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MDS Follows The Critical Path — And Sees Benefits

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In 2004, the FDA unveiled a project called the Critical Path Initiative. As then Commissioner of Food and Drugs Andrew C. Von Eschenbach, M.D., later explained to Congress, “This project has the potential to transform the way medical products in the United States are designed, developed, tested, and used.”

So-named for the “critical path” medical products must travel between conception and actually reaching the patient, the initiative’s purpose is to speed that process while maintaining safety. “The FDA identified concerning trends in drug development, including rising costs, increasing timelines, and declining probability of earning approval. The Critical Path Initiative was developed as a means of reversing these trends,” says Michelle Combs, Ph.D., VP/global clinical pharmacology at MDS Pharma Services.

Indeed, one report estimates that “if only 10% of failed trials were to succeed, the current success rate would nearly double.” While Combs can’t quote that statistic specifically, she does note, “Ultimately all such reports speak to the same point: Current study methods all have a very large failure rate. The sooner you can identify that something’s ultimately not going to be a viable product, the more money you can save, because you don’t invest the money in its development.” That being the case, she says, “Obviously, a different, more efficient, testing method was needed.”

Exploring FDA Opportunities

The FDA’s Critical Path offers numerous opportunities to speed drug development. These are outlined in its “Opportunities List,” which covers six overall topics. MDS took advantage of the opportunities listed under Topic 2 — clinical trial design — and specifically Opportunity #36: “Use of prior experience or accumulated information in the trial design.”

“That’s a pretty broad category,” Combs says, “so what we’ve been seeing over the last 18 months is a real trend toward trying to do more creative designs and also adding the target population as early toward Phase I as possible.” (For a complete opportunities list, check the FDA website.)

“More creative design” calls for changing a trial study’s traditional format. For years the progress of a study trial was simple: Start the trial, collect data, and finally analyze those results. Using this method, it’s presumably easy to minimize the entry of any mistakes.

However, it’s a method that takes a relatively long period of time. Except when red flags arise regarding safety, such data collection rarely allows for stopping or even modifying a study. One might call it the “Qué sera, sera” method of study analysis: Let the study progress, and whatever the outcome, that’s what is meant to be. This form of testing is fairly expensive and can be highly unsatisfactory since the outcome isn’t known until the end — at which point it may not prove viable.

By contrast, adaptive design allows for in-study modifications. Thus, if one aspect is seen to be contraindicated or in some other way not viable, it can be modified or even deleted as needed, without compromising the validity and integrity of the trial.

“We did a study for a company which contained only 24 subjects at the outset and was then stopped to determine how many more patients we’d need. The data we collected at that point seemed to be somewhat biased,” says Combs. “The good news is we could form an analysis earlier as to how to move forward, and the sponsor could restructure the method. Otherwise they would have had to wait for such adjustments until the end of the study.” For these and other reasons, adaptive design is seen as far more flexible and cost-effective.

Getting SAD And MAD

Time saving is another major advantage adaptive design can offer. “Some of the creative designs that we’ve developed at MDS include fusing studies that are typically run separately in early clinical research into a single study,” says Combs, pointing to the ability to run single ascending dose (SAD) and multiple ascending dose (MAD) studies simultaneously.

In a SAD study, the subject receives a drug at a very low dose, the study is stopped, and the subject's reactions observed before the next higher dose is administered. "In MAD studies, they get the drug every day for several days, which is more reflective of how a patient is likely to take it," says Combs.

In a presentation this fall, Combs pointed out that by themselves, either type of study might take 8 to 10 weeks. "But when we can begin the MAD study simultaneously [e.g. within the third day of the SAD study], we can shorten the time of the trial," she says. So, instead of a total of 16 to 20 weeks if each study is done subsequently, the simultaneous adaptive design can shorten the trial to a total of 12 to 14 weeks.

Technology's Role

While adaptive design has actually been available since the 1970s, only recently has it started to gain recognition and acceptance. Besides the FDA's role in spurring this acceptance, a key factor in this development has been strong technological advances.

"One of the debates against utilizing adaptive design is that it requires you have immediate access to the data. This is less of an issue than it was, even as recently as 2004, thanks to the availability of electronic data capture (EDC) systems, plus easier access to such systems," Combs says.

Skimming the Internet, one can quickly see a number of EDC options available. MDS has its own proprietary software, called ClinQuick. "With ClinQuick, the data isn't written down and typed in. The dose or the blood draw, for example, has a bar code on it. The study participant has the same code on their wristband, and you scan both," explains Combs. This scanning, versus human data entry, minimizes mistakes, needs less labor, and saves time.

Not Everyone's On The Bandwagon

One would think that since adaptive design offers so many benefits, everyone would be running to utilize it. That's not necessarily the case. There are various concerns and even downright objections to working with this method.

"We haven't seen the objections with the compounds with which we've worked, but I understand there are some in late stage research because of concerns about bias being introduced and concern that the FDA and other agencies might not accept it. But in early clinical research, the data from these designs have been found acceptable," says Combs.

Besides having immediate data access, another challenge of adaptive design trials is they can be statistically complex. Combs believes that this can be overcome with a qualified statistician, but notes, "It does take extra effort and planning." Along a related line she says, "You need scientists who have experience with this kind of work, and especially recent experience. You need to get those scientists involved to check for pitfalls or mistakes in the past.

"The designs have to be robust for all potential outcomes. When you plan the study, it might work well if you see an effect, but not if you don't see an effect. It has to be appropriately designed no matter how the data comes out," she adds.

Numerous Questions Need Answering

If a study changes regularly, it may require more drug doses and changes in their ratio. That means initial study costs might expand. How much will those costs be offset at trial's end? That still isn't known.

Among the many other questions that have already arisen:

- What changes need to be made in the data monitoring committee's work?
- Which trials are most likely to benefit from adaptive design, and who will make these decisions?
- If a trial has to make sudden and significant changes in patient population, how is fast recruitment going to be handled?
- There have already been changes seen in tools used to operate a study, such as fewer data entry personnel needed and EDC development. What other changes need to be made in computers, administration, and other areas if adaptive design is to be accommodated?

When all is said and done, utilizing adaptive design doesn't mean the work should be slipshod. "We still need to ensure the studies are well-designed. Saving time and money is fine, but not at the expense of the trial's integrity, which would ultimately

waste time and money," says Combs.

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