

## USE CASE FOR DEVELOPING NOVEL ENDPOINTS GENERATED USING MOBILE TECHNOLOGY: DUCHENNE MUSCULAR DYSTROPHY

### OVERVIEW

The Muscular Dystrophy Care Act was signed into law in 2001, resulting in a \$200M-300M investment in Duchenne muscular dystrophy (DMD). More than 40 companies are now working to develop medical products for the disease, and the U.S. Food and Drug Administration (FDA) recently granted accelerated approval for the first medication labeled for treatment of DMD.

Because of the lack of proven medical therapies, care varies significantly across the DMD patient population, with inconsistent use of steroids, night splints, daily stretching and other physical therapy, supplements, and cardiac medications. Further, while some aspects of disease progression are consistent—specifically, loss of ability to stand from supine, jump, climb stairs, walk, raise hands over head typically happen in a consistent order – the rate of progression is variable, and associated cardiomyopathy and respiratory issues vary significantly among patients. These factors make assessing the efficacy of interventions difficult.

Currently the six-minute walk test is a typical clinical outcome assessment (COA) used in trials of medical products to treat DMD. However, approximately 60% of DMD patients are non-ambulatory or cannot walk well enough to adequately perform the test, and are therefore excluded from participation in clinical trials. Other COAs typically used in this patient population are the 4-stair climb, North Star Assessment Analysis (a 17-measure functional assessment scale), and the recently validated DMD-specific upper limb patient-reported outcome measure (PROM).<sup>1</sup>

Clinical trial participants typically range in age from 7 years (though this has been noted to be lowering in recent years) to mid-teens, so issues of diminished patient volition are common.

To inform the discussions around concepts of interest that are important to patients, the use case team referenced a survey conducted by Parent Project Muscular Dystrophy.<sup>2</sup> DMD patients who completed this survey selected the following activities from a list as being most important to them: stand from sitting, pick up an object from floor, climb three stairs, put on pants independently, stand for ten minutes, cut food, and wash hands (ambulatory patients); and re-position self in bed and/or chair, bring hand to mouth, use wheelchair joystick, use gaming technology, use texting technology, use a urinal independently, assist with a chair to bed transfer, and stabilize self on a toilet or on a shower seat (non-ambulatory patients).

### SPECIFIC AIMS

The use case team set out to develop a hypothetical endpoint for DMD that measured physical activity level with an accelerometer.

### STAKEHOLDERS AND INTERESTS

#### Patients and caregivers/parents

Patient representatives expressed an interest in developing an endpoint that had the potential to allow inclusion of a broader range of patients (both ambulatory and non-ambulatory), rather than

one that relied on significant ambulation, in order to increase access to clinical trials for more of the DMD population.

Patient representatives expressed that maintaining some independence in activities of daily living (ADL) was a more meaningful evaluation of a potential treatment effect than maintenance of ambulation alone because of its wider applicability.

Patient representatives and clinicians also described the difficulty in assessing DMD patients at a centralized point of care (clinic-based office assessment at a specific date/time). They indicated that data acquisition allowing for longitudinal ADL assessment and mitigating the impact of fatigue during clinic visits would provide a more accurate indicator of treatment benefit.

### **Sponsors of Clinical Research**

Sponsors are interested in how trial feasibility may be improved in terms of size, duration, and expense. Sponsors are also interested in using novel endpoints for labeling claims and for improving attrition rates and/or predictability rates from phase II to phase III trials.

### **Technology manufacturers**

Device manufacturers are interested in better understanding the needs of Duchenne patients and researchers in order to provide better measurement tools. Similarly, device manufacturers are interested in earlier engagement in the process of novel endpoint development and greater clarity regarding the process.

### **Regulators**

Regulators will need assurance that the endpoint appropriately reflects meaningful treatment effects when the endpoint is intended to be an efficacy endpoint in phase III trials.

## **ASSUMPTIONS**

The technology generating the data for each use case is assumed to produce data that are reliable, analytically valid and sensitive to changes, and in this use case, specific to the population of DMD patients.

