LSP 6

Hierarchical Bayesian model of disease progression in centronuclear myopathy for demonstrating rare disease treatment efficacy with a small sample size

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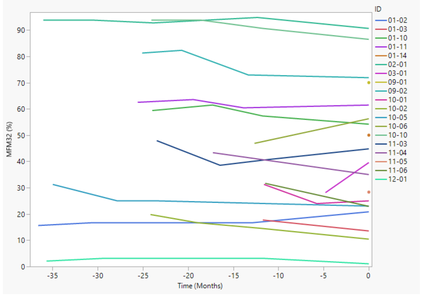
1 Clinical Trials in Centronuclear and myotubular myopathies (CNM)

- Rare disease (estimated less than 2700 MTM1 patients in EU and US) .
- Large Heterogeneity in the clinical response and genetic heterogeneity which must be accounted for in the determination of efficacy.
- Severe Illness. Is it ethical to put patients on placebo ?



The Figure shows individual patient data for MFM32 over time from the Prospective Natural History Study of Patients With Myotubular Myopathy and Other Centronuclear Myopathies (NatHis-CNM, NCT03351270)

2 Proposed Strategy

1. **Disease progression model.** A hierarchical Bayesian disease progression model that allows to avoid a placebo group by using available Natural History Study data is developed and documented. This model allows to predict the course of disease for an individual patient. Motor function as assessed by MFM32 was used as outcome to evaluate disease course for patients with MTM1-linked CNM aged 6 to 18 years (NatHis-CNM, NCT03351270).

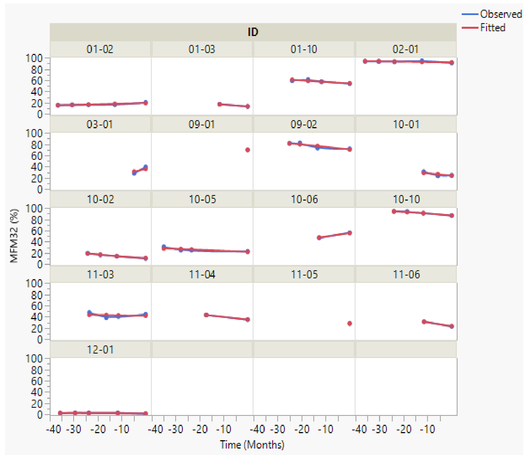
2. **Individual prediction.** In an investigational clinical study, a patient's individual predictive distribution of the endpoint or endpoints over time after treatment administration can be derived by combining the natural history data of this patient with the natural history data from the other patients enrolled in the trial. The natural history data can be generated either in a separate natural history study or from a run-in period in the investigational clinical study.

3. **Identifying responders to treatment.** To identify a response to treatment, we propose to use a deviation from the predicted course of disease to define a responder. We adopted a predictive probability-based definition of responder since
(a) there is little consensus on what constitutes a clinically relevant change and
(b) clinically meaningful change depends on the patient's state of disease (an increase of 3 points does not have the same value for everyone).
This responder definition does not account for a potential placebo effect, as it is here assumed unlikely to be very strong in younger children.

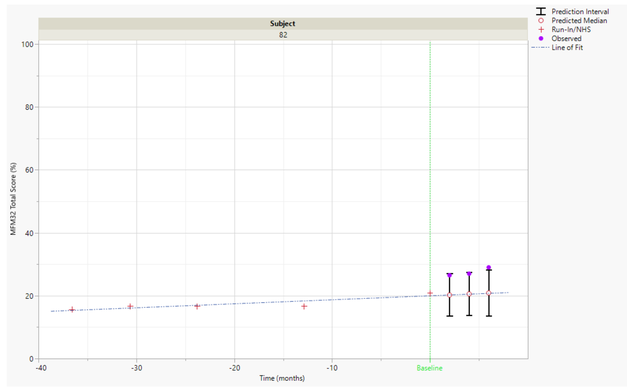
4. **Control of trial Type I error.** Statistical checks to ensure that the proposed methodology has acceptable operating characteristics (e.g.,* false positive rates...)

3 The Disease Progression Model

- Linear Hierarchical model (mixed model) with random slopes and intercept
  - Each patient has their own level of disease and trajectory, but is still slightly influenced by the level and disease progression of all the others (population effect)
- Logistic transformation of the equation of the mean and beta distribution to impose the lower and upper bound characteristics of the scale
- Good model fit as can be shown in the corresponding figure

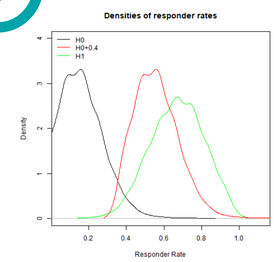


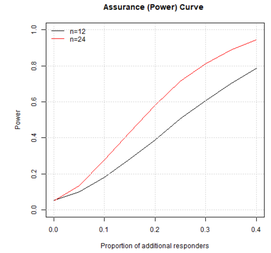
4 Predicting and Defining a Responder



The joint predictive probability of improvement (increase or decrease depending on the endpoint measured) assuming an ongoing linear trend post-intervention is computed for each patient.
If the joint predictive probability of the patient's observed improvement is smaller than or equal to 0.01, then a patient is declared to be a responder.

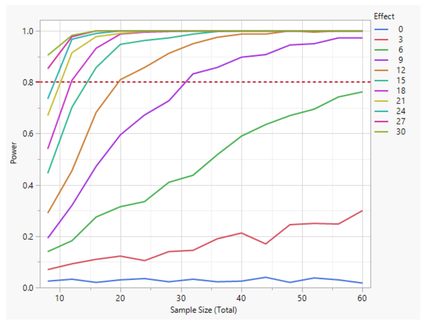
5 Examples of Power Curves





- **Figure on the left** shows the expected responder rates if:
  - No treatment effect is present (i.e. 20% naturally occurring responders from the model variability)
  - We simply assume an increase of 40% additional responders
  - We assume that there is a linear increase of 3 points on MFM32 up to the last treatment visit
- **Figure on the right** shows two power curve with 12 and 24 patients in the study
  - Assuming an increase in 40% of responders under treatment (which corresponds more or less to a 3 point increase) gives an 80% power with 12 patients.

6 What about Classical Change from Baseline Methods ?



- Using classical change from baseline differences and superiority from placebo to demonstrate treatment effect yields the power curves shown above.
- Each curve corresponds to a hypothesized average treatment effect.
- One can see that even with double the effect as before (6) it is still necessary to recruit around 60 patients to conduct the trial with a power of around 80%.
- 2:1 randomization is used. Hence 20 patients would be under placebo while under a severe rare disease raising ethical concerns.

Conclusions

Our proposed methodology allows to:
- Determine responders as subjects who differ from their own trajectory. Each patient is, in this sense, their own control. Based on the data we have of a given patient and what we know from the general disease progression, we can determine if a patient is responding to treatment or not (based on an unlikely deviation from their trajectory).
- Reduce the sample size and thus conduct a scientifically and ethically justifiable clinical trial in a very rare disease, by integrating real-world data into the decision-making process.
- Reduce burden on the patients that would be trial subjects without putting some of them through a long placebo arm

If ethics allow, the method can also be applied to patients on placebo, where responders on placebo can be compared to responders on treatment. Ongoing work involves investigating robustness of our design to changes in the disease progression model, e.g., nonlinear forms, where it will be tested what happens if there's a placebo effect

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