

INSIDE OUTSOURCING

A Guide to Pharma's Newest Core Competency



OUTSOURCING PHASE IV

Late-stage research is one of the fastest-growing areas in outsourcing. Here's how to get the results you need from your postmarketing studies.

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The fastest-growing area in outsourcing these days is late-stage clinical research. That's no surprise, since late-stage studies are the fastest-growing part of clinical research. In 2006, CenterWatch estimated that the development spend for Phases IIB and IV would go from \$9.2 billion in 2005 to \$15.4 billion in 2009—a jump of more than 60 percent. With the dramatic rise in late-stage studies, there is increasing emphasis on strategic planning to determine how sponsors should spend their budgets within the preapproval space.

There are several reasons for this rapid growth, including the recent intense scrutiny of the long-term safety of medicines on the part of worldwide regulatory and government bodies, as well as pressures from physicians, payer/formulary committees, and consumers to scrutinize the benefit-to-risk ratio of new products.

These factors are causing a shift in the industry's postapproval strategies away from purely commercially focused studies and toward increased postapproval monitoring of real-world utilization. The tools being employed include patient and disease registries, large streamlined trials (LSTs), expanded access programs, outcomes studies, and additional randomized clinical trials (RCTs).

Pharmaceutical and biotechnology companies now see postmarketing studies as drivers of evidence collection, resulting in fundamental changes in how late-stage trials are designed. Where once it was adequate to prove that a drug was safe and effective in well-controlled trials, sponsors now feel pressure to implement studies with endpoints that assess:

- ▶ Real-world safety and effectiveness: to collect evidence on how products work in the real world and to assess risk-benefit
- ▶ Preference, compliance, and adherence: to measure impact of physician- and patient-training strategies on products and to supply physicians with patient feedback on the products they prescribe
- ▶ Health outcomes and economics: to demonstrate cost-effectiveness, to provide patient-reported outcomes, and to collect healthcare utilization data.

What this means is that pharma companies, whether they plan to do late-stage research in-house or outsource it, need to start giving some hard thought to what sort of data they need from Phase IV and how they plan to obtain it.

STRATEGY AND TACTICS

From a strategic point of view, a great many decisions must be made during initial discussions of late-stage

studies, including a combination of big-picture questions (e.g., identifying the best program format) and detailed inquiries (e.g., selecting and training the investigators).

However the most important question is, What is the objective of your study? As with any study, this is the most critical decision point, as it drives all subsequent decisions regarding study endpoints to be collected, number of sites and patients, and overall logistics.

For a checklist of key questions, see page 76. While the answers to these questions require a great deal of thought and input from the entire team, they are worth the effort. By the time you've answered them, you'll be ready to formalize an attack plan to complete the late-stage program.

A warning: Often, in the excitement about potential access to a large cohort of patients, the initial study plan developed is too complex and, therefore, confusing to the sites. Streamlining study activities and forms requires extensive expertise to ensure a successful late-stage program.

In addition to strategic considerations, late-stage studies require a level of logistical expertise that far exceeds what traditional studies require, due primarily to their sheer size. A traditional study, for example, might include up to 100 sites with 500 to 1,000 patients. By contrast, a large, streamlined study or patient registry might require up to 8,000 sites and 60,000 patients.

Tactically, three issues are particularly significant:

▶ **Site recruitment and management**

A significant challenge in planning late-stage studies, is to decide how many community-based physicians (both generalists and specialists) to

target as investigators. Just as important is what percentage of the target sites will be research-naïve—that is, sites with minimal or no previous clinical-trial experience. Logistically, working with community-based sites (where the majority of patients are treated) requires an aggressive-yet-simplified training plan, detailed study processes, and increased mechanisms for communication with investigators. For the success of the program, it is equally essential to ease the burden of work on the investigators through all means necessary by simplifying processes wherever possible.

▶ **Simplifying protocols and case report forms**

Another great challenge in late-stage programs is streamlining complex protocols. This involves simplifying more than just the protocol itself; it involves streamlining data collection forms, regulatory documents, safety information collection, and all study

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processes—including site training. For late-stage studies to be completed efficiently, it is imperative to have standard operating procedures (SOPs) that allow for the appropriate logistical processes to successfully launch and manage the variety of programs available, such as patient registries, LSTs, expanded-access programs, and outcome studies. These SOPs need to cover the range of options in the areas of training, technology, data collection, monitoring, safety, statistical analysis, and report generation.

Comparison	Approval programs	Late-stage programs
Phase	Pre-approval	Peri-approval
Goal	Provide proof of efficacy	Demonstrate effectiveness and safety
Inclusion criteria	Narrow; small sample	Broad; larger sample
Type	Blinded	Open label
Comparator	Randomized	Appropriate
Monitoring intensity	High	Lower
Investigator population	Professionals	Practitioners, community-based physicians
Investigator quantity	Few	Many

For example, if you decide to collect responses to only four additional questions, but your late-stage safety trial sample size is 25,000 patients, that's a total of 100,000 questions. This volume will lead to additional burden on the investigators, increased data entry (EDC, paper, or hybrid system), and more queries. It is important to ask two questions continually throughout the planning process: Do we need to collect these data? And what do we plan to do with them?