The concept of interest selected for this particular use case, total arm movement, is measurable.

The COA, scored total arm movement, can be computed using an algorithm that incorporates various movement-related measurements captured by the accelerometer. Values generated can be correlated to functional ability as measured by the DMD Upper Limb PROM.

## **SCOPE**

The use case outcomes are intended to demonstrate the ability to measure disease progression or treatment benefit, not disease prevention. In other words: the patients in studies for which these endpoints will be used have been diagnosed with the stated disease.

The development of data standards is out of scope for this work, as is assessing the impact of the use case outcomes on survival. Work on these use cases is focused on the treatment benefit these outcomes can demonstrate at present.

## **OUTCOMES**

### **Success Outcomes**

Stakeholder needs will be met if an endpoint can be developed that includes a greater proportion of DMD patients (both ambulatory and non-ambulatory), reflects the ability of DMD

patients to maintain independence with meaningful ADLs, and more accurately reflects regular function than can be assessed at sparsely spaced timepoints (a clinic visit assessment every 1-2 months).

### **Failure Outcome(s)**

Development of the endpoint will not succeed if:

- ▶ Compliance is poor with respect to use and handling of the accelerometer; and/or
- ▶ Data from the accelerometer cannot be correlated with meaningful treatment effects or disease progression.

## **CONCEPT OF INTEREST**

The use case development team hypothesized that selecting **total arm movement** as the concept of interest for which to develop an accelerometer-based COA and related endpoint offers the highest likelihood of 1) reflecting maintenance of meaningful health aspects of great value to the patient population, 2) including both ambulatory and non-ambulatory research participants, 3) allowing assessment of meaningful function across lifespan to a greater degree, and 4) allowing accelerometer use with relative ease (assumption: total arm movement can be determined using an algorithm that incorporates various movement-related measurements captured by the accelerometer.) See “Additional Notes” for a description of the meaningful aspects of health and possible concepts of interest that the team explored.

## **CONTEXT OF USE CONSIDERATIONS**

- ▶ Age: the potential patient population ranges in age from 4-6 years to mid-20s
- ▶ Degree of disease progression in upper extremity: degree and rate of natural disease progression varies among patients (appropriate population must first be determined by natural history studies)
- ▶ Setting: Home-based measurement acquisition
- ▶ Confounding co-morbidities: e.g., fractures common
- ▶ Baseline standard of care: may vary significantly region-to-region or by primary care physician, including but not limited to use of steroids, braces and splints, daily stretching, etc.
- ▶ Caregiver compliance: placement and use of the accelerometer may vary and is dependent on caregiver for support
- ▶ Time of measure: both season (seasonal activity level is likely lower in the winter months) and day of week (school day vs. non-school day) may cause non-disease-based variation in activity levels

## **DESCRIPTION OF PROPOSED NOVEL ENDPOINT**

Difference in the rate of decline of total arm movement between treatment and control groups over 48 weeks of study participation, as measured by scored total arm movement (via an accelerometer worn on the upper arm) during waking hours every Friday and Saturday\* (clinical outcome assessment).

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\* Friday and Saturday were chosen to capture data/activity during a weekday/school setting and during a weekend/home setting. The team decided to use the accelerometer only 2 days per week, rather than continuously, for 48 weeks because of concerns regarding patient/caregiver compliance, and also current limitations of today's available technologies (battery life, adhesion to skin, etc.).

## MAIN SUCCESS PATHWAY FOR DEVELOPMENT OF ENDPOINT

### Step 1. Identify Meaningful Activities

- a. Ask of patients and caregivers: what are the activities most valuable to patients with the disease?
- b. Ask of patients and caregivers: what are the desired effects the medical product would have, if effective?
- c. Be specific. Independence is desirable for DMD patients, but cannot be measured with a single COA. Ask: how can independence be better represented by more discrete activities?
- d. Refrain from limiting the patient population due to context-of-use considerations such as age, stage of disease progression, etc., at this stage of the process.
  - ▶ Brainstorm what activities are relevant to the patient population first.
  - ▶ Categorize those activities into similar groups.
  - ▶ Later in the process, it will be valuable to consider how age group and degree of disease progression (among other possible context-of-use considerations) will narrow the range of meaningful activities that one seeks to influence with the treatment (see concept of interest).

