A Disease Progression Model for Analyzing Clinical Trials in Mucopolysaccharidosis type (MPS) IIIA

Joe Marion[b], Ben Saville[b] and Juan Ruiz[a]

[a]Abeona Theraputics, [b]Berry Consultants

Rationale for Natural History Control

Traditional randomized controlled trials (RCTs) in MPSIIIA face several challenges. The rarity of the disease presents a serious obstacle enrollment. This is compounded by the need to enroll young children who may respond the most to a treatment. Another concern is that caregivers may be unwilling to enroll children in an RCT, especially when administration of timely treatment is crucial to prevent neurodegeneration.

Single arm studies with a natural history control present an attractive alternative to RCTs for trials in MPSIIIA. The proposed disease progression model further augments the natural history, addressing potential short comings such as limited follow-up duration and patient-to-patient variability.

Disease Progression Model Overview

The DPM characterizes the progression of children in the natural history studies. This data consists of:

- Four prospective, longitudinal studies
- 220 measurements from 93 children
- Cognitive Age Equivalent (AEq) scores measured using the Mullen and Bayley scales

The DPM uses the natural history to estimate the average progression of children with MPSIIIA, shown in the next figure.

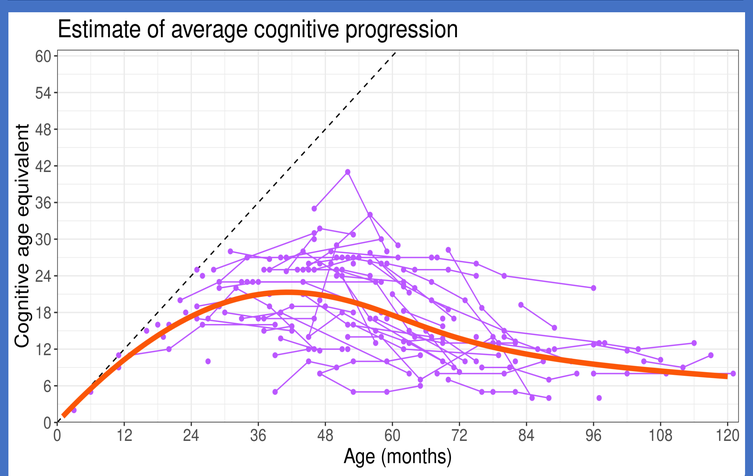

Figure 1: Natural history data (purple dots, each patient connected by a line). The median progression in MPSIIA, estimated by the DPM is shown by the orange line.

- The DPM quantifies the longitudinal pattern of cognitive growth, stagnation, and decline in MPSIIIA
- This pattern is modeled using a non-linear MMRM that assumes a common cognitive trajectory across patients.
- The timing of this pattern may vary from patient to patient, modeled using subject level random effects.
- These random effects allow for each child's peak AEq, and the age of peak capability to vary from patient to patient.

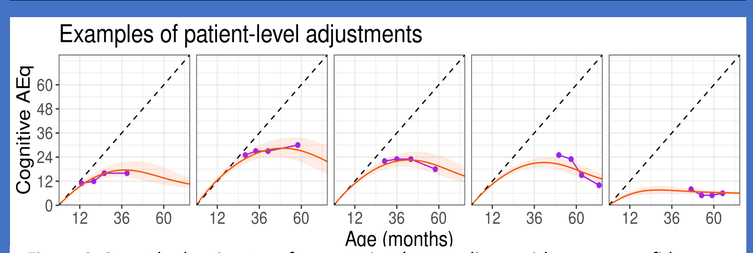

Figure 2: Smoothed estimates of progression (orange lines, with orange confidence intervals) for several natural history patients (purple dots and lines)..

Designing More Efficient Clinical Trials

Randomized clinical trials in MPS IIIA, paired with traditional statistical analysis, face substantial difficulties.

1. The pediatric patient population and the severity of the disease present substantial concerns about randomization.
2. The rarity of the disease (0.32-1.4 per 100,000 births) and the imperative to treat young children, before substantial neurodegeneration occurs, make enrollment challenging.
3. Outcomes in MPSIIIA vary substantially from patient to patient and are strongly confounded by biological age, duration of follow-up, and treatment age.

To address these challenges, we propose a single arm design that leverages natural history data as a comparator. The design is complemented by a disease progression model (DPM) that adjusts for key cofounders in MPSIIIA. Importantly, this analysis becomes more powerful as patients are observed for longer periods. These elements combine to create a clinical trial design that provides compelling scientific evidence with a small number of participants.

Estimating a Treatment Effect

The DPM estimates the effect of treatment on the rate of cognitive disease progression relative to the natural history. This change in rate is called a *slowing* of disease progression.

- For example, the DPM may estimate that patients on treatment progress 50% more slowly untreated patients.