► **Endpoint capture and design**

When planning a late-stage study, it is critical to ask precisely what endpoints you are seeking. While it is intriguing to imagine how much can be learned in these real-world trials, the financial burden requires that sponsors determine exactly which questions need to be answered.

DESIGN FOR SUCCESS

The following case studies demonstrate how late-stage, streamlined programs differ from traditional studies in terms of endpoint and design considerations:

► **Safety and Patient Outcomes of a Metabolic Product**

In a traditional Phase II or III study, a sponsor might collect efficacy and safety data on a metabolic product. This late-stage study focused instead

on how the product worked in the “real world” and on specific safety events of special interest. The product under study had a new delivery mechanism that cost more but was hypothesized to be easier for patients to use. The study collected patient-reported outcomes and data on whether the new delivery system was quantifiably simpler for the patient to use and transport, as compared with traditional treatment.

Since the delivery system was new to this therapeutic area, there were safety events of special interest that had to be studied. The collection of these events required a sample size involving more than 5,000 patients at approximately 500 community-based sites. The goal of increasing the number of patients and gathering more data about their actual use of the product was to build a robust database that gave the sponsor a better understanding of long-term compliance and its impact on control of the clinical endpoint in the real world. As a result, the study needed to include patients who would typically be excluded from this kind of study—such as those with extensive medical histories (e.g., with multiple co-morbidities), patients taking a variety of medications, or people who were older or younger than might be admitted to a controlled study.



Given the large cohort of patients enrolled in this program, there was quite a volume of specific safety events that needed to be reviewed by a specialty adjudication board. As part of this procedure, thousands of adverse events were eliminated that were not related to the safety endpoint, enabling a focus on the hundreds of events determined to need maximum follow-up for further adjudicated processing.

At the end of this program, the sponsor was armed with outcomes, effectiveness, and safety evidence that will truly aid payers in determining whether or not this product should be added to their formularies.

► **Unique Endpoints for an Antibiotic Trial**

In this late-stage program, the sponsor wanted to study unique endpoints for a newly launched antibiotic designed to treat uncomplicated urinary tract infections (UTIs), including gathering a large sample of safety and effectiveness data. In addition, the sponsor wanted to test a new educational tool that would improve the patients' understanding of the importance of full treatment compliance and reduce the number of individuals who discontinue therapy after a few days of treatment. Finally, the sponsor wanted to collect information on the difference between how patients and physicians assess UTI symptom pain.

The initial assessment of the protocol resulted in a projected sample size of approximately 8,000 people to complete all program objectives. Since females with uncomplicated UTIs typically present initially to GPs and FPs, it was anticipated that a large percentage of the sites would be research naïve.

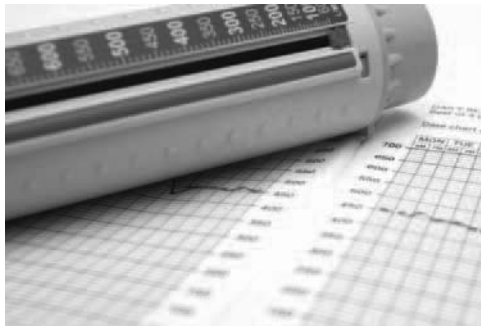
A randomized program was created with a streamlined protocol and clinical research facility in order to minimize the burden of work on the sites and allow for rapid training of potential investigators by telephone and via the Internet. Randomization was by site rather than by patient.

The study program was created to allow for patients receiving the sponsor's product (within product label) to be the target cohort. The measure used to test patients' understanding of the new study tool was simplified to ease both administration at the site and completion by the patient. Training DVDs were also provided to the sites to assist with instruction of patients and site personnel. In addition, at the initial visit, the patient's assessment of her symptom pain was kept separate from the physician investigator's assessment, enabling collection of a real-world sample demonstrating the variance between the two evaluations.

Finally, in order to control the study sample size, a series of interim analyses were conducted to ensure that the proper sample size was being collected to power adequately the study endpoints. This created a series of logistical challenges in data collection that required a very well-constructed site- and data-management plan. The study ultimately was successfully completed utilizing approximately 1,000 active sites.

► **Safety and Preference of an Alzheimer's Treatment**

For a late-stage program focusing on a new Alzheimer's treatment, a sponsor wanted to assess the success of a new formulation from multiple



points of view. Because of the controlled environment of a Phase III trial, it can be difficult, and at times meaningless, to collect information regarding preferences and compliance. Therefore, late-stage programs can be the best solution to provide these additional data.

