits.
- Where possible, the sponsor should consider building in flexibility into study visit windows. A wider visit window for some or all outcome measures allows a family to accommodate important school or family events, travel, and illness.
- Where possible, the sponsor should reduce the frequency of study visits. Sponsors should prioritize outcome measures linked to the primary study aims and reduce frequency of exploratory outcome measures.

### **Developmental and Functional Needs**

- Sponsors should include enough time for children to eat, to use the toilet, to transfer from one place to another, and to change clothes or shoes.
- We suggest a 15-minute minimum for each of these types of activities when planning the schedule of events.
- Sponsors should include breaks in the schedule of events, including a 1-hour minimum for lunch, with additional 15 minute breaks in the morning and afternoon. Consider additional breaks for children younger than 7 years old or who are non-ambulatory.

Many of the issues identified in this guidance may be avoided by consulting with provider and parent representatives during protocol development. In clinical trials, it is often unrealistic to engage in community based participatory research, which would involve including a parent in the entire study design process. Seeking out directed review of a few key portions of a new protocol by individuals who are representative of the study population and likely study sites may help sponsors identify avoidable problems early in the process. Sponsors may also consult with advocacy groups and non-profit groups for advice and support during product and trial development, but this type of support may not be detailed enough to address protocol design issues. Advocacy groups may be able to connect sponsors with appropriate parent or provider representatives who can help review protocols in more detail to inform final development of new Duchenne studies.

### **Provider Consultation**

Providers who care for children with Duchenne should be consulted regarding the inclusion and exclusion criteria and the required schedule of events prior to releasing the final version of the protocol. Providers can best inform sponsors of the feasibility of finding children who meet inclusion and exclusion criteria and can tolerate the required assessments for the study. By including one or more providers familiar with Duchenne in this process, sponsors can make any needed changes to the study design and avoid opening a clinical trial which fails to reach accrual.

### **Patient and Family Consultation**

Parents of children with Duchenne or patients with Duchenne should be consulted regarding the schedule of events (including time estimates). One or more consultants should review a new protocol, and should be or have children with Duchenne who are at least the same age as the children in the study or are older. To prevent desirability bias, parents or children could be given a standard set of questions with Likert style answer choices to evoke an honest response about the feasibility of the proposed study protocol. The intent of this consultation is to invite feedback from one or more families about how easy or difficult it would be for them to participate in an individual research study.

### **Possible questions include:**

- Imagining that your child were eligible for a study like this, would your/your partner's work leave policy allow you to attend the study visits described?
- Imagining that your child were eligible for a study like this, and that each visit would require missing part or all of the school day, would your child's school permit him to attend the study visits described?
- Each visit is about [ ] hours long. On a scale of 1 – 10, how easily do you think your child would tolerate that kind of visit?
- How easy or hard would it be for your child to tolerate all the items listed on the schedule?
- What supports would your child need to successfully complete the items listed on the schedule?



## Special Populations

Sponsors should endeavor to include children and adults with Duchenne who are representative of the likely patient populations who will use the new treatment when it becomes commercially available. This may include people with Duchenne but are typically excluded from clinical trials, people who have Duchenne and have developmental or behavioral problems, manifesting carrier females, and people with Becker muscular dystrophy (Becker). These populations have important needs that should be addressed in the protocol design.

Including a wider group of people affected by Duchenne and Becker into clinical trials allows sponsors to collect data to support wider approvals of new treatments and to support insurance reimbursement of commercially available treatments. Many in these groups might be unable to contribute data to the primary study endpoint, but may contribute safety data or exploratory functional data to the study analysis. While the list below is not exhaustive, it can be a starting point for sponsors who wish to develop more inclusive clinical trials.

### **Infants and Young Children with Duchenne**

Infants with Duchenne and younger children with Duchenne are important groups for sponsors to consider in development of clinical trials. As early screening becomes more common, determining whether or not new treatments could be of benefit to pre-symptomatic children will be an important goal for sponsors. Infants and younger children will require different functional outcome measures than older children, such as those which rely more on parent report, passive monitoring, provider observation, and other methods. Infants and young children experience distress upon separation from parents, and will be unlikely to tolerate intensive testing, long visits, or frequent travel to other study sites. Studies which include these populations will need to address these issues and other developmental needs, with approaches such as using a safety cohort design, collecting a more limited range of functional outcome measures, sibling protocols, or others.

### **Non-Ambulatory Teens and Adults with Duchenne**

Please refer to the **guidance document regarding non-ambulatory** Duchenne patients. Briefly, sponsors should consider including non-ambulatory teens and adults in clinical trials for Duchenne. These groups are important to include because as Duchenne treatment options improve, evaluating the safety and efficacy of treatments after loss of ambulation and during adulthood are necessary considerations for children who may begin treatment while still ambulatory and potentially continue treatment throughout the lifespan.

Non-ambulatory teens and adults have different functional abilities and social needs than their younger peers, which should be considered in protocol design. Non-ambulatory patients have a more difficulty with travel due to equipment needs, availability of vehicles that can transport the patient, tolerance of transfers, and need for increased caregiving while away from home. Protocols can mitigate the impact of travel by approaches such as reduced travel schedules, direct flights, procedures performed at a local site, or home visits.

Teens and adults have different social needs than younger children. They may have families of their own to care for, may attend college or advanced training, and may have jobs which do not allow for weekday study visits. Protocols can accommodate these needs by approaches such as offering home visits, weekend study visits, scheduling study visits in advance, or having flexibility in study visit windows. Studies which include these populations will need to address these issues with approaches such as using a safety cohort design, collecting a more limited range of functional outcome measures, using functional outcome measures specific to non-ambulatory people, sibling protocols, or others.

### **Autism and Developmental Delays**

Patients with Duchenne can also have a diagnosis of autism spectrum disorder, developmental delay, or behavior problems. Sponsors should consider including this population in clinical trials because they are representative of children who are likely to receive new treatments once they become commercially available.

Behavior and developmental problems can interfere with a child's ability to participate in functional testing for clinical trials, but can often be accommodated with protocol design, site training, and planning. Providing opportunities for children to learn a new test before the study visit can be helpful, particularly for difficult behaviors such as pulmonary function testing, or scary tests such as MRI. These can be taught using video, practice at home, practice at the research clinic, and other methods. Sponsors can provide support for these participants by providing study sites with training materials, by encouraging sites to include this practice time in their IRB application and site budget, and by allowing for re-screening if a child initially failed enrollment due to failure to comply with testing.

Children with these problems also benefit from routine, clear communication, and consistency. Sponsors can provide support for these needs by providing study sites with templates for study schedules to distribute to families and by designing protocols with predictable visit schedules (eg: not dependent on drug response or adverse event). Studies which include these populations will need to address these issues and other developmental needs, with approaches such as using a safety cohort design, collecting a more limited range of functional outcome measures, reducing the length of study visits, sibling protocols, or others.

### **Manifesting Carrier Females**

Manifesting carrier females show symptoms of Duchenne due to mutations or deletions on both copies of the dystrophin gene. While their needs are different than male patients with Duchenne, they also experience a progression of symptoms, yet are largely excluded from consideration in most clinical trials. If study sponsors predict that their investigational products or treatments could be of benefit to this population, they should work to include this group in clinical trials. While this would only be appropriate for a subset of investigational products, some may be reasonably expected to be effective in a female patient and to have a low risk for reproductive effects.

