

Opinion

What got us here will not get us there

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This is an exciting yet trying time for people living with neuromuscular diseases and those who care for them. The exciting aspect is that at last the advances in genetics and translational research have resulted in clinical trials testing novel compounds. Examples include the exon-skipping approaches in Duchenne Muscular Dystrophy (DMD). Resulting from a sophisticated understanding of the consequences of dystrophin gene mutations, ASOs were developed to help transform the “garbled” message resulting from a disrupted reading frame into a “translatable”, in-frame, message. This rational and targeted approach worked in pre-clinical studies, but it yet has to confirm its efficacy in patients.

The trying aspect illustrated by this example is that it has taken over 10 years to get from pre-clinical proof-of-principle studies to clinical trials. Some of this is the inevitable development time needed for candidate selection, lead optimization, pre-clinical toxicology, and manufacturing issues. However, an additional source of delay may be the limited tools and data available for trial planning:

The available methodology to measure dystrophin in muscle biopsies may not be sensitive enough, and may show too much variation due to sampling or differences in laboratory measurements. Similarly, existing clinical outcome measures have limitations in terms of floor and ceiling effects, in terms of their applicability to

only a subset of patients rather than a broader spectrum of patients in different disease stages or age groups, and in terms of the limited availability of datasets for trial planning.

Participant enrollment has been challenging for some trials, such as for example the FOR-DMD trial [1]. FOR-DMD aims to fill gaps in knowledge regarding steroid treatment, a better understanding of which would be helpful for any subsequent therapeutics development program.

These limitations may have contributed to negative trial results of interventions with a compelling rationale and strong pre-clinical data. This example from Duchenne Muscular Dystrophy also illustrates how in rare a disease the regulatory pathway may not be sufficiently “paved” even after many excellent academic studies examining the natural history and outcome measures.

The following are some of the opportunities for the advancement of neuromuscular therapeutics:

1. With regards to outcome measures: We need better coordination between the private and public sector in the development of outcome measures. This might include targeted initiatives in a pre-competitive space that focus on outcome measures that have potential for use in drug development, and aim to identify the most promising candidate measure so that in a collaborative effort across sites a robust dataset could be collected that would accelerate drug development.

2. With regards, to datasets: One could promote harmonized data collection so that datasets can be combined nationally and internationally for a stronger basis

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in trial planning. Larger natural history datasets could improve tying outcome measures to the stages of the disease.

3. Prioritizing efforts can help avoid a crowded landscape in which studies compete with each other and are thus slowed down. Better coordination could accelerate overall progress. This could be done through efforts such as the TREAT-NMD Advisory Committee for Therapeutics (TACT) review of projects [2]. It is important to take into account the incentives of academic and company investigators, and to find a system of prioritization that adds value to the field for all.

4. With regards to trials, it would be beneficial for the field if trials were following high standards of methodological quality. To minimize bias, this would require attention to randomization, blinding, and sufficient power to answer the question [3]. If resources and participants are engaged in trials that will not provide a sound and unbiased evaluation of the intervention, then these trials may actually slow down progress in the field.

5. With regards to publications, it would help advance the field if all studies, positive or negative, could be published or otherwise made known to patients, clinicians and researchers as soon as the results are available.

6. With regards to participant enrollment, it could accelerate progress if patients were more fully engaged in the trial development process, starting with the concept (to make sure that the questions asked matter to patients and families), and also included protocol development (to make sure the procedures are feasible and adequate in the burden they pose). It would also be beneficial if patients engaged with the research enterprise by for example volunteering information to a registry indicating that they are interested in trial participation so that a trial could enroll patients faster.

In summary, there are great opportunities to accelerate progress in neuromuscular disorders through increased stakeholder engagement, through greater collaboration or at least coordination between stakeholders, and through promoting high quality trials and transparent reporting.

REFERENCES

- [1] <http://for-dmd.org/en/>
- [2] www.treat-nmd.eu/tact
- [3] www.consort-statement.org