BLOG POST

# The Importance of Rigorous Study Designs

The recent FDA approval [1] of Sarepta's eteplirsen (Exondys 51), while generally welcomed in the Duchenne muscular dystrophy (DMD) community, was not without controversy. Eteplirsen is a gene therapy drug for use in DMD patients whose dystrophin mutation is amenable to exon 51 skipping. It was approved after a study of 12 patients, four of whom received placebo for 24 weeks before being re-randomized to one of two dosages. Questions have arisen regarding the use of historical data as a control in the absence of a concurrent placebo arm of the latter part of the study, the efficacy measures used, and the use of post-hoc analyses conducted by the study sponsors [2]. But in the end, Eteplirsen was approved by the FDA, and the process, regardless of attendant controversy, illustrated the potential for innovation in clinical trial design and methods of analysis.

## Producing High-Quality Data

In light of this approval, and the imperative for innovative clinical research in orphan drug development, it may be tempting for sponsors of clinical trials to want to push boundaries in order to get their drugs to market more quickly and at lower cost. This may be especially true for rare disease clinical trials where patient recruitment may be difficult and the unmet clinical need is substantive. In this process, part of our role as a contract research organization (CRO) is to help sponsors ensure that innovative trial designs and development programs maintain both methodological rigor and continue to ensure data integrity. The Commissioner of Food and Drugs says that in light of the controversy over eteplirsen "we must redouble our efforts to move the therapeutic development ecosystem to use methods that will produce high-quality data from the outset."[3]

## Requirements for FDA Approval

FDA approval requires evidence of efficacy and clinical utility of a candidate consistent with well accepted standards and trial design should reflect those needs. Considerable flexibility in evidentiary standards of approval has been noted by other authors in the orphan disease space, suggesting a portfolio of design options that might be possible contingent upon the nature of the product and the therapeutic target [4]. As in other therapeutic areas, endpoints should be clearly defined and time points should be clinically relevant. Although the use of historical control cohorts can be considered as a component of the review process (as in oncology drug development), patients must be appropriately matched and clinical assessments should be standardized across contributing trial centers. Statistical analyses should be prospectively designed to account for all time points and dosages, and potential heterogeneity across reference trials. Studies must be designed so that the protocol is consistent with the endpoints; in other words, test what you say you're going to test.

## Combining Scientific Rigor with Innovative Trial Designs

Therapeutic innovation usually highlighted within drug discovery is enhanced when accompanied by methodological innovation during clinical development. As more and more therapies for rare diseases start moving into clinical phases, Worldwide looks forward to working with our sponsors on rare disease clinical trials that are both innovative and rigorous!

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### References

[1] http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm521263.htm

[2] Aaron S.Kesselheim, MD, JD,MPH and Jerry Avorn,MD. Approving a Problematic Muscular Dystrophy Drug: Implications for FDA Policy. JAMA. October 24, 2016. doi:10.1001/jama.2016.16437

[3] Robert M. Califf, M.D., Commissioner of Food and Drugs, letter accompanying Summary Review of NDA application 206488Orig1s000 http://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/206488_summary%20review_Redacted.pdf, page 13

[4] Sasinowski, F, Panico, E., Valentine, J. Quantum of Effectiveness Evidence in FDA's Approval of Orphan Drugs: Update, July 2010 to June 2014. Therapeutic Innovation & Regulatory Science. 2015, Vol. 49(5) 680-697.

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