### Step 2. Group Meaningful Activities into Meaningful Aspects of Health<sup>†</sup>

- a. Consider how the meaningful discrete activities can be grouped into categories of “meaningful aspects of health.”
- b. Refrain from focusing on what can be measured at this stage in the process. Focus instead on what are *meaningful aspects of health*.
- c. The more related the group of meaningful activities, the easier it will be to identify a concept of interest. Further, the concept of interest will likely be easier to measure, and it will be easier to establish a relationship between the concept of interest and the meaningful activities.
- d. Not all meaningful activities have to fit into any one meaningful aspect of health.

### Step 3. Describe Possible Concepts of Interest for Each Meaningful Aspect of Health<sup>‡</sup>

- a. Identify a concept (or concepts) that reflects or underlies most of the related meaningful activities (grouped in the given meaningful aspect of health).
- b. Consider whether the meaningful aspect of health can be measured directly, or whether it is preferable and more feasible to measure some simplified action that would be informative of the meaningful activity.
- c. There may not be any obvious, related, measurable concept of interest for each meaningful aspect of health. Example: “independence” is a meaningful health aspect that does not have an obvious, related, measurable concept of interest.

### Step 4. Choose a Concept of Interest to Pursue

- a. Identify what types of functional abilities do not benefit from existing treatment and/or are important but are not currently being assessed. Next, focus on new endpoints to address those functional abilities.

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<sup>†</sup> See Additional Notes section for examples.

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- b. Identify what is potentially measurable using a mobile technology. Consider measurement feasibility (in other words, across a wide range of the patient population).
- c. Choose only one concept of interest (in general, only one concept of interest can map to a COA.)<sup>§</sup>
  - ▶ There may be many concepts of interest that on the surface seem as if they would be good choices for pursuing development of a COA and endpoint.
  - ▶ It is acceptable to determine that no one concept of interest, and related COA, will be adequate to describe the treatment benefit from the investigational medical product, but they should each be explored independently.

### **Step 5. Identify the Clinical Outcome Assessment (COA) that Will Measure the Concept of Interest**

- a. Separate the concepts of 1) assessment from 2) data from the technology. The data from the technology may be very robust, but assessment of what is really going on with the patient is different. An assessment must focus on something that can be explicitly interpreted in terms of clinical effect (for example, scored arm movement correlates to preservation of function in the arm, allowing continued ability to manage ADLs independently).
- b. Consider whether compliance with technology use would be problematic for the intended duration of use.
- c. Consider rate of progression. Can the accelerometer detect the size of changes in patient function that occur over the duration of study period? Is the rate of progression (per the natural history of the disease) such that an accelerometer would detect these changes in a “control” patient?<sup>\*\*</sup>
- d. Are accelerometer measurements a better COA than a questionnaire or other clinic-based assessments, and appropriate for the patient population?
  - ▶ Because DMD is marked by slow deterioration of the patient’s condition, the team asked themselves whether measurements taken at a single, fixed timepoint are sufficient. Is it possible to learn more with longitudinally collected accelerometer data?
  - ▶ Although DMD is a slowly progressing degenerative disease, it was noted that the rate of decline varies, and measurements taken at a single fixed timepoint are challenging in patients because of volitional and environmental factors. There is concern that this kind of environmental variability could create significant and unnecessary noise. A larger, “real-world” data set may eliminate some of that noise.
  - ▶ Further, for a rare disease in which the population is smaller and geographically scattered and participating in clinical trials is a burden on patients and caregivers, gathering data at home can alleviate some of those challenges and make trials more accessible to a larger patient population.
  - ▶ “Real-world” assessment can complement clinic-based assessments.
- e. Can the accelerometer (or any technology outside of the use case constraints) measure the concept of interest? If what is being measured cannot be interpreted as meaningful, it is futile to measure it. When first collecting exploratory accelerometer data:

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<sup>§</sup> More than one COA may be used to generate an endpoint (for example, a composite endpoint).

