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Maximizing Early Development Clinical Trials with Adaptive Study Designs

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Introduction

Early phase clinical trials offer valuable insight into the pharmacology of a new chemical or molecular entity (NCE/NME) under development; however, they continue to be high stakes and often require complex study designs, high numbers of procedures and the use of special populations.

A current trend is adaptive study design, also called "umbrella protocols." Umbrella protocols combine healthy normal volunteer, First-In-Human studies with Multiple Ascending Dose studies and patient studies to obtain early efficacy, which in turn provides the potential to save sponsors significant time and money.

Advantages of Adaptive Study Design

A Phase I trial is a representation of years of work and testing, and it is a major milestone in drug development. Years ago, early development studies would have been conducted sequentially beginning with the Single Ascending Dose (SAD), followed by the Multiple Ascending Dose (MAD), then other studies like food effect, etc. If all studies were successful, then the drug would move into a Phase II trial.

There are several advantages of adaptive study designs. The SAD and MAD trials can be combined into one trial along with a food effect study or an evaluation of a special population. Occasionally, First-in-Human studies are conducted in a target population, especially with biologics, or as an additional cohort added in an adaptive manner for a Proof-of-Concept trial, potentially demonstrating a direct effect in special populations of either biomarkers (e.g. viral load) or an alteration in disease state (e.g. reduction in tumor size).

By combining several protocols into a single umbrella protocol, sponsors can evaluate multiple endpoints and achieve multiple objectives at once, which translate into both time and cost savings. Hence the motivation for the implementation of umbrella protocols and the logic behind their increasing popularity.

Special Population Early Development Clinical Trials

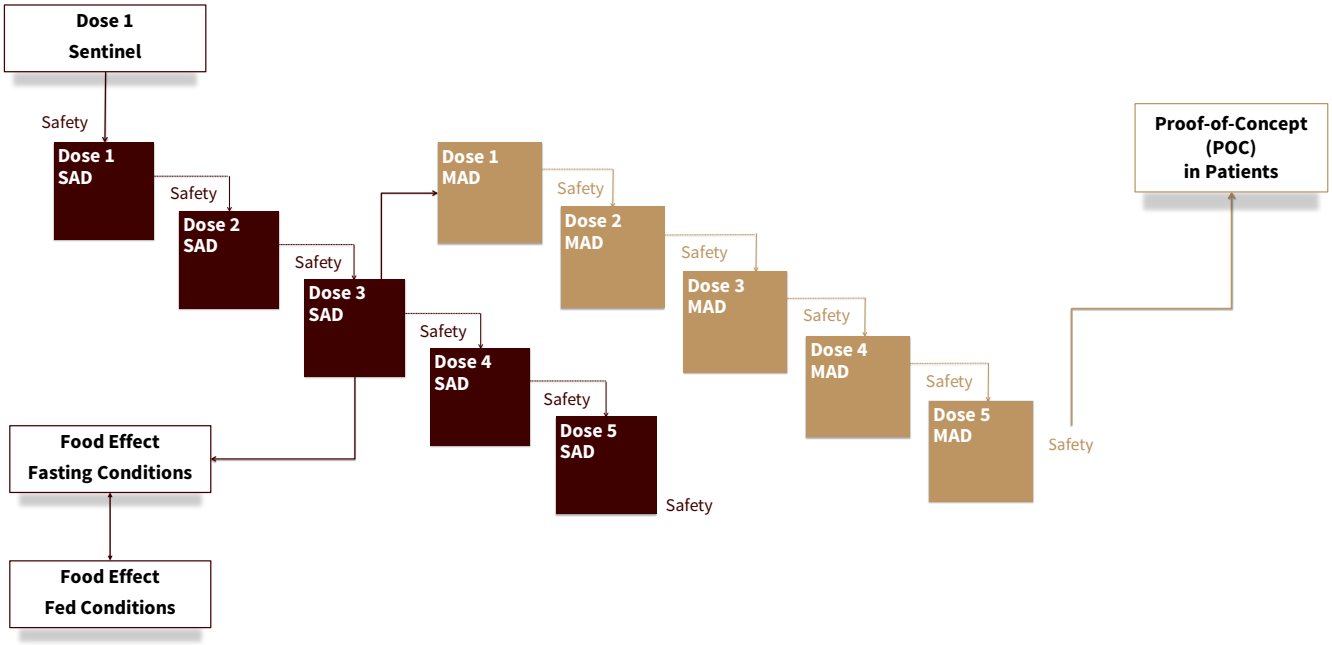
"Special population," what exactly does that mean? Special populations are volunteers diagnosed with a disease or condition, such as hypertension, gout, psoriasis, etc. In special populations, safety concerns are amplified, and the medical management and supervision of these volunteers becomes more challenging.

The protocols for special population studies are more complex due to the multifaceted nature of the safety assessments, procedures and biomarkers. Each protocol requires a population-specific review by the clinical pharmacology unit for operational feasibility. When recruiting special populations, a clinical research site must take into consideration the recruitment challenges, concomitant medication issues, competing Direct-to-Consumer medications and other ongoing trials. Additionally, the motivation for special populations to participate is not always money, and confinement periods become more challenging.

Why Incorporate Special Populations

While healthy normal volunteers and special populations require significant oversight in early development clinical trials, special populations require significantly more skill, training and expertise from the clinical pharmacology team conducting these highly specialized trials.

Ideal case of adaptive integrated design involving SAD, MAD, Food Effect and Proof-of-Concept



So, why use special populations in early development trials?

Special populations facilitate early decision making about potential drug candidates.

An increased number of trial designs have a traditional SAD study in healthy volunteers followed by a study arm of a specific special population within the same protocol. The purpose of this adaptive design is to assess whether or not the drug being evaluated is actually hitting the relevant target in the intended special population.

The name of the game with special populations is to get as much information about the drug candidate from an early clinical program, so sponsors can get a better idea of drug efficacy, dose range and safety considerations. The end goal is to provide drug developers with clear decision pathways for go/no-go decisions before moving their drugs into time consuming and costly later stage trials.

Conclusion

With the increased pressure for pharmaceutical and biotech companies to get new drugs to market as quickly as possible, it is imperative to implement processes to shorten timelines and reduce study costs while maintaining high standards of quality and safety. Adaptive study designs provide sponsors with this very solution.

By incorporating several protocols into one umbrella protocol it allows the aspects of safety and tolerability to be addressed while obtaining Proof-of-Concept data to provide scientific guidance for further development as well as create value to an organization.

While the adaptive design model and the use of special populations in early development trials is being used by some companies, it is not yet a requirement or industry standard.

The ability to obtain efficacy data for an intended disease state population early on in drug development can be essential for go/no-go decisions, which enables companies to effectively manage their drug development pipeline and determine where time and money can be used most successfully.

For a more in-depth discussion regarding your special population or adaptive design program, contact our clinical team.

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