

The Changing Face of the Early Phase Volunteer

What “Learn and Confirm” paradigm means for patients, early phase clinical trials

By Sy Pretorius, MD and Thomas Senderovitz, MD

“THERE HAS TO BE A BETTER WAY.” It’s a constant theme in the drug development industry, where financial risks (especially those associated with failed compounds) are great and the safety of human life is of utmost importance. Some in the industry believe that one such better way is to switch from the traditional, stringent phased approach to the more flexible “Learn and Confirm” model. A growing trend associated with this new model is that patient groups are involved earlier in the development cycle to test a wider array of hypotheses, blurring the lines between Phase I and Phase II trials and redefining the goals of these early clinical trials.

PAST PROCEDURES

In early clinical research, when a compound is first tested on a human volunteer, companies want to increase the probability of clear, interpretable results. The current model to achieve this goal is by enlisting the help of healthy, normal volunteers in Phase I to test primarily for safety, and then to bring in patients afflicted by the targeted disease in Phase II, to start testing efficacy and confirm proof of concept.

This existing model comes with a number of limitations that are too numerous to include in this article. Suffice it to say, it makes the problematic assumption of a biological baseline to what is healthy and normal. The current approach also places restrictions on a company’s flexibility to take action during trials in which the compound is ineffective in the target population/disease.

In 1997, partially in response to some of these challenges, Lewis B. Sheiner introduced the “Learn and Confirm” model. Over the years, the number of industry proponents of this model as a way to improve the process has increased.

PRESENT THINKING

In the “Learn and Confirm” paradigm, Phase I and II become the “Learn” phase. Instead of regimented stages that represent a single-minded pursuit of one hypothesis formed much earlier in development, first-in-human trials become a learning experience; a way to create experts on a compound at that important stage. Hypotheses can be tested and refined, new developments can be taken into consideration, safety and efficacy can be tested alongside each other. As a result, data can be gleaned that is deeper and more actionable than what is usually sought in Phases I and II.

Increasingly, this results in greater patient enrollment earlier in the drug development process (i.e., in Phase I, often as an arm in the multiple ascending dose, or MAD, study). In healthy, normal volunteers, data gathered are seldom disease-specific and are primarily related to the compound’s safety and general biological effects.

With so much activity taking place during the “Learn” stage, what has traditionally been studied in Phase III acts now as the “Confirm” stage, where the single key hypothesis that emerges from the “Learn” phase - the one with the best chance of yielding a safe, effective drug-is tested and refined on a much larger scale.

Interestingly, this model also appears to be more ethically and scientifically valid than conventional methodology.

In conventional methodology, companies ask healthy volunteers to assume an element of risk for a financial reward, as opposed to health benefits. By bringing in patients who have a direct stake in the success or failure of a treatment earlier, we are asking them to become more invested in that treatment. To put it simply, we’re working to heal the sick instead of potentially risking the healthy. In addition, there are often drugs (e.g., cytotoxic cancer drugs, antipsychotics, etc.) that are not tolerated by healthy volunteers and thus need to be tested in patients from the outset.

Modern medicine is also trending toward the specific over the general. Medicine is becoming more personalized, and advances such as disease-specific biomarkers are often best studied in patients with the relevant disease. Additionally, having valuable safety and dose-related data in a target patient population early in the development process can be a substantial benefit.

FUTURE CONSIDERATIONS

Involving patients earlier in clinical trials allows for in-depth data collection and meaningful modeling and simulation much sooner, thereby significantly improving the design process of larger Phase II/exposure-response studies. Furthermore, real-time data collection and results evaluation empower faster decision-making. All of this shortens development cycles and could potentially reduce costly Phase III failures. Of course, using patients earlier in the drug development process comes with its own set of substantial challenges and open questions:

First, bringing patients earlier into the process impacts recruitment. Patient populations are more difficult to recruit than healthy volunteers because they are fewer in number and are geographically dispersed. This challenge is often magnified and further complicated when dealing with more vulnerable populations such as pediatric patients, as well as lower socio-economic patients. Both of these patient groups are currently hot topics given the requirement to submit pediatric investigational plans (PIPs) and the recent revelations in India and its subsequent regulatory changes.

Second, the support infrastructure around patients is considerable and specialized. Patients require a higher degree of ongoing medical care than healthy volunteers, so testing locations will need to develop direct relationships with hospitals for treatment facilities, medical equipment, emergency services, and specially trained staff.

These considerations are not at all unsolvable for companies looking to enroll patients earlier, but they are fundamental to doing so successfully. If the “Learn and Confirm” model can deliver on its promises, it’s worth it. After all, “There has to be a better way” is not merely a call of frustration, but one of innovation. 

Sy Pretorius, MD, is corporate vice president & worldwide head of early phase, PAREXEL International; **Thomas Senderovitz, MD**, is senior vice president, clinical research services, PAREXEL International.