<sup>\*\*</sup>While it is ideal to ensure this at the point of COA selection, further evidence may be captured on this later as part of assessing the utility of the COA.

- ▶ Assess what measurements are best for use in a clinical trial. Try different frequency and duration of data collection schedules to determine what is most reliable.
  - ▶ Conduct studies to collect baseline accelerometer data from DMD patients. Examples may include a longitudinal natural history study to collect data on rate of decline as measured by accelerometers, or a larger, short-term, cross-sectional study to examine variability in accelerometer data.
  - ▶ Compare exploratory Duchenne datasets to healthy controls to assess validity of data.
- f. Does the measurement reflect a clinical effect that is meaningful to patients?
- ▶ Assess functional ability per the Upper Limb DMD PROM with the accelerometer on the patient to understand how the accelerometer data correlates to meaningful activities.
  - ▶ Note that it may also be possible to consider other approaches to measuring upper limb mobility to provide reference data, such as a direct high-frequency survey of the patient (PRO) or caregiver at home.
  - ▶ It is important to understand that a patient who can do some set of activities falls within some limited range on the COA score, so that when a patient has moved out of that range, it represents a definite change in functional ability and the activities that they can no longer do can be described.
- g. Determine how the accelerometer will be used.
- ▶ Determine frequency of measurements. Consider balancing patient compliance with a desire for longitudinal data that spans the spectrum of daily life (school versus weekend) so that variability in type of activities that occur on these days does not bias the results.
  - ▶ Also consider that while currently available tests are not sensitive to detect small changes that may be significant in short timeframes, we might find that week-to-week the accelerometer can detect a quantifiable and possibly significant trend.
  - ▶ Collecting data weekly may lead to a more reliable assessment over the course of a month. For example: this may reduce variability caused by school schedule, illness or other confounding variables.
  - ▶ Determine whether the COA should be clinic-based or in a “real-world” setting.
- h. Add information about how the algorithm is developed to produce “total” arm movement score.
- ▶ It is not necessary to decide which kind of arm movement is most important.
  - ▶ A computer program can identify the algorithm that combines the multiple ways an arm can move into information that is instructive regarding the patient’s actual activities.<sup>††</sup>

## Step 6. Determine the Study Endpoint

- a. Determine whether the endpoint will be prognostic or contemporaneous with the meaningful treatment benefit.
- ▶ Contemporaneous measurement provides information about how the patient is functioning on the day of measurement. Contemporaneous measurements may be made over a period of time, and a string of contemporaneous measurements may suffice to establish trend lines to make predictions. A major advantage of wearable accelerometer sensors is that they increase the frequency of measurements, allowing these trends to be quickly identified (see 5d and 5g).
  - ▶ Prognostic measurement predicts how the patient will function in the future.

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<sup>††</sup>Note: this information may be collected in Step 5.e. One approach to this step may be training the algorithm to a reference standard such as the Upper Limb PROM.

The evidence that goes into justifying the acceptance of the endpoint and its intended interpretation is very different for these two categories of endpoints.

- b. Determine what type of change will be measured (for example: improvement, stable function, or decline).
  - ▶ In DMD, seeking to increase function is not appropriate, because patients do not typically regain lost function.
  - ▶ In DMD it is more appropriate to name the “responder” as a research participant whose score did not change over time, and a “non-responder” as a research participant whose score declined.
  - ▶ Responder analysis might be valuable to assess the difference in the slope of decline between the two groups.
- c. Formative research should include evaluating the slope of decline in an observational natural history study over time in order to determine which method of data analysis provides the greatest statistical advantage in a clinical trial. Model this with anticipated drug effects.
- d. Describe how the endpoint will be interpreted to reflect a meaningful treatment effect.
  - ▶ Formative research will be required to correlate the COA data with other, validated outcome measures (ClinROs and PROs) in order to gain an understanding of the kinds of activities that patients can and cannot do for any narrow range of scores. Therefore, when a patient exhibits a change, it will be feasible to describe the change in terms of functional ability.
- e. Clearly identify the patient population for which the endpoint is relevant.
  - ▶ Formative research should include collecting information about how the concept of interest can be measured in different patient populations (age; disease severity) in order to gain insight into which patient population may show benefit for the novel endpoint.
  - ▶ Different concepts of interest, COAs, and endpoints may be necessary to appropriately evaluate patients in different stages of the disease.