Protocols designed to accommodate manifesting carrier females should include appropriate measures for surveillance of pregnancy and adverse events. Female

patients are at risk of becoming pregnant during a clinical trial, and should be tested for pregnancy prior to any radiation exposure or exposure to an investigational product if they are of childbearing potential (eg: has had first period and is not sterilized). Female patients enrolled in clinical trials should be counseled to avoid pregnancy through the use of two forms of birth control. Prior to including manifesting carrier females in clinical trials, sponsors should conduct preclinical animal trials with female animals and healthy adult studies with adult healthy women. This would help identify possible differences in treatment effect or safety profile due to gender.

Finally, manifesting carrier females have a different disease progression than males, and are likely to have different priorities for clinical trials. It would be important for sponsors to engage with this group to learn what symptoms are important to them, and how they view risk and inconvenience in clinical trials. Due to their milder phenotype, manifesting carrier females might not be appropriate for inclusion in a primary analysis sample, but may be able to participate in a safety cohort of clinical trials for Duchenne treatments.

### **Becker Muscular Dystrophy**

Becker muscular dystrophy is a milder phenotype of muscular dystrophy resulting from mutations or in frame deletions on the dystrophin gene. Patients with Becker also have progressive weakness and cardiologic and pulmonary symptoms and are often excluded from clinical trials for Duchenne. Sponsors are strongly encouraged to include patients with Becker in clinical trials for investigational products that are likely to be of benefit to them. While their symptoms are less severe than those in Duchenne, it is important to identify any potential for treatment related adverse events in this population and to identify treatments which do or do not improve or maintain their symptoms. Studies which include these populations will need to address these issues with approaches such as using a safety cohort design, using different functional outcome measures, or others.

### **Additional Resources**

Unique Burdens of Pediatric Clinical Trials in Duchenne Muscular Dystrophy, April 20-21, 2017, Bethesda, Maryland, USA

<http://journals.sagepub.com/eprint/KfGxXtwBCvdtsJCHcV3x/full>

# INFORMED CONSENT GUIDANCE FOR DUCHENNE CLINICAL TRIAL STUDY SPONSORS

## Clinical Trial Harmonization Working Group

The Clinical Trial Harmonization Working Group represents sponsors, CROs, advocacy organizations, and sites supported by Parent Project Muscular Dystrophy (PPMD) working together to harmonize clinical trial processes in Duchenne. A key role of this group is to provide tools, templates and guidance to encourage and facilitate quality, efficiency and consistency across Duchenne clinical trials.

One of the foundations of ethical research is informed consent. Informed consent is a process that should extend throughout a clinical trial. Both the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) Guideline for Good Clinical Practice (GCP) (E6, R2) and the US Food and Drug Administration (FDA) have guidelines for the informed consent process (<https://www.fda.gov/RegulatoryInformation/Guidances/ucm126431.htm>).

A survey of industry sponsored Duchenne trials revealed significant variability in the content and readability of consent documents and variability in how consent is obtained, increasing confusion for study participants and their families. The Sponsors' role in improving and standardizing informed consent and assent for their clinical trials is to provide site training and to develop study specific resources and language for sites to use. Improving the informed consent experience for this population could help potential participants understand what is involved in the clinical trial, leading to increased participation and retention.

## Informed Consent Process During Clinical Trial Participation

Informed consent is a process. Study investigators are largely responsible for ensuring that families have enough time to make a decision, understand the decision, and that they have not changed their mind during the course of a study. Study sponsors can support the successful implementation of this process by providing training to study investigators, by creating resources for sites to use with families, and by building opportunity to consider the decision into their clinical trial protocols.

### **Sponsor Processes for Creation of Informed Consent Documents:**

While each sponsor will have their own company specific process, below are the common steps that result in the approval of a consent form at each site. This process can limit a sponsor's control over specific language in a consent or assent form, and is regulated by IRB/EC and regulatory agencies (eg: FDA/EMA).

- Each company has their own ICF starting generic template according to the respective internal SOPs.
- The template is then populated to reflect the study/protocol while continuing to adhere to company standards.
- The study-specific ICF is then submitted to study site staff to modify according to their institutional process.
- Then, the ICF is submitted to IRB/EC for review and approval; often-times changes are made according to the requirement of the IRB, in order to receive approval.
- IRB approval is required and is a rate limiting step in initiating a study. Note: If a study has 40 sites, there could be up to 40 different approved ICFs (if central IRB is used there would be less)
- EU has different ICF requirements compared to US.

**General recommendations to sponsors:**

- **Build flexibility into the screening period in the protocol.** Families may need more time to discuss a new study prior to the screening visit. Families might be learning new concepts, might be negotiating complex logistics with caregivers, and might be considering different clinical or research opportunities. Sponsors can provide this time by building flexibility into the screening period in the protocol. This might allow families to provide informed consent prior to the screening visit, to receive the consent form prior to the first visit by email, or to consent for different phases of the study on different forms.
- **Create study specific language libraries for sites.** Sponsors should develop glossaries to help sites describe common concepts in simple language to study families. Sponsors should write these glossaries at literacy levels on par with the youngest eligible child in the study. This will allow sites to educate their patients and parents of any literacy level about a specific trial. Sponsors can develop a language library that supports their own product's development, and could use the same library to support multiple clinical trials about similar products. Language libraries may be used by sites to standardize language used in the consent and assent forms as appropriate.
- **Create educational materials for families across sites.** Sponsors should create or find resources to help sites teach families about the study and its key concepts. Visual aids such as slide decks, simple handouts, and diagrams can be created and provided to sites for use. Multimedia approaches such as websites and videos can be created by the sponsor and either given to sites to use with the families or provided to PPMD and families directly. Many resources exist for Duchenne clinical trials and for clinical trials in other diseases which may be useful to sponsors. If an existing resource would be appropriate, sponsors can provide their sites with access to them in lieu of or in addition to creating study specific materials.
- **Provide educational and practice opportunities for site investigators and coordinators to improve skills in obtaining informed consent.** Sponsors should provide opportunities for their site investigators and coordinators to learn about best practices for obtaining informed consent and assent. This could be incorporated into investigator meetings or site initiation visits, and should focus on

live, in-person teaching and practice. Many site investigators lack opportunities for continuing education in consent, and are likely to need periodic opportunities to learn and improve.

### The Continuous Process of Assent During Clinical Trial Participation

Many clinical trials in Duchenne include children, who are legally unable to consent to study participation. Age-appropriate assent for pediatric patients should be obtained. IRBs will provide specific guidelines for each site that must be followed. These may vary from written assent being required at a certain age or developmental age, to complete waiver of assent, and many other variations. Sponsors can support sites by providing teaching and practice opportunities, and by providing resources for sites to use with children.

- **Create educational materials for families across sites.** Sponsors should create or find resources to help sites explain a study or its procedures to children. Children may have cognitive limitations in addition to their Duchenne, so developing child-friendly content is important. This could include YouTube videos, websites, comic books, and other materials that would help a child understand a new study and a new team. Sponsors should provide materials appropriate to the youngest eligible child for their protocol. If an existing resource would be appropriate, sponsors can provide their sites with access to them in lieu of or in addition to creating study specific materials.
- **Provide educational and practice opportunities for site investigators and coordinators to improve skills in obtaining assent.** Sponsors should provide opportunities for their site investigators and coordinators to learn about best practices for obtaining assent. This could be incorporated into investigator meetings or site initiation visits, and should focus on live, in-person teaching and practice. Many site investigators lack opportunities for continuing education in consent, and are likely to need periodic opportunities to learn and improve. Sponsors should focus training to match the age, literacy, and developmental needs of likely study participants.

