4 Types of Dose Finding Studies Used in Phase II Clinical Trials

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One of the key goals of phase II is to determine the optimal dose that you will use going into your phase III trials and that ultimately will be used on your product label submitted for approval as part of the new drug application (NDA). The optimal dose is the dose that is high enough to demonstrate efficacy in the target population, yet low enough to minimize safety concerns and adverse events. There are a number of strategies to determine the optimal dose, but here we will look at the four most common dose finding study designs.

PARALLEL DOSE COMPARISON

Parallel dose comparison studies are the classical dose finding study and are still one of the most common study designs. In parallel dose escalation study, several potential doses are selected and subjects are randomized to receive one of the doses or placebo for the entire study. At the end of the study, you can compare each treatment group to the control group and examine both safety and efficacy. Because all treatment groups, including the higher dose cohorts, are dosed at the same time, this study design is best suited for situations where you have a good idea about the safety profile before the study starts. This design is also the basis for some adaptive studies (such as adaptive randomizations or pruning designs) that can reduce the number of subjects exposed to unsafe or ineffective doses.

CROSS-OVER

In a cross-over design, subjects are randomized to a sequence of investigational product (IP) and placebo. Specifically, they are given a dose of the IP and then switched to dosing with a placebo or they start dosing with a placebo and then are switched to a dose of IP. The difference between the subjects' response to placebo and IP is the result of interest and by having different groups of subject exposed to different doses, you can pick the optimal dose. The value of cross over studies is they can determine efficacy of a dose within a subject because subjects act as their own control. This reduces the variability and can therefore reduce the number of subjects you need to study. However, cross-over designs only work when the drug is quickly eliminated from the body. You need to be able to give a subject the treatment, wait for it to clear, and then give the second treatment in the sequence. It also requires a product that is designed to be used multiple times. For example a product that is intended to be given once, such as a drug to lower blood pressure during heart surgery, can't be tested in a cross-over study because you won't do the surgery again just to give the second treatment in the sequence.

DOSE TITRATION

In a dose titration study, you titrate to the maximum tolerated dose within a subject. This means that each subject will start at a low dose and receive an incrementally higher dose until the maximum dose is reached. In some studies, like chemotherapy for cancer studies, this dose is determined by the onset of side effects—this dose is called the Maximum Tolerated Dose (MTD). In other studies where the product is less toxic, it may depend on blood levels of the IP, a metabolite, or a maximum dose determined from preclinical studies. Dose titration studies work well for treatments of chronic conditions where a drug will be used for a long period of time and where the dose is likely to be tailored to the subject's weight or reaction. This design is also good for situations where it is likely that you will see significant differences in the way each subject reacts. Chronic hypertension medications are a good example of products where dose titration is useful. There is a lot of variability in how individual patients respond to hypertension products and with titrating the dose, you can give a lower dose to those who respond to it.

DOSE ESCALATION

If you are unsure of your safety profile and want to start exposing subjects to lower doses first, consider a dose escalation study. In this type of study, you start with one group of subjects (often referred to as a cohort) and give them a low dose. You observe this group for a period of time and if no safety issues are noted, you enroll a new group of subjects and give them a higher dose. This process is repeated until either you reach the maximum tolerated dose or you reach the highest dose you plan to consider. This design increases patient safety because you can start by exposing a small number of subjects to the lowest dose possible. You are mitigating risk both by limiting the initial number of subjects and limiting the exposure of each subject to study drug. You can also add control subjects to each cohort if you want to look at efficacy measures with an appropriate comparison group.