#### **Step 7. Determine Whether Research Should Be Conducted to Identify Issues Related to Context of Use**

- a. Conduct parental focus groups to assess potential compliance with the proposed assessment regimen.

### **ISSUES**

The use case team discussed the importance of continuous community-wide sharing of new learning during the endpoint development process in order for the field to advance more quickly. This would allow for building upon others’ learnings, facilitate FDA input at various points in the process, and help engage multiple stakeholders.

A questionnaire and accelerometer together may make a better assessment than an accelerometer alone. Also, technology including both an accelerometer and gyroscope to assess a more wide range of motion may be more suitable for this patient population. Specifically, a more complex technology than an accelerometer may be better for measuring rotational movement that DMD patients may use to compensate for loss of function.

Following completion of writing the use case, the team consensus was that step 6e should have been completed earlier in the process. Specifically, the use case team recommends that the target indication and patient population should be more clearly defined after selection of the

outcome assessment and technology. Waiting until the end to define these parameters was problematic for the team, causing them difficulty in narrowing their focus.

## EXCEPTIONS

Exceptions were not explored.

## TO DO

Feasibility studies must be conducted first to establish baseline feasibility of using this approach. See *Main Success Pathway for Development of Endpoint Steps 5 and 6*.

## CONCLUSION

It is difficult to assess the viability of the clinical outcome assessment and endpoint described because only a very small number of pilot studies have been conducted.<sup>3,4</sup> Formative research on the use of an accelerometer on the upper extremity in this patient population, the natural history of upper extremity decline, and how data generated from the accelerometer may correlate to maintenance of meaningful activities is still required. However, the team identified an endpoint that is important to DMD patients that could be successfully captured using a mobile technology. Specifically, the team defined an endpoint that 1) is not dependent on significant ambulation and therefore can possibly include a larger proportion of all DMD patients, and 2) allows for collection of longitudinal information over typical days of patients' lives.

Exploratory research on the use of an accelerometer placed on the upper arm of DMD patients would be an important first step in developing the endpoint for use in registrational clinical trials.

## REFERENCES

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## ADDITIONAL NOTES

The use case development team used a list of health activities meaningful to the DMD patient population to identify four discrete meaningful aspects of health: core-dependent activities (postural stability), ambulation-dependent activities, arm-dependent activities (functional use of upper extremities), and finger–dexterity-dependent activities. The team explored potential concepts of use (sub-bullets below) that could be associated with each meaningful aspect of health (main bullets below).

- ▶ Core-dependent activities (postural stability)
  - Frequency of moving from one position to another
  - Duration of maintenance of position
  - Frequency of bending at core
  - Frequency of nocturnal position changes
  - Frequency of falls
  - Avoidance of falls
- ▶ Ambulation-dependent activities
  - Stair-climbing frequency, duration, or quality
  - Walking frequency, duration, or quality
  - Running frequency, duration, or quality
- ▶ Arm-dependent activities (functional use of upper extremities)
  - Arm raising frequency, duration, and intensity (speed), or total arm movement
  - Range of motion
  - Muscle strength
- ▶ Finger dexterity-dependent activities
  - Finger movement frequency, duration, or intensity (speed)

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- ▶ *This Use Case was developed at a CTTI-hosted multi-stakeholder [expert meeting](#) in September 2016 as a part of the [MCT Novel Endpoints Project](#). Three additional Use Cases were created for trials involving:*
    - [Parkinson's disease](#)
    - [Heart failure](#)
    - [Diabetes](#)