### Information Dissemination Regarding a Clinical Trial

Families participating in clinical trials need information throughout a clinical trial. Sponsors can support sites to keep their participating families well informed by distributing appropriate resources about clinical trials in general, and about a specific clinical trial.

#### **General Information About Research**

Families may be unfamiliar with how the drug development process works and with general concepts about research (eg: randomization, study phases, etc). Existing resources exist that could be used in lieu of or in addition to study specific materials.

Good, general research videos and webpages exist at the National Institutes of Health website, The Duchenne Registry, Parent Project Muscular Dystrophy, and others.

### **Study Specific Information**

Family friendly materials should be developed that keep everyone who cares for a participant informed about the study. Participation in a clinical trial impacts the entire family. Creating appropriate materials that keep siblings, caregivers, teachers, and other relatives informed can prevent problems with study compliance and retention. These materials should be written at a low literacy level and should explain any scientific concepts simply to maximize their utility. Patient groups are a great resource to review and comment on these materials.

### **We recommend that study specific materials include:**

- Simple reference table listing what happens at each visit.
- Brief summary of the research study.
- Contact information for the study team

# TRAVEL GUIDANCE FOR DUCHENNE CLINICAL TRIAL STUDY SPONSORS

## Clinical Trial Harmonization Working Group

The Clinical Trial Harmonization Working Group represents sponsors, CROs, advocacy organizations, and sites supported by Parent Project Muscular Dystrophy (PPMD) working together to harmonize clinical trial processes in Duchenne muscular dystrophy (Duchenne). A key role of this group is to provide tools, templates and guidance to encourage and facilitate quality, efficiency and consistency across Duchenne clinical trials.

These guidelines are built on the foundation of key premises related to how clinical trials should be conducted in the field of Duchenne muscular dystrophy.

### **Clinical trials should:**

1. Be accessible to families.
2. Be designed in a way that minimizes the clinical trial burden associated with travel.
3. Take into account the needs of the family unit as a whole.
4. Conducted with the highest level of scientific rigor, while incorporating patients and advocacy groups in the protocol design.
5. Be cost-neutral for families to participate.
6. Inclusive to fullest extent possible; for example all who are potentially included in sub-populations, such as non-ambulatory boys and young boys, and those transitioning to adulthood.

**This guidance pertains to travel during a clinical trial and provides key considerations to reduce the overall burden of the family during clinical trial participation.**

Our recommendation is guided by the following key values:

- Participation in a clinical trial should be cost neutral for the entirety of the trial duration.
- Travel support provided should be communicated as transparently as possible to sites and families.

The guidance is divided into the following broad categories:

1. Facilitation of Travel Services for Clinical Trial Participation
2. Recommended Travel Policy during a Clinical Trial
3. Considerations for Compensation during a Clinical Trial



## Facilitation of Travel Services for Clinical Trial Participation

A survey of industry sponsored Duchenne trials revealed **there is no uniform approach to logistics coordination**, (Franson, Tim et al. "Unique Burdens of Pediatric Clinical Trials in Duchenne Muscular Dystrophy, April 20-21, 2017, Bethesda, Maryland, USA"). Some sponsors use non-profit companies to book flights and travel; others utilize travel companies; in one instance, a patient advocate managed the activity while others left the responsibility with the sites — and the sites have different institutional guidelines and approaches to coordinating travel.

While we recognize there are several factors that determine how travel needs are arranged and covered throughout a clinical trial, sponsors should coordinate pre-payment as much as possible to avoid burdening families with a reimbursement. \*The family should not be expected or required to use a personal credit card for any costs associated with the clinical trial including travel to the Screening visit as this has the potential to impact credit scores and the financial health of the family, and many families may not have access to a credit card.

In general, the following types of travel related expenses should be pre-paid by the third-party:

- Airfare [including seat selection and baggage fees]
- Hotel / lodging
- Transportation to/from the airport [can group with below]
- Car rental [including car seats as needed] or car service/taxi

Anticipated as well as unexpected expenses that occur during travel should be managed through use of a pre-paid credit card loaded by the third-party in advance of travel. It is recommended sponsors address the potential to re-load the credit card during travel to manage unexpected expenses.

Examples of travel related expenses to be covered by a pre-paid credit card:

- Per diem meals
- Airline baggage fees [if unanticipated, covered here]
- Airline seat selection [if unanticipated, covered here]
- Transportation to/from the airport [can be moved to pre-paid category if car service/Uber]
- Taxi during travel
- Tolls [determine if the pre-paid credit card can be used at ATM for cash]
- Parking
- Childcare considerations (i.e. when both parents need to travel leaving siblings at home, or opt to have siblings accompany child included in travel)\*\*

\*\* cash expenses such as childcare can potentially be reimbursed by reloading the credit card on issue of receipt

## Recommended Travel Policy During a Clinical Trial

The survey of industry sponsored Duchenne trials also discovered **a wide array of travel policies including a wide range of coverage and dollar limits for flights, hotels and car rentals.** Some companies had an initial position on the preferred number of travelers to cover while others were more liberal or flexible or made exceptions on a case-by-case basis.

A one size fits all travel policy may not be possible given multiple factors including patient age, ambulation status, stage of Duchenne, distance to site, family structure. As a community we strive for consistency and believe that the Duchenne community benefits from harmonization. The following elements should be addressed by all Sponsor travel policies:

### **Participation in a clinical trial should be cost neutral.**

- All **protocol required site visits**, including the Screening visit, should be covered by the travel policy. Sponsors anticipating a high screen to enrollment ratio should consider additional efforts to reduce screening costs including potential combination with the baseline visit and/or remote prescreening activities.
- Families who do not require flights to/from the site should have **a reliable mode of transportation**. Depending on proximity to the site, accommodations should be made for a rental car or car service/taxi/Uber/other. Use of personal vehicles should be at the discretion of the family. Travel policy should be flexible enough to accommodate changes in travel needs throughout the course of the study.
- Families who require flights to/from the site should have some input on **flight preferences** including direct vs. connecting, arrival/departure times. Imposing a pre-specified cap on flight costs [to the family] should be avoided since air travel costs fluctuate significantly based on the airline, time of year and departure/arrival airport.
- **Lodging for overnight accommodations** should be treated in a similar manner to flights. While a price cap, or selection of a chain or hotel/lodging class may be easier than securing cost efficient air travel, lodging will also fluctuate based on destination and time of year. Depending on length of site visit and location, it is recommended to offer extended stay type lodging with built-in kitchenette.
- Regarding the **number of travelers** covered by the travel policy, this is intended to serve as a general guide and each unique circumstance should be reviewed and considered. Sponsors are recommended to cover, at a minimum, the patient and at least 1 caregiver. Scale up factors should include logistical considerations (e.g., duration of site visit and/or distance from home) as well as individual considerations (e.g., family structure, required support during travel, sibling care, etc.). Allowances for additional travelers and/or coverage of childcare services should be considered based on the length/duration of the site visit. Characteristics of the target study population (i.e. age of study participants) may impact number of family members needing to travel. Travel allowances should be consistent throughout the duration of the study.

