

# A NEW ERA IN CLINICAL RESEARCH

P. RANGANATH NAYAK, Ph.D., Chief Executive Officer of Cytel Inc., gives insight into the adaptive clinical trials process.



## What challenges does the industry face regarding clinical trials management? How do adaptive clinical trials help alleviate some of these issues?

The industry faces many challenges. One of the most pressing challenges that the industry encounters today is patient recruitment. Patient recruitment is becoming increasingly difficult and, therefore, clinical trials are reaching overseas and becoming more global. The globalization of trials has its own set of challenges in that different countries have different protocols, regulatory bodies, etc. Another challenge that the industry faces is the pressure to reduce the number of failures in confirmatory Phase III trials. Despite all these challenges, the most critical problem of all is that the industry is

spending a vast amount of money on drug development and not getting an adequate return on investment while generics are cannibalizing their profits. This is hurting the stock market performance of biopharmaceutical companies.

In the past, the biggest challenge that the industry faced was in regards to drug discovery in that there were not enough new molecules coming out of the laboratories. Today, the challenge lies in the fact that clinical development is time consuming, costly and does not result in enough successful drugs entering the market. Too many drugs fail at the end of the clinical process in Phase III, when all the money has already been spent. The question is whether the failed drug was an actual failure or if the design of the trial was faulty and thus resulted

in the failure of a successful drug. This is where adaptive trials can alleviate some of the challenges. A Phase III trial can be stopped early if the drug does not work. It can also be stopped if it is apparent halfway through the trial that the drug works well. If this is the case, the drug can go to market early, thereby saving a significant amount of time and money.

**Why are there issues with dosing in traditional early phase trials? How do adaptive clinical trials offer a solution to these dosing issues?**

People have gotten accustomed to trying out just two or three doses against a placebo in a dose-finding Phase II trial because it appears to keep costs under control. Because of the limited number of doses, it is easy to miss the right dose and move on to Phase III. Yet conducting a trial in this way may, at the end, reveal that the efficacy of the chosen dose is inadequate or that the dose is unsafe. This is a penny-wise, pound-foolish investment decision; if more is spent on Phase II and better information obtained about the dose, then the success rate climbs in the much more expensive Phase III trial. Nevertheless, it is possible to get better information on the right dose without spending more money simply by doing an adaptive Phase II dose-finding trial. This involves selecting five or six doses, thereby covering the range in which the best dose lies. The best dose is likely a safe dose that has the greatest efficacy. If there are five doses and a placebo instead of three and a placebo, it

of formulas becomes acute when trying to do a Phase II dose-finding design using Bayesian techniques, because the Bayesian probability calculations are incredibly complex. Here, simulation is absolutely essential. Simulations also allow the performance of the design under varying assumptions to be tested.

For a conventional, non-adaptive design, the needs of the whole trial are known at the start. But with an adaptive design, changes take place as the trial progresses and it is unknown in advance which doses are going to be dropped or added and when. Substantial uncertainty is introduced into the supply plan. If the supply planning is done as usual, there is the possibility of as much as a 500 percent overage, meaning that more than 80 percent of what was supplied is wasted, thereby driving up cost of the trial substantially. By simulating the needs of the trial for medical supplies, we can develop a supply plan that greatly reduces the overage.

**How are those responsible for clinical supply responding to the demands of adaptive trials?**

In a conventional trial, the supply people become involved only after all the statistical work has been done. In an adaptive trial, the supply people have to be part of the discussion on the number of doses, the frequency of the adaptations, what probability of stockout is acceptable as well as the number of trials that need the same active pharmaceutical ingredient and the alternative forms of packaging that are feasible. The supply people respond

“THE BEST DOSE IS ONE THAT IS SAFE AND HAS THE GREATEST EFFICACY. IF THERE ARE FIVE DOSES AND A PLACEBO INSTEAD OF THREE AND A PLACEBO, IT SEEMS THAT THE TRIAL WOULD COST 50 PERCENT MORE, BUT THIS IS NOT THE CASE IF IT IS ADAPTIVE.”

might seem that the trial would cost 50 percent more, but this is not the case if it is adaptive. A few patients are recruited and dosed, and their responses are measured. For the next group of patients, the proportion of patients for those doses that elicited a low response in the first group is lowered. As time goes on, a couple of best doses are identified and taken into a Phase III trial. This can be done with the same number of patients as there would have been in a conventional Phase II trial.

**Can you explain how simulation technology helps in both an adaptive trial’s design and the actual implementation of a clinical study?**

When doing the statistical design of a clinical trial, especially in Phase III, it must be proven to the FDA’s satisfaction that the false positive error (when a drug that does not work appears by chance from the trial results to work) has been kept below a specified level. For some adaptive designs, it is possible to do the calculations using statistical formulas. But for many adaptive designs, such formulas do not exist and the statistical properties of the design have to be determined by simulation. The absence

by asking for this early involvement. They are also asking for the tools they need to manage this process. Some tools for trial management that have been created are CTMS, EDC for data capture, IVRS for dose assignment and East for statistical calculations. Yet there are still opportunities here for a smart software entrepreneur to develop tools for supply managers.

**I have heard that some forms of adaptive trials may actually have options to prolong the trial and add patients. Why would a sponsor desire a longer trial with more patients than originally planned?**

The only reason to prolong a trial is to increase the probability of success. For example, let us suppose that a Phase III study is begun with 2,000 patients, 1,000 on a dose and 1,000 on a placebo. These numbers are determined by estimating what advantage the drug has over a placebo and what the patient-to-patient variation is in response to the drug; and these estimates come from a relatively small Phase II trial. Now suppose the estimate of the variance is too low. Then, at the end of the study, it will not be possible to prove that the drug works



because the sample size will have been too small. If this occurs, the drug will have wrongly failed.

