# Clinical trial strategies for rare neurodevelopmental disorders: challenges and opportunities

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Novel clinical evaluation strategies are needed to fulfil the potential of targeted therapies for rare neurodevelopmental disorders.

Rare neurodevelopmental disorders (RNDDs) are neurological conditions caused by genetic mutations and variants. Although they are individually rare, RNDDs collectively affect 2–5% of children with neurodevelopmental disease and have substantial societal and economic impact, with lengthy diagnostic odysseys and lifelong disease management by affected families.

RNDDs are characterized by features such as severely impaired cognition, sleep, communication, adaptive behaviour, social and psychomotor skills, and a high prevalence of epilepsy, which are key clinical outcomes in RNDD trials. Preclinical studies have elucidated mechanisms in specific RNDDs and informed the development of targeted therapies. However, despite recent advances, translational research in RNDDs faces specific challenges that have made it difficult to bridge the gap from bench to therapies. Here, we highlight key points from a panel of experts including clinical researchers, preclinical scientists and industry partners convened to discuss current insights and future avenues for clinical development of novel therapies for RNDDs (see Supplementary information).

## When to intervene?

People with RNDDs can now be diagnosed earlier in life, even in utero, owing to wider availability of genetic testing and changes in clinical genetic testing practices. Early intervention is likely to provide the best chance of disease modification, although the ideal window may vary between disorders and functional domains for a given disorder. There are also many challenges for intervention in early infancy, such as developmental regulation of molecular processes and how this may be altered in each RNDD, availability of early detection and diagnosis, correlation of early presentation with more severe phenotype in some instances, and immature physiological systems including immunity and excretion, as well as broader aspects such as unknown safety profile, unclear pharmacodynamics and lack of validated clinical end points. Accordingly, dedicated research is required to address when and how best to intervene for each specific disease and pathophysiology.

## Impact of placebo in trials for RNDDs

When technically feasible and ethically acceptable for RNDDs, placebo-controlled trials remain optimally free of assumptions or reliance on external information. However, clinical trials in RNDDs have been challenged by placebo effects, in part driven by observer-reported behavioural outcome measures as primary end points, regression to the mean, public expectation of success increased via social media, and complexities in implementation of blinding with invasive routes of administration and in-depth safety monitoring[1]. Mitigation of the placebo effect needs innovative trial designs involving pre-treatment and post-treatment disease trajectories and external controls from natural history, as highlighted in FDA guidance. Appropriate outcomes and targets can be defined in such studies, and they are also an opportunity for education, including the responsible use of social media for trial sponsors and participants. Careful protocol design is needed, including objective performance-based outcome measures and clinically reported outcomes and informative biomarkers.

## Clinical outcome assessments

One major challenge in RNDDs is the quantification of disease progression and early therapeutic benefit. While observer-reported behavioural outcome measures can capture informative complex constructs, they are also prone to bias[1]. Performance-based outcome measures are considered more objective but also pose challenges. First, most neurodevelopmental performance-based outcome measures are designed to track sequential acquisition of skills as observed in typical development

and to identify developmental delay compared with a typically developing normative population, which may not be an appropriate comparator in RNDDs. Second, the method of administration of such scales is tightly controlled to minimize inter-rater and intra-rater variability and ensure validity. These constraints are problematic in RNDDs owing to the wide range of age, developmental level and co-morbidities. It is also unclear how best to quantify an individual's baseline performance and track change. Derived scores require transformation of raw scores, often resulting in floor effects in RNDDs. However, raw scores do not measure a single construct and can have responsiveness limitations due to uneven steps and problems with linearity, as well as floor or ceiling effects. More recently, growth scale or "W" scores that are based on the ability scale created by a calibration of a subtest or composite have been used to provide a common scale across forms and levels of a test. They are closer than raw scores to an interval scale of measurement, allowing the user to interpret change in the same way wherever it occurs on the scale[2].

It is also unclear whether current neurodevelopmental scales are ideal for measuring response to therapies, given that they were originally designed to identify delay in normative development. Their administration and scoring implicitly assume that acquisition of skills follows a canonical sequence that has been delayed by disease and, if rescued by therapy, would be expected to resume according to a sequential ontogeny. An alternative hypothesis is that the sequence of neurodevelopment in at least some of the RNDDs is not simply delayed but altered, so skills may be acquired in an atypical order and respond differently to intervention. Finally, these measures are often administered outside of their designated chronological age range, as older individuals with RNDDs may demonstrate skills typically observed at younger ages. Therefore, any study must not be overly constrained by prior assumptions that may not apply to the population under evaluation.

Another challenge lies in defining a minimal clinically important difference in response to therapy. Difficulties in RNDDs include lack of precedent, expected gradual rate of change of neurodevelopment versus the shorter length of clinical trials, limitations in eliciting from patients themselves what is meaningful, heterogeneity within the population and lack of natural history. Despite the commonalities in unmet need among RNDDs, the unique underlying biology, distinctive clinical aspects and specific priorities for each RNDD require a bespoke consideration of each community. This requires alternative approaches such as individual-level rather than group-level attainment goals and analyses, rate of change rather than point measurements, biomarkers as surrogate end points and composite rather than single primary end points, guided by definition of specific 'core outcome sets'[3].

Epilepsy is highly penetrant in most RNDDs, and seizure severity is a key outcome measure for many trials in RNDDs. Seizure diaries remain the monitoring standard but depend on accurate recognition and recording of events, and thus there is considerable variability between caregivers. Ambulatory devices can provide alternative methods for seizure detection, with the added benefit of monitoring seizures in the home and throughout the night, including sleep data.

## Biomarkers

The inter-individual heterogeneity, placebo effect with behavioural measures and gradual rate of response to therapy in domains such as cognition underscore the need for biomarkers in trials for RNDDs[4]. Biomarkers derived from electrophysiological signals, foremost electroencephalography (EEG) and magnetoencephalography (MEG), provide a direct window into brain function and can quantify relevant pathophysiology at rest or within specific tasks. EEG-derived biomarkers are feasible in RNDDs and being actively explored for diseases such as Angelman syndrome, Rett syndrome and fragile X syndrome. Plausibly, these measures can reflect restoration of normal physiology with intervention in these and similar disorders. As with EEG and MEG, transcranial magnetic stimulation (TMS) can also provide a range of cortical excitability and plasticity measures, particularly when combined with electromyography to record the motor evoked potential, or with EEG to detect the cortical TMS evoked potential.

Sleep abnormalities are prominent in RNDDs and tied to learning, cognition and quality of life of the individual and family, and thus intrinsically meaningful. Novel approaches are emerging to quantify sleep parameters as a biomarker in trials with RNDDs, using technologies that allow accurate minimal or non-contact assessment such as actigraphy, accelerometry, radio signals or under-mattress ballistocardiography signals, combined with advanced analytics[5]. A caveat is often the need to adapt technologies and algorithms from the healthy adult context in which they were developed to the specific RNDD.

## Conclusion

Key themes that emerged from the workshop included a need for innovation in trial design and analysis, to bring the potential benefit of novel transformative therapies to RNDDs. The needs of patients and families in each population should be central, while building on the commonalities between RNDDs.


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**Competing interests**
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