Medical Xpress

Pharmaceuticals Look to Adaptive Trials

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Adaptive trials are gaining in popularity. Image source: University of Wisconsin-Extension.

(PhysOrg.com) -- For years, trials of pharmaceuticals have revolved around the double-blind test, controlled with a placebo, in which not even those conducting the investigation knew who was receiving what treatment. Tests moved through various phases, and months of evaluations were made between each phase. All the while, participants and investigators were kept from knowing who had what treatment, in the hopes that it would limit the bias involved. But now that traditional method of testing is being challenged. Instead, pharmaceuticals are considering "adaptive design", which allows them to change the trial's set-up to adapt it to the information being received.

Adaptive design allows for data to be continuously captured and analyzed, and it also implies that the investigators know exactly who is taking the pill under observation, and who is taking the placebo.

Additionally, adaptive design also allows for pharmaceuticals to test the effectiveness of different dosing arrangements at the same time. Data is looked at in the interim -- between phases of the trials -- and unblinded at that time. The Scientist reports on arguments in favor of using adaptive design:

"The reasons to do it are pretty clear," says Janet Wittes, president of the clinical trial design firm Statistics Collaborative, Inc., in Washington, DC. Adaptive trials "hold the potential and the promise for doing trials faster and getting answers faster." Plus, assessing assumptions you made in planning a trial as it proceeds can strengthen a trial's scientific merit, says Scott Evans, a biostatistician at Harvard University.

Not only that, but pharmaceuticals can reduce their costs. Companies estimate that they could save between 20% and 50% if they could adjust drug trials -- or drop them altogether -- by studying interim data. Unblinding the trials and looking at data that shows that a drug has turned out to be totally ineffective prior to entering later phases of a trial could save millions, or even billions, of dollars by giving investigators what they need to halt the trial. Being able to tweak would also allow investigators to focus on dosing arms that appear more effective or try something a little different in the final phase.

But, of course, there are problems with adaptive trials. While few protest against adaptive design at the initial stage, late stage trials present problems. First of all, the FDA is uncertain how to proceed when it comes to regulating adaptive design. Even the term "adaptive" is in question. What does it require? Another issue is that drug companies may change their hypotheses about certain treatments and their expected effectiveness partway through. And there are other issues:

1. Multiple repetitions of a statistical test can increase the chances of a false positive.

2. Tweaks to tests and statistical measures, looking for best possible results, are more likely to show what the investigators want them to, biasing the final result.
3. Bias can also be introduced as subjects and investigators look at the changing design. Both may make assumptions based on the adaptations and act accordingly, biasing the results.

And, of course, there is the danger of shoddy practices in the name of business concerns. The Scientist reports also on the argument against adaptive design:

Some say that the pressures of efficiency push some companies to misuse it. One strategy Wittes has encountered is undersizing trials in order to bait investors, she says. A company that can't afford to run a full trial might plan an adaptive trial that stipulates an "outrageously large" effect for their treatment and contains a built-in plan to increase subject numbers if this noncredible effect size isn't met. "Then at some planned interim they look at the data and they say, 'Oh, the observed effect size is smaller than anticipated.'" Still, that limited data can be used to lure investors to fund the larger trial. "What I worry about is that in part [adaptive design] has caught on because of business pressures," Evans says.

In the end, there is likely use for adaptive design in some trials, especially at the early stages. It would help investigators catch some problems earlier, and allow investigators to make small changes that could make for a better trial. However, adaptive design should probably be used carefully, especially as the phases of clinical trials move forward.