CBER Explores Scientific Rigor in the Pilot Natural History of Metachromatic Leukodystrophy (HOME) Study to Augment External Controls for RCTs

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Abstract

BACKGROUND

Rare disease therapeutic development faces challenges as randomized clinical trials (RCTs) are often difficult to conduct in small patient populations. Sample sizes for trials are often limited, patients may be less inclined to participate in trials with an assigned control group, and rapidly progressive diseases may not allow for longer-term involvement in trials.

PURPOSE

A natural history study (NHS) could augment or act as an external control for current and prospective RCTs. This study aims to develop a natural history study for Metachromatic Leukodystrophy (MLD). It is a pilot to understand best practices for rare disease natural history development for regulatory use. Innovative data collection methods are used to ease study burdens on patients.

METHODOLOGY

A multi-stakeholder approach was employed to incorporate input from patients and caregivers, clinicians, industry, and the FDA to balance scientific rigor and patient-centricity. This consortium designed a set of longitudinal natural history study questions for MLD and explored innovative and pragmatic approaches for patient experience data collection.

Responses to the study questions will be collected via scheduled visits with participants through site-less tablet-based video sessions. This strategy leverages telehealth technology advancements and its adoption, allowing patients to perform clinical endpoint assessments in their home setting and eliminating travel burdens while maintaining data collection compliance. Statistical analyses will be performed to learn best practices in analyzing external control data from the natural history study and concurrent data from a prospective single arm study.

RESULTS

Patient-centric data collection protocols for the natural history questions were developed. To address common challenges of attrition and missing data in natural history studies, a mobile application – Survey of Health and Patient Experience (SHAPE) - was developed to collect participant-provided data relevant to regulatory decision-making and patient health outcomes. The app allows participants to enter primary clinical endpoints and other episodic health events. Study recruitment efforts are still ongoing.

Introduction

Selection of Metachromatic Leukodystrophy (MLD)

- MLD is a rare disease with dire outcomes (Prevalence rate is estimated to be between 1 in 40,000 ~160,000)
- There is an unmet medical need due to lack of treatments approved for this indication
- There are CBER-regulated products in the pipeline
- Drug development is challenging given the small patient population
- A regulatory-grade natural history study (NHS) can serve as an external control group for drug development trials
- To reduce study burdens for MLD families, developing innovative and rigorous ways to conduct a NHS is crucial

Methods

Figure 1. HOME Study (https://rarediseases.org/mld-home-study)

The National Organization for Rare Disorders (NORD) was awarded a grant from FDA CBER to lead this project, called the Natural **H**istory **O**f **Me**tachromatic Leukodystrophy (HOME) Study.

As part of the multi-stakeholder approach, two Advisory Committees (AC) were established to inform the design and development of the study. Study questions were developed with FDA reviewers to ensure the study can be useful for regulatory purposes. This includes determining which endpoints need to be collected.

Stakeholders Involvement

1) Patient and Caregiver AC (n=5)	Goal: To ensure the study collects information important to the patient community, reasonable in terms of expectations for participation, and sustainable for the prospective duration of the study.
2) Industry and Clinician AC (n=1o)	Goal: To ensure the data collected is clinically relevant; and the study design reflects current clinical & scientific understanding, therapeutic development trends (e.g., study endpoints), and data sources that support using NHS as external controls.
3) FDA Reviewers	Goal: Ensure study includes endpoints that are needed for regulatory decision-making for MLD therapeutic development

Site-less Video 'Visits'

- To reduce patient burden, a site-less approach is adopted that includes scheduled video assessments by a study coordinator with a clinical background
- Conducted using standardized tablets sent to participants
- Conducted at baseline and then every 3 months (at least till 12-months)