- **Sibling travel and/or childcare** should be addressed by the travel policy since many families need to manage home life while participating in a clinical trial. See above.
- Sponsors should make plans for travel support upon the initiation of OLE protocol development internally.

Study sites are encouraged to review the clinical trial travel policy thoroughly with trial participants as a part of the informed consent. Sites are asked to alert the sponsor if it is discovered that the travel policy does not meet these guidelines.

### Considerations for Compensation During a Clinical Trial

During PPMD's "**Unique Burdens of Pediatric Clinical Trials**" meeting, it was noted that while IRBs sometime see paying trial participants as undue inducement, the FDA has no such position on the topic that would prevent the community from setting standards for payment of reasonable costs so that the economic burden to families is not extreme.

# COMMITMENT TO NON-AMBULATORY DUCHENNE COMMUNITY

## Clinical Trial Harmonization Working Group

The Clinical Trial Harmonization Working Group representing sponsors, CROs, advocacy organizations and sites supported by Parent Project Muscular Dystrophy (PPMD) working together to harmonize clinical trial processes in Duchenne. A key role of this group is to provide tools, templates and guidance to encourage and facilitate quality, efficiency and consistency across Duchenne clinical trials.

This guidance pertains to our Duchenne community's commitment to the inclusion of individuals with Duchenne who have lost ambulation within clinical trials. The guidance is divided into the following broad categories:

1. Importance of including non-ambulatory individuals in Duchenne clinical trials
2. Clinical trial endpoints & strategies for including non-ambulatory individuals in a trial
3. Special considerations & accommodations during the trial
4. Access to experimental therapies outside of a clinical trial

## Importance of Including Non-Ambulatory Individuals in Duchenne Clinical Trials

According to PPMD's Duchenne Registry, 40% of the U.S. Duchenne patient community reports being non-ambulatory. With the average loss of ambulation in middle school, and average life expectancy of someone with Duchenne being in the mid-to-late 20's, most individuals with Duchenne currently spend more than half of their life navigating the world with the assistance of mobility equipment. However, current clinical trial inclusion criteria which typically focuses mainly on a younger population of ambulatory boys with Duchenne, not only significantly limits the available trial participant population, but also introduces limitations around access to the broader community upon approval.

Inclusion of non-ambulatory individuals with Duchenne should occur throughout the drug development lifecycle. In early development, input can contribute to a sponsor's analysis of unmet need in Duchenne, current treatment options, patient preferences, and burden of illness. As product development continues, patient community members can provide input on endpoint selection, benefit/risk trade-offs and tolerance for risk, potential ways to mitigate risk, and opportunities to inform community engagement and informed decision-making.

Beyond engaging non-ambulatory individuals with Duchenne in order to solicit input to enhance product development, sponsors must work to enable access to experimental

therapies at the earliest moment possible and include individuals with Duchenne who are non-ambulatory within active trial populations whenever feasible. Doing so serves to establish safety and efficacy, supporting a broad label upon product review and approval.

## Clinical Trial Endpoints & Strategies for Including Non-Ambulatory Individuals in a Trial

While the majority of clinical studies in Duchenne currently include functional endpoints focused on ambulation (6-Minute Walk Test, Four StairClimb, North Star Ambulatory Assessment), there is a growing set of potential outcome measures and endpoints that are available to sponsors wishing to include non-ambulatory participants in trials.

### **They include:**

- The Performance of Upper Limb Scale (PUL), which is an upper extremity measure that focuses on the continuum of functionality and on the basic functional workspace;
- The Brookes Scale
- Quantitative strength testing;
- Quantitative measure of reachable workspace;
- Quantification of elbow, wrist, and digit strength movement;
- The nine-hole peg test; and
- The Motor Function Measure (MFM).

Multiple pulmonary clinical outcome measures and endpoints are utilized to measure strength and cough function.

### **They include:**

- Forced vital capacity (FVC);
  - Peak expiratory flow (PEF);
- (Finder et al., 2017; PPMD Pulmonary endpoints workshop)

It is now recognized that in patients above 10 years of age, Maximum inspiratory pressure (MIP) and Maximum expiratory pressure (MEP) are endpoints that are not reliably assessed in Duchenne and therefore difficult to interpret. Especially, the fact that at this age MIP/MEP do not reliably decline (jn a placebo group) makes these endpoints more problematic (see also Finder et al., 2017)

In addition, cardiac measures are also critical in the non-ambulatory Duchenne population and may include cardiac imaging based on appropriate presentation, echocardiograph, cardiac MRI, and ECG.

Whenever possible, quality of life and patient reported outcomes should be included in the trial to assess aspects of the disease important to a non-ambulatory population, but this must be delicately balanced to ensure prioritization of endpoint collection and reduction of fatigue on the part of study participants. These tools can measure aspects

of the disease such as mood, fatigue, sleep, upper body function, and caregiver burden. The creation of innovative PROs and quality of life tools is encouraged.

Sponsors should consider sibling protocols that enable compassionate access to non-ambulatory patients who have a sibling who is included in the study. Policies should be established prior to the start of the trial and consistent – and include a mechanism to include the non-ambulatory sibling who falls outside of the trial’s inclusion criteria, once safety has been established.

## Special Considerations & Accommodations During a Clinical Trial

Participating in clinical trials presents unique challenges for participants who are non-ambulatory due to the decreased mobility as a result of disease progression, which can create physical barriers to trial participation and increased social isolation, or alternatively, as increased social activity and commitments that teens and adults who are attending school or who are employed may face. Designing trials to accommodate the unique needs of this community will help facilitate participation of non-ambulatory individuals in Duchenne trials.

### **Sponsor considerations when working to accommodate non-ambulatory trial participations should include:**

- Reducing travel burden
- Accommodating school & work schedules
- Consent/assent when participant turns 18 during a trial
- Providing psychological support to participants when necessary
- Acknowledging the limited mobility and increased medical needs in adulthood
- Addressing potential high-risk behaviors of adult trial participants such as sexual activity, recreational drug use, medical marijuana use, alcohol consumption, smoking, etc.

### **Reducing Travel Burden**

Participation in a clinical trial should be **cost neutral** and to the greatest extent possible travel policies should be consistent throughout the trial and across trial participants. The following guidelines should form the foundation of any clinical trial travel policy involving non-ambulatory participants:

- Families who do not require flights to/from the trial site should have **a reliable mode of transportation** and this should be discussed during trial screening. Depending on the participant’s proximity to the site, accommodations should be made for a rental car or car service/taxi/Uber/other in situations when the family is motivated to participate in the trial but lack of transportation prohibits their participation. Travel policies should be flexible enough to accommodate changes in travel needs throughout the course of the study.

