

STRATEGIC RESEARCH: A Practical Handbook for Phase IIIB and Phase IV Clinical Studies

Chapter 13. Expanded Access Programs

This article is the 13th part of a 15-part series from STRATEGIC RESEARCH: A Practical Handbook for Phase IIIB and Phase IV Clinical Studies by Hugo Stephenson, MD, President, Strategic Research & Safety, Quintiles.

Expanded access programs, also known as "early access" or "compassionate use" programs, provide access to unapproved products for patients with life threatening or significant illnesses. They usually take place during Phase IIIB after a general safety profile for the product has been established. Expanded access programs do not have a research rationale, but can provide an opportunity for a large scale assessment of risk/benefit for products that have not been fully evaluated by regulators.

For the community, expanded access programs provide patients with months, and sometimes years, of access to life-improving or life-saving treatments. In addition to their public benefit, expanded access programs offer pharmaceutical companies an opportunity to provide prescribers with pre-market product experience. Companies can establish a base of patients who will already be on treatment once approval has been granted, and sometimes they can collect additional safety data that may be used to supplement the original NDA submission.

The regulatory framework for expanded access programs varies dramatically between countries; this is true even within Europe, where the European Medicines Evaluation Agency (EMA) has attempted to harmonize approaches to pharmaceutical regulation. Expanded access programs can take one of three approaches: the clinical trial approach, the named patient approach, and the cohort approach.

Clinical Trial Approach

The clinical trial approach establishes a prospective observational protocol with one treatment arm for the expanded access product. There are no endpoints and no limits to sample size. In most markets, this approach requires that the program be executed in the same way as a normal clinical study. In the United States, sponsors must proceed by submitting a special investigational new drug application known as a treatment IND. The program protocol is usually filed under the treatment IND, which is granted on the basis of medical need.

Improving Access to Treatment

In March 2002, as Gilead Sciences was preparing to submit marketing authorization applications for adefovir dipivoxil (Hepsera) to treat chronic Hepatitis B, the company also announced the initiation of an expanded access program. The program was designed to provide Hepsera as a therapeutic alternative for patients with lamivudine-resistant chronic Hepatitis B infection not suitable for treatment with interferon-alpha. Gilead made Hepsera available to patients 16 years or older with chronic Hepatitis B infection resistant to lamivudine and who were at risk for disease progression. Participation was subject to evaluation at baseline, after one month on therapy, and every two months thereafter. The Hepsera expanded access program continued until the drug obtained marketing approval in the United States (September 2002) and Europe (March 2003), by which time over 1600 patients had been enrolled in the program.¹

An expanded access program using the clinical trial approach requires approval by ethics committees in the usual manner. The ethics committee will review the risk/benefit posed by the protocol rather than the usual research rationale. Data collection is usually limited to the collection of safety information. The protocol must define strict inclusion/exclusion criteria for participation in the program, as well as mandate any necessary patient monitoring required to maximize safety. Study monitoring is almost always confined to monitoring of inclusion/exclusion criteria to ensure that the product is used in a manner approved by the ethics committee.

The clinical trial approach places responsibility for tracking adverse events with the program sponsor, creating a dual-edged sword. On the one hand, sponsors remain in control of this pharmacovigilance data and can manage their product safety strategies accordingly; on the other hand, they are bound by the same adverse event reporting and medico-legal obligations as for other clinical trials. A higher than expected rate of serious adverse events, which can occur because the expanded access protocol is less controlled than a standard clinical trial, can jeopardize the breadth of a product label. In addition, holding a large amount of adverse event data on file can increase a company's medico-legal risk in the future.

Named Patient Approaches

Named patient approaches represent a regulatory compromise that allows physicians to seek regulatory approval for patient treatment on a case-by-case basis. Named patient approaches are commonly used in Europe, although the mechanics of each approach still varies from country to country. In the United States, the Emergency Use IND allows physicians to seek case-by-case treatment approval, although the FDA discourages this approach for large programs. In Australia, the Therapeutic Goods Administration provides named patient access through the Special Access Scheme (SAS). In most cases, manufacturers can streamline the named patient process for physicians by centralizing administrative resources and supporting the submission of individual patient applications on behalf of the physician.

The named patient approach toward expanded access requires less setup effort than the clinical trial approach. There is usually no protocol involved, and ethics committee approval is often not required although I have seen a growing expectation from regulators that physicians document risk management plans as part of the application process. Importantly, named patient approaches place greater responsibility for appropriate patient care on the medical community. Adverse event reporting usually follows the same approach as spontaneous post-marketing reporting, with investigators notifying the regulatory agency directly. While this can significantly diminish workload for a sponsor, there exists a disadvantage that the regulator has access to safety data that the sponsor does not.