Advantage of Study Coordinator Video Assessments

- Coordinator-facilitated scheduled data entry may reduce missing data
- Coordinator can support the data entry process and answer any questions the families may have –enhancing accuracy in data collection
- No traveling required which minimizes patient burden. Participant and families can join the study from home
- The primary endpoint, the Gross Motor Function Classification MLD (GMFC-MLD), is designed to be collected by clinicians
- Support and provide patient families with meaningful resources as needed
- Allows for active feedback from participant/families about study survey and questions

Results and Discussion

Development of the SHAPE App

To further develop innovative methods for collecting and understanding patient experiences, the SHAPE app was designed to be a generalizable, disease non-specific, mobile-friendly progressive web and mobile application for collecting patient experience data. The app allows for:

1. Integrated collection of different types of endpoints
   - Scheduled quarterly: Primary endpoint (GMFC-MLD)
   - Unscheduled: Relevant health events (e.g. hospital visits)
2. Comparison of clinician-reported outcomes & patient/caregiver responses to a disease-specific outcome measure (e.g. GMFC-MLD is assessed by the coordinator over video and participants also reports it on the app)

Key Advantages of Using the SHAPE Mobile App:

1. Reduce burden on patients for traveling to study sites (especially during the pandemic)
2. Reduce missing data by using in-app and text messages to remind timely data entry
3. Engage patients through tools they are already familiar with: their own smart devices

IBM led the effort in building IT infrastructure, integrating compliance & interoperability standards for SHAPE, and beta-testing the app with NORD and FDA collaborators.

The app is currently available on the Google Play Store and Apple's App Store for download.

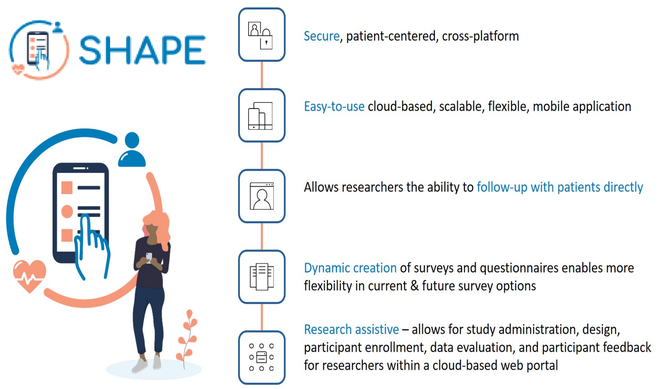

Figure 2. SHAPE App design features

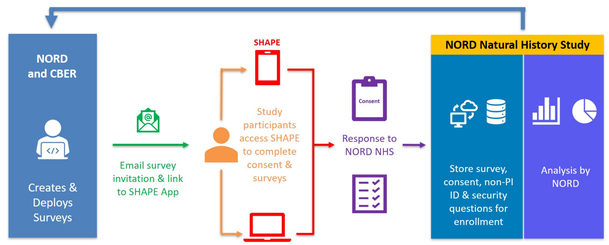

Figure 3. HOME study flow diagram

Study Enrollment (as of 3/10/2021): 9 participants

Current Recruitment Channels

- NORD's network and patient organizations
- Outreach through the Advisory Committees
- Centers of Excellence & academic centers
- Social media platforms (e.g., Facebook, Twitter)
- A public online event on Jan 20th, 2021 (The video recording is available on the HOME webpage)
- Follow-up with participants of the online event

Conclusion & Future Directions

- To address the unmet needs in rare disease therapeutic development, this pilot study is being conducted to understand how to design a NHS to serve as an external control for clinical trials
- Through a multi-stakeholder approach in the development of the HOME study and SHAPE app, we explored innovative data collection methods that are patient-centric and can generate high quality data fit for regulatory use
- We aim to understand best practices on how to analyze NHS data and how to mimic a RCT using analytical methods and rigorous planning at the study design phase to control for confounding and biases
- As a next step, the study will explore linkage of electronic health records to the NHS to enrich information needed and reduce patient burden
- This study will demonstrate the value in designing and conducting NHSs for use in future trials to advance and identify treatments not only for MLD, but also for other rare disorders