- Families who require flights to/from the site should have some input on **flight preferences** including direct vs. connecting, arrival/departure times. Imposing a pre-specified cap on flight costs [to the family] should be avoided since air travel costs fluctuate significantly based on the airline, time of year and departure/arrival airport.
- **Lodging for overnight accommodations** should be treated in a similar manner to flights. While a price cap, or selection of a chain or hotel/lodging class may be easier than securing cost efficient air travel, lodging will also fluctuate based on destination and time of year. Depending on the length of the trial visit and location, it is recommended to offer extended stay type lodging with built-in kitchenette. Rooms deemed accessible for wheelchair users should include roll-in showers with shower chairs, and double beds, of which one should have room underneath to roll a patient lift up to the bed.
- To minimize extraneous travel costs and burden, it is recommended that families be **paired with the closest trial site**. If a site is not yet opened [but likelihood is high], it is recommended that the family's expectations be managed to wait until the site closest opens to enroll.
- The **number of travelers** covered by the travel policy should serve as a general guide given the many factors previously mentioned. Sponsors are recommended to cover, at a minimum, the patient and at least one personal care attendant or family caregiver. Scale up factors should include logistical considerations (e.g., duration of site visit and/or distance from home) as well as individual considerations (e.g., family structure, required support during travel, sibling care, etc.). Characteristics of the target study population (i.e. age of study participants) may impact number of family members needing to travel. Travel allowances should be consistent throughout the duration of the study. In some cases, participants may opt to hire personal care attendants in the trial site city/location and care attendant costs should be reimbursed by the sponsor.
- **Durable medical equipment costs** to facilitate overnight stays such as patient lifts, bedside commodes, and shower benches should be reimbursed by the sponsor. Additionally, a durable medical equipment vendor should be available for any wheelchair repairs or replacement necessary for participants traveling via airline whose equipment has been damaged or lost.

Participation in clinical trials can be a burden for the patient and his family — particularly in older non-ambulatory boys with limited mobility. Making trials more patient and family friendly, including employing innovative clinical trial designs such as allowing for home visits and hub & spoke models, could increase recruitment and retention in studies.

## Access to Experimental Therapies Outside of a Clinical Trial

While a sponsor's ability to offer access to experimental therapies is limited by safety and efficacy concerns about the clinical compound, sponsors are urged to consider mechanisms for access to non-ambulatory community members once safety has been established.

Sponsors are expected to establish consistent and transparent policies related to access for Duchenne community members who are non-ambulatory.

These policies should be posted on the sponsor's website. **When devising policies, the following should be taken into consideration:**

- Opportunities for pre-approval compassionate use on an individual patient basis
- Plans and timelines for an expanded access program
- Plans for open label extension phases of a study and the length of this phase for non-ambulatory trial participants
- Access through innovative trial design and potential for sibling protocols
- Exploration of combination therapies for individuals already taking an approved therapeutic
- The collection and publication of data and case studies from expanded access and compassionate use programs that could support broader access to the Duchenne community



# COMMUNICATIONS GUIDANCE FOR DUCHENNE CLINICAL TRIAL STUDY SPONSORS

## Clinical Trial Harmonization Working Group

The Clinical Trial Harmonization Working Group represents sponsors, CROs, advocacy organizations and sites supported by Parent Project Muscular Dystrophy (PPMD) working together to harmonize clinical trial processes in Duchenne muscular dystrophy (Duchenne). A key role of this group is to provide tools, templates and guidance to encourage and facilitate quality, efficiency and consistency across Duchenne clinical trials.

This guidance pertains to effective communications practices for sponsors conducting clinical trials in patients with Duchenne muscular dystrophy (Duchenne) and includes recommended strategies for ongoing communication with study sites, families, and stakeholders during the life of a clinical trial. Also included are important insights regarding the Duchenne patient population that may help sponsors develop materials and strategies to reach families who may be interested in investigational products and devices.

## Introduction to the Duchenne Community

Understanding the community of patients and families affected by Duchenne and the providers who care for them and conduct research studies is an important first step to creating effective strategies and materials to communicate during clinical trials. While sponsors may have worked with other rare disease populations in the past, they should be aware of unique aspects of the Duchenne community as they consider approaches to communication for their clinical trials.

Below is a brief summary of characteristics of the Duchenne community to consider during the development of a clinical trial. Sponsors should also consider reaching out to Duchenne advocacy, parent groups, and/or study sites for feedback when developing a clinical trial for Duchenne for more support and education and to include important insights from the patient community into the trial design and implementation.

### Patients with Duchenne and their Families

- **Interconnected Community:** Families of children with Duchenne tend to be very well connected with other families online and by phone. Patients and parents often meet each other at PPMD or MDA conferences, at clinic, or at Duchenne specific summer camps and other programs. Parents often share information with each other about clinical trials, and are very likely to share any news that they receive quickly throughout their networks. Common topics include which sites are open, travel details, any published information about study data analysis or results,

regulatory approvals or progress, investor information, and the possible drug development pipeline.

- **A Global Community:** As a result of social media and internet resources, the Duchenne community is truly global in nature and trial-related events in Europe or in the United States could greatly impact the study PIs or patients on the other side of the world and raise additional questions. Additionally, families have chosen to relocate to a different country to access clinical trials. This global perspective should be taken under consideration when planning clinical trials and communicating with clinical trial participants.
- **A Diverse Community:** Duchenne has a diverse patient community, which crosses ethnic, racial, socioeconomic, educational, geographic groups. At times, the needs of the most vocal advocates in a patient community are not fully representative of the broader community. It is important to seek ways to actively engage a diverse cross-section of the community and to seek out underrepresented groups of patients and families, both in clinical trials (by removing barriers to participation) and in advisory boards.
- **Information Seeking:** For families of children with Duchenne who seek any available information about a sponsor or its products, they tend to do so regardless of the source. In addition to patient advocacy groups and their physicians, this can include investor facing information from money management websites or blogs, national or local news media, other parents, academic conferences, closed to the public Facebook groups, and educational conferences for parents. Some families make a Google News Alert or similar system to automatically monitor any mention of a company or its products.
- **Gaps in Knowledge:** While families of children with Duchenne may have deep knowledge about some aspects of a clinical trial, they may still have gaps in knowledge about the science, biology, clinical trials, or some combination of these topics. For example, a family may know about a certain trial, know about prior data, but may not understand about what part of the body the drug acts in. Some families struggle with understanding the goals of each stage of clinical research and sponsors should take advantage of opportunities to educate the patient community about fundamental aspects of clinical trials and to manage expectations of families accordingly.

#### **Duchenne Clinical Trials Sites**

- **Site-to-site Variability:** Duchenne clinical trials sites may be led by principal investigators of different disciplines at study sites, whose institutions have widely variable approaches to public relations and communications. This variability means that study teams receive information from different academic and professional associations and have different policies and practices about communication at their home institution. Different sites might not be able to use all materials, due to restrictions on posting printed materials, on branding requirements, ability to email study families, and other differences.

- Clinical Trial Communication: Industry sponsors should create a central study-wide recruitment, retention, and communication strategy and disseminate this broadly across trial sites. Companies should bear the greatest responsibility in developing and disseminating communications to trial participants, and to limit the burden of study communication on trial sites as much as possible.** Most site teams conduct multiple Duchenne studies at a time. Most Duchenne trials enroll small numbers of patients per site, so most teams are supported by multiple grants and contracts. Many clinical trials teams are also responsible for conducting clinical duties in addition to their research responsibilities, and so may have limited availability to participate in additional community outreach activities, such as communicating with local media, leading “lunch and learn” seminars with other providers, or hosting educational seminars for families.
- Response to Information Seeking:** Most families primarily communicate with principal investigators and study coordinators at their local sites. This close relationship over a long period of participation in research means that new information released in the public domain or from other parents will trigger numerous phone calls and emails to a study site in a short period of time about the same topic. Sponsors will also receive requests for information directly from families and should be prepared to answer these questions in a timely fashion and develop a strategy around addressing questions.