This particular study had to be designed to provide input for both physicians and caregivers on real-world treatment compliance and on how ease-of-use might reduce the number of hospital visits. To gather these data, a study design was developed to (1) track specific safety events required by various regulatory bodies and (2) collect data from caregivers and physicians on their preference for this new formulation.

But in order to conduct this study in a non-controlled environment, careful thought needed to be given to several measures. For example, caregivers can experience a real burden in administering pills to Alzheimer's patients—including confirming that it was swallowed and ensuring that the timing of pill ingestion was acceptable with the patient's other medications. It was important to determine whether caregivers found this non-pill product easier to administer, in both a home setting and a long-term care setting.

It was also necessary to address the broader issue of caregiver productivity. In this kind of complex situation, consideration must be given to the direct impact on a spouse or partner, as well as on the patient's adult child, if he/she is the primary caregiver and also has a full-time job outside the home. Therefore, it was necessary to assess the number of workdays a caregiver

would miss with pill administration versus the new product.

Finally, with a goal of determining whether improved training for both physicians and caregivers might ultimately enhance compliance, information had to be gathered on how physicians were being educated on the new product. Educational training had to be implemented in a similar manner across all sites in order to determine the direct impact of the program.

This case study exemplifies the careful consideration necessary to move beyond the traditional clinical trial and efficacy-data collection to a more complex environment including caregiver impact and physician preferences.

► Health Outcomes and Economics of Asthma Treatments

In Phase III clinical trials, improvements in respiratory function endpoints are assessed and compared with placebo or an equivalent product in a controlled environment. However, in a well-established marketplace, physicians and formulary committees want to know the benefits of newer products compared with usual treatments beyond the traditional endpoints and in a real-world clinical setting. This was exactly the premise behind the research conducted by O'Connor et al. (and reported in *Current Medical Research and Opinion*, volume 22, number 6) comparing the combo product of fluticasone/salmeterol (Advair) to montelukast.

The study design was a 12-month multi-site patient registry involving 1,414 patients, 494 GPs and specialists, and 17 physician groups and practices. The patient endpoints collected included quality of life, treatment satisfaction, and

START WITH THE RIGHT QUESTIONS

The key to a well-designed late-stage study is asking the right questions. Here's a checklist.
Study Design & Logistics

- ▶ What is the most appropriate study design to accomplish the endpoints? Patient registry? Large streamlined study? Disease registry? Randomized clinical trial?
- ▶ Which physicians should be targeted as investigators? Community-based specialty practices? General practitioners/family practitioners (research-experienced)? GPs/FPs (research-naïve)? Traditional clinical research sites?
- ▶ What is the monitoring plan for the study? No on-site monitoring? A percentage-based monitoring plan? 100 percent source verification? Other?
- ▶ How will the data be collected from the investigators? Web-based? Paper-based?
- ▶ What expectations will the study place on the target investigators? Specialty testing? Follow-up safety exams by other specialists (cardiologists, pulmonologists, oncologists, etc.)?
- ▶ How will information be communicated rapidly to everyone in the company who needs to be kept in the loop? Status reports? Weekly team calls? Study portal?
- ▶ What method of training is most appropriate for the sites?
- ▶ What method should be utilized to train physicians on new products, and can we test this method in our late-stage programs?

ENDPOINTS

- ▶ What endpoints are important to track when collecting data on real-world patients who might be taking numerous medications or have an extensive medical history?
- ▶ Are there specific safety events that we are tracking? How will they be reported? Will they be adjudicated?
- ▶ What are the long-term safety effects of drugs or devices on the patients?
- ▶ Will we be collecting only serious adverse events (SAEs) in the programs? Or all AEs?
- ▶ What information should we collect from patients using the study product so that we can distribute it for the greatest benefit of physicians and the sponsor?
- ▶ How can we structure the trials to learn about specific patient or caregiver outcomes?
- ▶ Which data should be collected to convince government or third-party payers that the product is the best choice?

productivity losses. In addition, administrative claims were used to assess hospitalizations, emergency room and outpatient visits, and pharmacy utilization. The results demonstrated that real-world use and differences can be collected and, at the end of the day, provided decision makers with data approximating the real-world use of these treatments.

VALUE OF LATE-STAGE STUDIES

The momentum to collect evidence in the late-stage research area continues to grow each day because the advantages are so important, allowing:

- ▶ Significant expansion of a product's safety and effectiveness database
- ▶ Better understanding of product use and training in real-world use
- ▶ Collection of patient-reported outcomes (PROs)
- ▶ Feedback loop directly from the patient to the physician investigators
- ▶ Clarity of physician practice patterns
- ▶ Entry into many new community-based physician practices
- ▶ Ability to track healthcare utilization data for future use
- ▶ Information about comparator products in head-to-head studies

With the recent evolution of late-stage studies, the opportunity exists for sponsors and pharmaceutical service organizations to gather and analyze data and use them to support the quest for real-world evidence in decision making.

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