As success depends upon commercial as well as regulatory approval, clinical trials need to produce evidence for safety, efficacy and cost-effectiveness. That can lead to trial bloat. To strike a balance between rigor and cost-effectiveness, trials must be right-sized and the mistakes of the past avoided.
As obtaining reimbursement as well as regulatory approval has become an ever higher hurdle, drug developers are seeing the need for trials that will produce evidence for two different purposes.

Phase III trials place a particular focus on achieving regulatory approval. They are typically conducted to demonstrate the effect of a drug candidate versus a placebo or standard of care (SoC), which will be less effective than active treatments coming onto the market.

Regulators are focused on a new drug’s benefits and safety. They are less concerned whether the drug is more effective than other drugs for the same indication, or if it’s cost-effective. But payers do care. Therefore, data collected by a trial designed for regulators may not convince them, and they may deny or restrict a drug that already has received regulatory approval.

Trials generally are not designed to cover additional needs for payers, because that might make them both overly lengthy and expensive to conduct. Developers, however, can design trials that strike a balance between thoroughness and cost-effectiveness by taking three steps: avoiding mistakes others have already made, managing the bloat of sample groups for secondary measures, and performing power analysis to ensure that the trial is sized appropriately for reimbursement.

Step 1: Avoid Mistakes Others Have Already Made

Reviewing previous submission histories for similar compounds, PAREXEL can identify the main causes of uncertainty for reimbursement decisions. That allows PAREXEL to identify what data might be important, and prioritize what developers should collect. We thereby can recommend either additional studies or changes to the trial protocol with the inevitable reimbursement decision in mind. Sometimes it can be relatively easy to collect the data from a single trial that will meet the needs of multiple agencies.

In one instance, PAREXEL saw several trials for an orphan disease that had many quality of life (QoL) measures, each trial using a slightly different QoL measure. However, reimbursement agencies may require a demonstrated difference in effect against any one of the many drugs already on the market. Our client therefore, designed a trial that collected data against its own specific measure for regulatory purposes, but also collected all the EQ-5D health status data it needed to make a comparison against any other treatment on the market.

In another project, we examined the cost of severe hypoglycemic events in diabetes to reduce uncertainty in an economic argument. Up until that point, the costs associated with these events were uncertain, and so was the client’s overall economic model. In hindsight, the costs of hypoglycemic events could have been recorded during the trial, when the machinery to record resource use was already in place, instead of being worked out later.

Similarly, if your drug might lead to fewer hospitalizations, recording the incidence of hospitalization might help your cost case with payers. Or, if your treatment can reduce the total cost to the payer through lower associated costs for administering the drug or for transporting patients, then measuring these costs during the trial may give you powerful ammunition when it comes to reimbursement submissions.

“We thereby can recommend either additional studies or changes to the trial protocol with the inevitable reimbursement decision in mind.”
In medicine, the outcomes that are most stark (such as death and disease progression) are not effective in measuring subtle differences between groups. They are like measuring the height differences between two groups of people by counting how often people bang their head on a doorframe as they pass through. You would need a very large sample of people to compare the heights of two similar groups. Similarly, one needs a large sample population to compare overall survival rates for two groups in a trial, and the trial would have to be lengthy.

Conversely, other measures (such as biochemical variables) that may be less clinically meaningful can show more finely grained differences with smaller sample groups.

The trial itself needs to be powered for the primary clinical outcome, but it is often possible to get good, precise measures of other variables using a sub-sample of patients.

This can reduce the burden on patients, lower the cost of the trial, and allow more variables to be investigated.

In a heart disease trial, for example, one outcome may be reduced incidence of death which, given the timescales involved, may require a large population. But if reduced damage to blood vessels is a useful secondary outcome, that can be measured directly and need not be monitored for the whole set.

Oncology trials often use progression-free survival (PFS) as a proxy for overall survival (OS) to reduce trial time and size. But it’s often difficult to show the relationship between PFS and OS. However, if you know you will be up against that challenge from the beginning, you can make sure it’s part of the statistical analysis plan so that it gets done properly, defensibly and on time. This will make the reimbursement submission easier without affecting the size of the trial or the amount of data that has to be collected.

The larger a trial, of course, the greater its power and its cost. Usually trials are sized so that they have only a 10 percent or 20 percent chance of not detecting a significant effect if that effect exists—that is, they have 80 percent or 90 percent power to detect it.

However, drug developers tend to assume that for a new drug, there are no data that can help them estimate the difference in effect and therefore optimize the size of a trial.

Where developers do compare with drugs in the same class, they tend to compare with the successful ones, which obviously show a significant effect. Add to that a natural inclination to believe one’s own drug is better, and the scene is set for overly optimistic expectations of effect, a trial that is too small and finally, a failure to show differentiation.

One client recently came to PAREXEL at the beginning of Phase III trials with a new drug in a new class. The
disease the drug targets is hard to treat; it is difficult to measure response to treatment, and the new drug presumes a different etiology than its predecessors. Phase III trials will be run against a placebo. Experience from earlier trials together with the unmet need suggested to the developers the likelihood of regulatory approval.

However, payers will judge the drug against those already in the market. These therapies are partially effective and, as noted, it is difficult to compare their effectiveness. Therefore, introducing them to the analysis necessarily introduces noise and uncertainty. And if the new drug does not show an improvement over those already available, it may not get access to market.

At this point the company can’t change its Phase III trial (to run against the other drugs in the market, for instance). But it can improve its risk-management plan.

PAREXEL can do network analysis against the other drugs to determine the power of the trial against those, and we can determine the size of the effect that will have to be shown to prevail over them. We might find that the 80 percent power of the trial to show a difference in effect against the SoC equates to 50 percent power to demonstrate (indirectly) against an active comparator that is relevant to payers, such as the market leader. This analysis, of course, can inform estimates of ultimate market share and success, and thereby the risk-management plan for the drug.

A literature search almost always will find more data on a class of drugs that can inform the estimate of difference in effect and lead to better power analysis. Additionally, meta-analysis shines light on the uncertainty in that estimate. Together these data can help better size trials for success.

**BREAKING THE BARRIERS TO ADOPTION**

Avoiding mistakes others have already made, managing the bloat of sample groups for secondary measures and doing the power analysis will improve your chances of success and help you better manage the cost of trials. But there are common barriers to taking these steps.

One major stumbling block is the separation of regulatory and reimbursement functions in pharmaceutical companies, which leads to limited health economics and outcomes research (HEOR) input in trial design. PAREXEL has found that companies with high success rates for payer submission approval involve HEOR from the beginning. At one leading firm, HEOR staff join development teams to provide insights in Phase I trial design, and HEOR participants sit on the Phase II program-review committee to comment on the likelihood of the compounds being commercially viable.

Another issue that arises in clinical trial design is the lack of awareness of power analysis and issues of uncertainty. Developers don’t always know that relatively minor assumptions or estimates can have a significant impact on the power of a trial. They also may not understand the uncertainty in the effect difference they are using to estimate trial power, and how that uncertainty should impact decision-making. Again, involvement of HEOR early in trial design can help make sure that important implications of power and uncertainty are not overlooked.

Overall, increasing demands for disparate evidence from a variety of agencies are driving up the demands on clinical trials, which risks driving up their cost and complexity. But thoughtful research and design early on often can accommodate multiple needs and increase the chances of proving drug effect at reasonable cost. As agencies continue to raise the bar on evidence for drug approval, optimized trial designs are ever more critical to getting drugs over the bar and into the market.

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