## Recommendations for Effective Communication

We recommend that sponsors develop a proactive communication strategy for use throughout the life of a clinical trial. While each sponsor will develop their own approach, the following features should be considered.

### Real-Time Study Site Communications

- Use quarterly or monthly newsletters to communicate trial updates, advocacy events, and other news to clinical trials sites. These newsletters can also be a method to distribute educational materials, articles, and other tools to study sites.
- Use ad hoc newsletters issued simultaneously to parent advocacy groups, study sites, and other stakeholders at the same time as press releases. Sites can get newsletters IRB approved and then distribute to their participants in addition to a broad distribution. Sponsors should provide a clear path for sites to talk with their study participants regarding data flow, questions or concerns that the family might have.
- Sponsors are aware that multiple stakeholders, including families of children with Duchenne (either in the study or not) participate in investor calls and monitor publicity intended for shareholders and investors. Substantive changes or updates distributed through these channels should also be communicated to study sites, advocacy groups and the broader patient community through either a separate update, letter, webinar, or newsletter. Every effort should be made to ensure that families participating in the clinical trial learn of important study milestones and

updates via their physician, trial site, or advocacy group and not on the internet, during investor calls, at scientific conferences, etc.

### **Timing and Notifications**

- Prior to any data releases or publicity regarding a data release, sponsors should first discuss the planned communications with the study sites, including coordinators, data safety monitoring boards, and other stakeholders. Providing advance notice of important communications will help study teams to inform their participants proactively and to respond appropriately to questions from the community.
- On the morning of any trial related publicity, sponsors should individually notify any major stakeholders by email, including vendors, consultants, study sites, and others. This approach reinforces the partnership between sponsor and the rest of the clinical trial community, and gives the sponsor a chance to manage their message proactively.

### **Resources for Sites and Families**

- Develop and distribute appropriate educational materials and tools that sites can use to help inform study families. These can include providing links to existing resources, creating study specific materials (eg: slide decks, flyers, websites, etc), educational presentations, and other approaches. Sponsors are encouraged to utilize patient representatives and patient groups to review materials to provide feedback.

### **Social Media Considerations**

- Sponsors should be aware of the pervasive and powerful use of social media within the Duchenne community and should consider creating social media guidelines for trial participants. Guidelines should be thoroughly reviewed during the informed consent process and represent the company's expectations about what information will be shared via social media about the trial.

# OPTIMIZING CONTRACT RESEARCH ORGANIZATION (CRO) ENGAGEMENT

## Clinical Trial Harmonization Working Group

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Contract Research Organizations (CROs) serve as a critical component of successful clinical trial experiences for all stakeholders within the clinical trial ecosystem, including the Duchenne patient community, clinical trial sites, and sponsors. In an effort to increase consistency across clinical trials and clinical trial sites, and improve the trial experience for all stakeholders, recommendations include:

- Considerations during the initiation of engagement with a CRO
- Considerations when preparing the CRO for engagement with the Duchenne community; Resources for orienting CROs

### Considerations for Sponsor During Engagement with a CRO

When selecting which Contract Research Organization (CRO) to engage, it is recommended that the following consideration be made:

- **Evaluation of CRO and monitoring staff turn-over**
  - CRA turn-over at a clinical trial site is not only frustrating but disruptive and requires additional effort each time a new CRA is placed at the site. Recommend Sponsors perform diligence to evaluate CRO historical turnover and ensure appropriate mechanisms are in place to prevent disruption at the site if this does occur.
- **Previous experience with Duchenne trials and Duchenne community, in general.**
  - Lack of previous experience does not disqualify a CRO but does necessitate disease specific orientation/training before any interaction with clinical trial sites and Duchenne Community. Recommend the Sponsor develop orientation/training for CRO team members including CRAs as well as documentation materials for training records. Recommend core set of training materials including items for Resources for Orienting CROs section below.
  - Recommended Duchenne training materials:
  - Duchenne Natural history video, Duchenne introductory video, CDC Care Guidelines (links below)

- **Evaluation of CRO's demonstrated ability with prioritizing critical trial related activities including those highlighted below:**
  - Budget negotiations and clinical trial agreements are critical to study start and ultimately, a successful clinical trial. All parties involved in the budget and contracting process should be mindful of the process to ensure unnecessary study delays are minimized. Best practice type of tools such as a communication plan or defined process is recommended.

### Considerations When Establishing Communications Plan

Communication is critical to any successful study, so all parties should have access to study team contact information including, at a minimum, site, Sponsor and CRO as appropriate.

#### **Communication Strategies for Consideration by network/study size:**

All studies:

- Create a document to distribute to sites with contact information for types of questions/issues likely to arise (eg: escalate a problem, medical questions, protocol questions, urgent supply issues, etc).

Small networks/studies or shorter studies:

- Copy Clinical Trial Manager or other delegate on all communications with CRO
- Forward communication thread to designated person if no response within 2 business days or if urgent response is needed
- Provide guidance on calling team members' cell phones after hours

Medium networks/studies:

- Create auto-distribute email address for sites to forward problematic threads (this would require assigning team members to check the account each day of the week)

Large networks/studies, long studies:

- Establish 24/7 hotline service that sites can call (some companies have online portals for protocol questions)
- Assign admin staff team to check a shared inbox and forward to correct team members

### Considerations When Preparing CRO for Engagement with the Duchenne Community – Resources for Orienting CROs

[Understanding Duchenne](#)

[Duchenne Journey Overview](#)

[Brain Pop Educational Video](#)

[Duchenne Care Guidelines](#)

[PPMD's video library on Duchenne clinical trials](#)

# WELCOME PACKET

The following Welcome Packet includes examples of materials that are helpful for families navigating clinical trials. The goal with this series of documents is to provide general templates that can be repurposed by sponsors for their own studies. Some of the documents are written as forward facing and others are specific to a topic area intended for guidance to the sponsor.

**The Welcome Packet documents include:**

- Patient's Bill of Rights for clinical trials
- The informed consent process
- Frequently Asked Questions
- Advocacy organization contact information
- The importance of reporting adverse events
- Trial participation and coordination of care with the patient's neuromuscular specialist
- Social media use during clinical trial participation

# WELCOME PACKET

## CLINICAL TRIAL PATIENTS' AND CAREGIVERS' BILL OF RIGHTS

### Clinical Trial Harmonization Working Group

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### The Duchenne Clinical Trial Patients' and Caregivers' Bill of Rights

The concern and wellbeing for every research volunteer is linked closely to the successful conduct of clinical research. The purpose of a clinical trial is to advance clinical research and to measure response to treatment.

If you or your child is eligible for a clinical trial, you will receive information to help you in determining whether participating in the study is right for you. You have time to ask any questions before you make this decision. Educating yourself about patient rights prior to enrolling in any clinical trial and throughout the study is helpful.

Your rights and safety are of utmost concern and priority.