Now suppose that this is an adaptive trial designed in which the data can be looked at half way through the study to get a better estimate of the variance. If evidence of higher variance is found, 400 more patients are added for a total of 2,400. Now the trial costs 20 percent more than the conventional design and takes 20 percent longer to complete, but there is a hugely important difference in the result. Instead of the trial resulting in a failed drug, it results in a success that may be worth billions. Therefore, it can be well worth it to extend the trial to this degree to achieve success.

**How receptive are trial regulators now to adaptive designs? What can a sponsor do to best prepare if called to defend these new strategies?**

Regulators are receptive, but they want solid evidence. First, they want to know that you have done the best you can to learn about the drug in the Phase I and Phase II trials and are not using the adaptive technique as a band-aid for sloppy development. Second, they want a clear description of why an adaptive trial is necessary and what will be gained by conducting it. Third, they want a convincing presentation that the statistical calculations have been done correctly. Fourth, they generally want the calculations and choices for the adaptive change defined before the trial starts. Finally, the FDA usually wants to make sure that no one from the sponsor sees the unblinded data until the trial is complete and the database has been locked.

**Does this “new era” of adaptive trials spell the end traditional, fixed trials or will there continue to be instances when an adaptive approach is not an improvement over a more traditional study?**

There are circumstances in which an adaptive trial is neither possible nor necessary. For example, if it takes a long time after the medication is given before the patient’s response is known, then an adaptive design is not possible because patient recruitment and dosing might be complete before response of the first patient is known. The situation can change if there is a surrogate end point (e.g., something that can be measured quickly and strongly predicts the final outcome such as a biomarker). If a surrogate endpoint is not available, then an adaptive trial is not feasible. In other situations, the additional information gained by being adaptive is not valuable enough to justify some of the complexities of an adaptive trial, including the need to unblind data.

However, an adaptive option should be evaluated for any trial. The conventional design may be used in the end, but the advantages of an adaptive trial can be profound.

**What are the obstacles to the implementation of adaptive clinical trials and how can they be overcome?**

As we work with biopharmaceutical companies, we have found that the first thing that most people are apprehensive about is whether or not the statistical methods for adaptive clinical

trials are well established. At this stage, this should no longer be a concern because the statistical methods are, indeed, well established.

The second thing that most people are unclear about is whether the FDA will approve an adaptive clinical trial. If you’re looking at Phase I and Phase II adaptive trials, the FDA will almost certainly approve the designs so long as the methods of analysis and design are sound. If you’re looking at a Phase III adaptive trial, the FDA will want to look at what you did in a lot of detail and then decide whether or not the trial design will pass.

The third obstacle people discuss is logistics. How exactly do you supply a trial where you’re going to make some changes in the middle and yet not know ahead of time what changes you’re going to make? There are a few things that people need to do in order to deal with these logistical issues, one of which is for the people who are responsible for supplying trials to get involved in the planning at a very early stage. You don’t want to have the clinical and statistical people doing the work and then, a few weeks before the trial is supposed to start, turn it over to the supply people and ask them to supply the trial. You can do that with a conventional trial (even though you shouldn’t), but with an adaptive trial, you cannot do that without incurring very high costs of supply. You need to involve those people at an early stage.

You also need to move into more strategic considerations such as how many manufacturing campaigns you’re going to have. How exactly are you going to package the drug? Can you do just in time packaging and labeling? The last question here is, “Who can look at the data at intermediate points?” In this regard, the FDA is adamant that people from the sponsor company cannot look at unblinded data because once you begin to understand those data, the potential arises for biasing the future course of the trial. For example, if you discovered that white males under 25 respond better to your drug, you may have some kind of an inclination to make sure that more white males under 25 get on to the drug than on to a placebo. If you do that, then you bias the outcome. So the FDA’s position has been that only people who are independent of the sponsor company can look at unblinded data. For this reason, Cytel is often involved in doing the interim analysis and reporting to an interim analysis committee to say, “We’ve looked at the data. We can’t tell you exactly what is happening. But here’s our recommendation.”

In reality, many of the difficulties people were talking about a year or two ago are being dealt with and none of them is intractable. Talk about obstacles used to be a reason not to do adaptive trials. That reason is no longer a good one.

**What is your advice on how companies should move ahead?**

There are some things you need to establish as policies. One of these policies is that in every trial, an adaptive design has been evaluated as an alternative before a conventional design is used. It may indeed turn out that the conventional design is a better choice because the adaptive approach doesn’t gain you that much and causes complexity. But, nonetheless, an

adaptive trial design should at least be considered before any method is deployed. Secondly, start with the early phase trials and make them adaptive because this makes it easier for gain FDA approval for those earlier adaptive phases. Moreover, the extra information you gain from early phase trials is one of the best ways to make your Phase III trials successful. Finally, start putting together a cross-functional team of people from statistics, clinical operations, medical supply and logistics and manufacturing and get them to start working on the changes that need to happen in terms of processes to get work done. By employing this cross-functional approach, an adaptive trial no longer requires a heroic effort, but can become routine so that as a team looks at a trial and considers whether to use an adaptive design; it is no longer such a daunting task that people

just naturally go toward the conventional alternative. Now's the time for companies to say, "This is a real cross-functional process. We need a cross-functional team. We're going to work on it." That's the best way for companies to move ahead.

In the end, spending money on clinical development is an investment made by biopharma companies in their futures, and improving the return on this investment is crucial to assuring these features. That is what the whole adaptive trials paradigm is all about. A better return on investment also means more new, successful medications making it to market, which is a benefit to society as a whole.

Another significant benefit is that adaptive trials are more ethical from the patient's point of view because fewer patients are put on drugs and doses that fail. **FP**



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