Cohort Approach

The cohort approach is the simplest way of conducting an expanded access program, but it is currently limited to only a handful of countries such as France and Italy. Regulatory agencies require a special application from a sponsor, but they do not demand that physicians apply on behalf of individual patients. In effect, the cohort approach is tantamount to highly restricted regulatory approval, with significant responsibility resting with the physician to evaluate the appropriateness of treatment on the basis of available data and on an individual patient's condition. In France, companies can apply for a cohort ATU (Autorisations Temporaires d'Utilisation or Temporary Authorization for Use) at the time that they submit their application for marketing authorization. The cohort ATU allows companies to make their products available for restricted use, while committing them to a

program of regular progress reporting and pharmacovigilance activity for the duration of the program.

Reimbursement

Most markets provide manufacturers with the ability to recover costs from patients or insurance companies for products provided within an expanded access program. The cohort ATU in France allows companies to seek full reimbursement from the government pharmaceutical benefits scheme. In the United States, where insurers are reluctant to add non-approved products to their formularies, some companies have chosen to recover costs directly from patients. Although a sponsor can recoup some of the costs associated with running expanded access programs, pre-approval prices have historically been significantly lower than postapproval prices obtained for similar treatments, and there is little opportunity to renegotiate higher prices after approval has been granted.

Investigator Dynamics

Expanded access programs do not offer scientific immediacy or financial payment, but they do offer a significant patient benefit—the opportunity to access a treatment that is not yet publicly available. Since most programs address patients with life-threatening or debilitating diseases for which limited treatment opportunities exist, patients' motivation to participate is extraordinarily high. Irrespective of the workload imposed on investigators, site motivation is also high and over-subscription is common. Over-motivation of sites can result in significant investigator disappointment when program entry is capped or subsidy discontinued. Over-motivation of sites can present deeper problems than undermotivation of sites because it can result in a negative attitude toward a sponsor's whole product line as opposed to impacting only study performance.

Pitfalls

Providing subsidized product represents a significant cost to a sponsor. Running a program for a product that costs only \$100 per month, in anticipation of marketing approval twelve months later, is an investment of \$1,200 per patient in product alone. For every 1,000 patients enrolled in the expanded access program, the sponsor must make a \$1.2 million commitment. A year delay in approval can cost the sponsor the same amount again.

High drug costs drive most pharmaceutical companies to limit enrollment by region, type of physician, and number of patients per site. Because of the over-motivation normally associated with these programs, managing investigator expectations regarding caps and quotas is a difficult and sensitive process. How do you tell a key

Public Relations and Expanded Access

Managing public expectations regarding the limitations of expanded access activities can be a difficult commercial exercise. In 1997 Glaxo Wellcome announced the initiation of a 2,500-patient expanded access program for Abacavir, a promising new antiviral agent for the treatment of HIV. With only a limited range of HIV treatments available at the time, and with over 30,000 patients in the United States alone likely to qualify for treatment, patient activists severely criticized Glaxo for the size of the program. In June 1997 the AIDS activist group ACTUP seized the investor relations office of Glaxo Wellcome in New York, leading to numerous arrests. In parallel the group coordinated a boycott of Glaxo products including Zantac and Zovirax through a mass-mailing campaign to doctors and politicians. The group called off the boycott after Glaxo executives agreed to meet with advocacy leaders to discuss changes to the program.²

opinion leader keen to offer more patients access to the life-saving properties of a new drug that their cap has been reached? How do they communicate this to their patients?

A delay in market approval can place a sponsor in a difficult position. It is not uncommon for delays of six to twelve months to cost between \$1,000 and \$5,000 per patient. Multiply this by 5,000 to 10,000 patients enrolled in a successful program, and a market delay can cost up to \$50 million in additional drug alone. The alternate is canceling access to a truly life-improving drug, resulting in such bad feelings from patients and physicians toward a manufacturer that sales of their other brands may be affected.

Confronted with a possible catastrophic loss of goodwill, sponsors frequently choose to keep programs going in the face of authorization delays. Any pharmaceutical company considering an expanded access program must factor in a delay of between six and twelve months for approval and have a clear, up-front commitment to physicians regarding the size and length of the program in the absence of marketing approval. If it is necessary to end the program, a step-down approach is more palatable than sudden cancellation. Do this initially by limiting resupply to patients already enrolled.

It is good practice to involve a set of key opinion leaders in a steering committee from the beginning. The steering committee should participate in the design of the program and should be aware of total budget and cost of supply, so that they can take responsibility for establishing quotas. Having an independent steering committee can cushion negative market sentiment when expanded access programs need to be limited or delays in regulatory approval forces sponsors to reevaluate program costs.

References

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* Note: All citations to websites listed in this book were verified in May of 2005.