#### **You have the right:**

- To safe, considerate and respectful care, provided in a manner consistent with your beliefs.
- To expect that all communications and records pertaining to your care will be treated as confidential to the extent permitted by law.
- To know the physician responsible for coordinating your care at the Clinical Center and to have contact information for the clinical trial nurse or coordinator.
- To receive complete information about your clinical trial, any treatment that is involved, and regular updates on the progress of the trial from the physician, in terms that are easily understood.
- To receive information necessary for you to give informed consent prior to procedure or treatment, including a description of the procedure or treatment, any potential risks or benefits, the probable duration of the entire trial and the time to ask questions about participation.



- To receive routine services when hospitalized at the Clinical Center in connection with your protocol. Complicating chronic conditions will be noted, reported to you, and treated as necessary without the assumption of long-term responsibility for their management.
- To know in advance what appointment times and physicians are available and where to go for all trial related visits.
- To request play therapists or child life specialists throughout the duration of the trial.
- You have the right to agree or refuse to take part in medical research studies.
- You may withdraw from a study at any time without impacting your access to standard care.
- Understand how long the study will last, where it will be conducted and the overall plan for the trial. You have the right to ask for regular updates during your trial participation.
- Understand what will be expected of you as a participant in the clinical trial.
- Be sure to ask any questions and express all concerns about your participation in the study.
- Know that participation is voluntary, but intend on completing the study before enrolling.

**Your Patient Rights After Clinical Trial Enrollment:**

- Know that you can decline participation or withdraw from the clinical study at any time without prejudice or loss of future treatment.
- Ask questions and voice concerns at any time in regard to the new drug or treatment.
- Stay informed of all the latest findings during the clinical trial that may affect your commitment to participation.
- To expect that a medical summary from the Clinical Trial Center will be sent to your referring physician;
- To designate additional physicians or organizations at any time to receive medical updates.
- You have the right to effective communication and to receive information in a manner that you understand.

# WELCOME PACKET

## THE IMPORTANCE OF THE INFORMED CONSENT PROCESS

### Clinical Trial Harmonization Working Group

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### Importance of the Informed Consent Process

The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) for Good Clinical Practice (GCP), E6 R2, dated November 2016 defines informed consent as “A process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.”

#### **The informed consent process should tell you:**

- What the clinical trial is about
- What is expected of the participant/caregivers – what will be done/ how long you will take part
- Expected benefits
- What's known and not known about the new drug
- Any possible risks to you (if known)
- Whom to contact if there are questions about or problems with the study
- Other possible treatment options
- That you can leave the study with no penalty and opt for standard medical care at any time
- How your personal information will be protected

Informed consent is a process that does not stop after the consent form is signed or after treatment has started. At each clinical visit, members from the clinical trial site should talk with the participant/ caregiver about the clinical trial and any changes that may have occurred since the trial started.

The informed consent process is meant to give you ongoing explanations that will help with making educated decisions about whether to start or stay in a clinical trial. The most important part of this process is continued discussions with the research team and other medical staff before, during, and after the trial. The consent form can be a great tool to help get this conversation started.

Before you decide, the research team will talk with you about the clinical trial's purpose, procedures, risks, possible benefits, and your rights as a participant. If a decision is made to take part, members from the clinical trial site will provide updates on new information that may affect decision making. Before, during, and even after the clinical trial, the participant/caregiver will have the chance to ask questions and talk about concerns. Informed consent for clinical trials goes on for as long as the research lasts, and even afterward.

### Check on Your Understanding of the Information

The clinical trial site should make every effort to be sure that you understand the information they give you. They can do this in a few different ways whether it is by having you fill out a questionnaire, asking you questions, or having you tell them about the clinical trial in your own words. You also should tell team members about anything you don't understand. If you find that the consent form or other information is written in words that are too technical for you, let them know. Otherwise they will assume that you understand when you really don't.

### Chances to Ask Questions

During the first meeting and in later discussions, you should be given the chance to ask questions and raise concerns. Keep asking questions until you feel you know enough to make your decision.

### Continued Updates on New Information

As the clinical trial goes on, the clinical trial site may make new discoveries that could affect your health, well-being, or willingness to stay in the study. They will share this with you and might ask you to sign a new consent form. Of course, you are free to leave the study if this information leads you to have doubts about staying in it.

### Tips About Clinical Trials

Keep a copy of the consent form handy and write questions down as they come to you. You may also request a copy of the protocol (full study plan) that describes all the details of the clinical trial.

# WELCOME PACKET

## FREQUENTLY ASKED QUESTIONS

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The following FAQ's are often raised by families interested in participating in clinical trials. They should serve as a guide for families who are exploring trials and are having discussions with their healthcare provider.

### Frequently Asked Questions

- How long will the trial be?
- Are trials ever stopped early and what does this mean?
- What happens when a trial is put on hold? How will I be notified?
- Do clinical trials always end on time?
- What is my responsibility post trial?
- Can I drop out of the study?
- What is a Trial Protocol?
- Who can participate?
- What is the purpose of the trial?
- Does the trial involve a placebo?
- What are my chances of being assigned to the placebo group?
- How will the treatment be given?
- How long will the trial last and what will I be asked to do?
- Is there any reimbursement for travel or other expenses?
- Will I be able to see my own doctor?
- Will my test results for the study visit be sent to my regular doctor?
- Can I continue to take the drugs or supplements that I am currently taking?
- If the intervention works for me, can I keep using it after the trial?
- Can anyone find out that I'm participating in a clinical trial?
- How will my information be kept confidential?
- What happens when a trial ends?
- Why does it take so long for a therapy to get to market?
- How can I get involved?
- What do I do if the study drug makes me sicker?

# WELCOME PACKET

## KEY CONTACT INFORMATION

### Clinical Trial Harmonization Working Group

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Access to the Duchenne advocacy networks is critical, especially for a family with a new diagnosis. This document provides the contact information and links to the larger Duchenne advocacy organizations. The advocacy organizations are here to help you, so you may find information on their website helpful including information on currently enrolling clinical trials, tips on navigating insurance, calendar of events and even stretching exercises. There are many smaller (but mighty) advocacy organizations which may be focused in a particular region so while not all are captured below, please be sure to ask one of the organizations listed below for more information in your area.

### Parent Project Muscular Dystrophy (PPMD)

Founded by Pat Furlong, PPMD's program areas include accelerating research, promoting advocacy, providing education, optimizing care and uniting the community.

Parent Project Muscular Dystrophy

Phone: 201-250-8440

401 Hackensack Avenue, 9<sup>th</sup> Floor

Toll-free: 800-714-5437

Hackensack, NJ 07601

Fax: 201-250-8435

Web: [www.parentprojectmd.org](http://www.parentprojectmd.org)

Email: [info@parentprojectmd.org](mailto:info@parentprojectmd.org)

## Jett Foundation

Founded by Christine and Stephen McSherry, the Jett Foundation is focused on increasing worldwide awareness of Duchenne with the purpose of raising and appropriating funds for education, research and advocacy that will help to identify treatments.

Jett Foundation

Phone: 781-585-5566

68 Evergreen Street, Suite One

Fax: 781-585-5233

Kingston, MA 02364

[www.jettfoundation.org](http://www.jettfoundation.org)

## CureDuchenne

Founded by Paul and Debra Miller, CureDuchenne was founded to pursue better medical and therapeutic treatments for Duchenne.