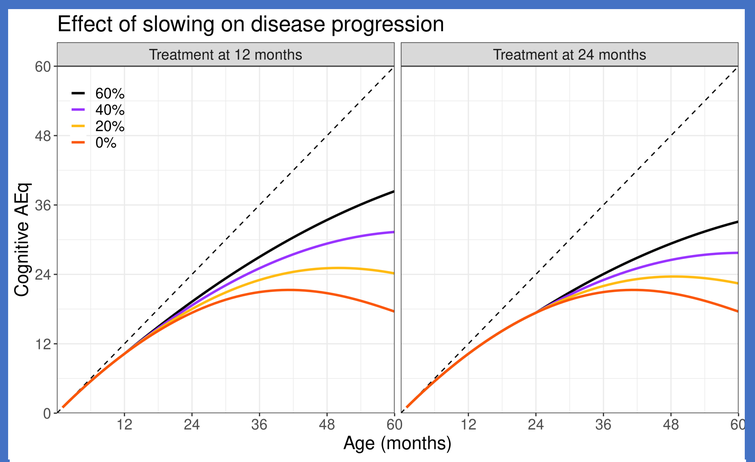

Figure 3: Each line shows cognitive development of children on treatment for different effect sizes and treatment ages. The orange line, a 0% slowing, is the same as the natural history median progression

The clinical benefit of slowing depends on the size of the effect, the age at treatment, and the duration since treatment. We anticipate that children who are treated earliest and followed for the longest duration will show the largest benefit.

A 40% or greater slowing of disease could be a clinically meaningful treatment effect.

- Treatment at 18 months would result in at least a 12-month improvement in AEq when the child is five years old.
- In terms of capabilities, the child on treatment could have a vocabulary of 500-900 words, speak in small sentences, and be better able to communicate their needs.
- In comparison, the average untreated child would have 50-300 words and speak in phrases of three or fewer words.

Example Trial Design and Analysis

- Single arm study with comparison to natural history data
- Enroll 6 children aged 12-36 months
- The primary analysis occurs when all participants have been followed for at least two years and are >42 months old
- Success is claimed if the estimated treatment effect is >40% slowing and the effect is superior to 20% at the 0.025 level.

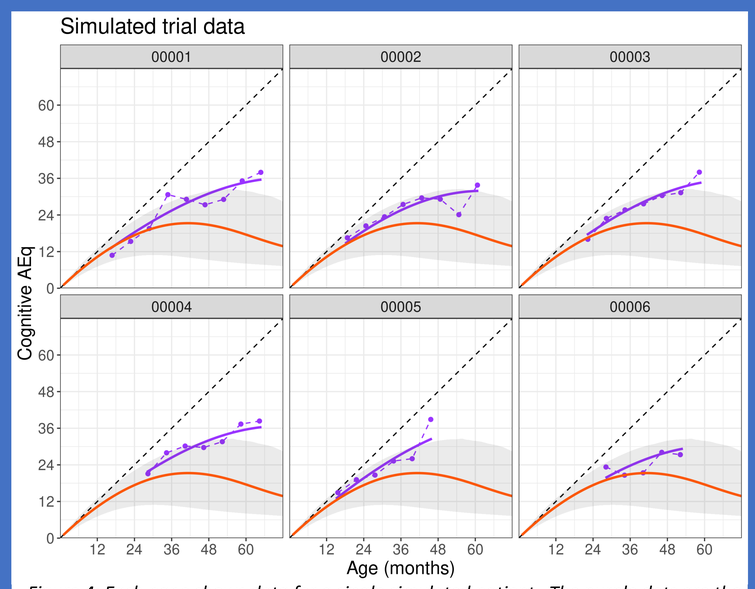

Figure 4: Each pane shows data for a single simulated patient. The purple dots are the observed data and the purple lines show a smoothed estimate from the DPM. The orange line and shaded grey area show the natural history median and 95% interval.

In the above example, the DPM analysis estimates a 43% slowing of progression. The 95% credible interval is (21%, 60%), leading to a declaration of success..

Comparison to Alternate Analysis

The power of the DPM analysis is compared to two alternate methods that also utilize the natural history data.

1. A Wilcoxon test comparing AEq at to an age-adjusted performance goal informed by the natural history.
2. A linear mixed model for repeated measures (MMRM) estimating the rate of log-DQ change from baseline.

Theses analyses were calibrated to have approximately 0.025 probability of success when the true effect is a 20% slowing.

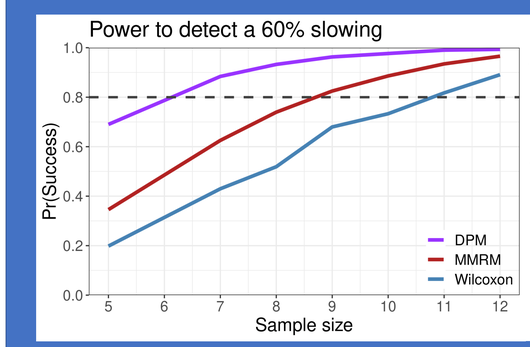

Figure 5: Power as a function of sample size for three analysis methods. The dashed black line is a reference showing 80% power..

1. The DPM analysis has 78% power to detect a 60% slowing of disease with a sample size of 6 patients.
2. The performance goal has lower power because it doesn't adjust for treatment age, duration, or incorporate follow-up
3. The linear MRMR is biased upwards by young participants, requiring a stringent success criterion (lowering power).