CureDuchenne

Phone: 949-872-2552

1400 Quail Street, Suite 110

[www.cureduchenne.org](http://www.cureduchenne.org)

Newport Beach, CA 92660

[info@cureduchenne.org](mailto:info@cureduchenne.org)

## Muscular Dystrophy Association (MDA)

Founded by a group of families in 1950, MDA covers the neuromuscular disease spectrum but at the heart is the family. MDA helps to accelerate treatments, and support care for kids and adults through their MDA Care Centers.

Muscular Dystrophy Association

Phone: 800-572-1717

222 S. Riverside Plaza,  
Suite 1500

[www.mda.org](http://www.mda.org)

Chicago, Illinois 60606

# WELCOME PACKET

## IMPORTANCE OF ADVERSE EVENTS

### Clinical Trial Harmonization Working Group

#### Adverse Events – What Are They and Why Does It Matter?

The purpose of clinical trials is to test drugs in areas that they have not been tested before. Sometimes this is new drugs and the studies are first in human, sometimes these are drugs that have been approved for other conditions but are being tested in new conditions, sometimes these are drugs that did not go forward for development and are brought back to be tested in a different condition. In each of these scenarios, patient safety is always the number one concern.

One of the ways we focus on safety is through the reporting of adverse events throughout the trial. In every study, there is a process to report adverse events and you should be well informed about how and when to report.

**Adverse “event” (AE):** 'any' untoward medical occurrence associated with the use of a drug in humans whether or not considered drug related.

The last part of the definition is very important because you do not have to decide if an adverse event is drug related, you simply report the occurrence and the investigator takes it from there. Sometimes adverse events are considered to be serious and these are called SAEs. An adverse event can arise from the study drug itself or from any route of administration or formulation or dose.

Safety is often one of the protocol objectives when testing new therapies so adverse event data must be collected and reviewed by the Principal Investigator.

If you or your child experiences any medical occurrence during your participation in a clinical study, please let your site coordinator immediately.

The medical doctor who is the trial investigator must ensure the safety of the trial patients. This includes providing the best possible care for patients experiencing any trial-related adverse events and conducting a thorough investigation to determine causality.

**It is important for you to report any adverse events you or your child experience while in the study to your physician immediately.**

# WELCOME PACKET

## TRIAL PARTICIPATION AND COORDINATION OF CARE WITH THE PATIENT'S NEUROMUSCULAR SPECIALIST

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### Patient/Family Communication with a Neuromuscular Specialist

According to *The Diagnosis and Management of Duchenne Muscular Dystrophy: A Guide for Families*, the person living with Duchenne "...should have regular checkups with a specialist doctor who has the expertise to monitor how things are going and to understand if there is anything unusual that might need additional evaluation. This is important to make decisions about new treatments at the most appropriate time and to anticipate and prevent problems to the maximum extent possible. It is recommended that all patients see the doctor every 6 months and the specialist physiotherapist and/or occupational therapist about every 4 months if possible."

One of the most important aspect of communicating with the neuromuscular specialist (NMS) is so that interventions, including clinical trial participation, can be properly monitored, especially if the trial participation occurs at a different location than the NMS care team.

The recommendations are based on an extensive study conducted by international experts in Duchenne diagnosis and care chosen to represent a broad range of specialties. The experts stressed that the best management of Duchenne requires a multidisciplinary approach, with the input of specialists in many different areas, and that there must be a doctor or medical professional that coordinates these efforts. Because everybody is different, the person with Duchenne and his family should be actively engaged with a medical professional who will coordinate and individualize clinical care.



**There are a few potential scenarios for consideration:**

1. Person living with Duchenne is interested in a clinical trial and is actively engaged with a neuromuscular specialist who is coordinating their care, and the NMS is at the same institution as the clinical trial site.
2. Person living with Duchenne is interested in a clinical trial and is actively engaged with a neuromuscular specialist who is coordinating their care, but the NMS is not at the same institution as the clinical trial site.
3. Person living with Duchenne is interested in a clinical trial but not currently engaged with a NMS.

In scenario 1 and 2, the recommendation would be for the clinical trial site to contact the coordinating NMS and ensure they are aware that their patient is interested in participating in a clinical trial. A copy of the communication should be filed in both locations; in the medical chart at the NMS's location as well as in the clinic chart with the Principal Investigator.

In scenario 3, the recommendation would be for the clinical trial site to refer the patient living with Duchenne to a NMS either by their own effort or through the assistance of an advocacy organization. It is also recommended the patient living with Duchenne be counseled on the importance of centralized care.

In some instances, Sponsors may want to confirm the person living with Duchenne is actively engaged with a NMS.

# WELCOME PACKET

## SOCIAL MEDIA USE DURING CLINICAL TRIAL PARTICIPATION

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### Social Media

Social media has the power to reach many in record speed. According to Statista.com, there are more than two billion users on Facebook and nearly 400 million users on Twitter. Within clinical research, social media can be an easy way to connect with others with the same diagnosis or condition. It offers the opportunity to get personal with people who are also open and willing to share their journey regarding a diagnosis or condition.

As wonderful as social media can be to many, there are potential downfalls if not used in the right way in the situation. Information exchanged between the clinical trial site and person living with Duchenne and/or caregiver is confidential and trial sites should emphasize the confidential nature at each opportunity however, it may not be realistic that all information shared during clinical trial participation will be held in a confidential manner.

MassBio hosted a series around Clinical Trials in the Age of Social Media: Strategies for Increasing Trial Awareness and Patient Recruitment during their 2017 meetings. The concept of social listening was discussed throughout the meeting. Panelists urged the audience to listen to patients on social media to help identify gaps in patient education, avoid search for “unicorn subjects” in clinical trials, find patients who can contribute content and serve as a support system for fellow patients, and to help design a strategy for how to engage with patients.

It was also reiterated that patients don't like being kept in the dark. Do your best to help patients to understand how important the integrity of the trial is while also disclosing as much as you can to help them feel in the know. Patients will appreciate the candor.

## Welcome Packet Example

*This document serves as an example letter for a Welcome Packet.*

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To members of the Duchenne community,

While Duchenne muscular dystrophy is a devastating diagnosis, the Duchenne community is an amazing network of people dedicated to helping families like yours. This Welcome Packet is intended to help you navigate the world of clinical research or clinical trial participation.

### **Enclosed you will find information on:**

- Patient's Bill of Rights for clinical trials
- The informed consent process
- Frequently Asked Questions
- Advocacy organization contact information
- The importance of reporting adverse events

In addition to the details contained in this Welcome Packet, you can find more information at these sites:

- [Clinicaltrials.gov](http://Clinicaltrials.gov)
- Parent Project Muscular Dystrophy ([EndDuchenne.org](http://EndDuchenne.org)) or The Duchenne Registry ([duchenregistry.org](http://duchenregistry.org))
- Jett Foundation ([jettfoundation.org](http://jettfoundation.org))
- CureDuchenne ([cureduchenne.org](http://cureduchenne.org))
- National Institutes of Health (<https://www.nih.gov/health-information/nih-clinical-research-trials-you>)
- Muscular Dystrophy Association ([mda.org](http://mda.org))

If you do not have access to the internet, please call Parent Project Muscular Dystrophy at: 800-714-5437.

You may also ask your clinical trial site to connect you with a social worker and the clinical research staff at any time.

Choosing to participate in a clinical trial is a big decision a requires a significant commitment of time, perseverance, and patience. Today's trials lead to tomorrow's standard of care. **Thank you for participating in the research for our future!**