"ONE SIZE DOESN’T FIT ALL": Applying an Innovative Mindset to Post-Approval Research

A Bioclinica White Paper
Author: Kirsten Colling, Senior Director Global Operations, Bioclinica Post-Approval Research

Powerful Post-Approval Operational Strategies for the 21st Century

Post-approval research studies are becoming increasingly large and complex in the clinical research landscape. These programs are often massive in scope, engaging thousands of physicians and tens of thousands of patients. Unfortunately, post-approval operational strategies have not kept pace with the needs and demands of post-approval (Phase IV) research. Companies frequently apply the same rigor and processes to post-approval research that are used in pre-market studies designed for the registration of a new drug or device. Companies ought to leverage strategies, processes, standard operating procedures (SOPs), and technologies that are specifically designed for and more relevant to post-approval research.

Investing in Post-Approval Research

The pharmaceutical industry is making significant investments in Phase IV studies, as shown in this pie chart. In 2013, 13.7% of the total R&D expenditure of $52 billion was in the post-approval research space.

While overall R&D spend has experienced a 10.4% compounded annual growth rate since the 1980s, post-approval research has grown at an astonishing 15-16% each year.

Additionally, it should be noted that in the last 5 years, the number of agency-requested Phase IV studies has dropped from 39% to 17%. This indicates a shift away from regulatory-imposed Phase IV research to pharma companies taking greater control of their futures and proactively performing post-approval research. Of 16 companies polled, 82% were conducting post-approval research voluntarily.

The bottom line: There is a growing need to ensure that post-approval studies are conducted successfully and that companies achieve a healthy return on investment.
Common Challenges of Post-Approval Research

Registration studies (Phases I-III) conducted under an Investigational New Drug (IND) application are primarily designed to develop drugs that are safe and effective. For this reason, registration studies are closely scrutinized by regulatory authorities and companies have to apply strict regulatory rigor when executing these protocols.

Post-approval research, on the other hand, is conducted to satisfy regulatory commitments and/or to nurture marketed drugs. Additionally, post-approval research may be designed to:

- Collect data in a real-world setting to understand population demographics and epidemiology.
- Evaluate long-term safety in a more heterogeneous population as part of the drug approval process.
- Compare effectiveness of varying healthcare interventions in real-world practices.
- Support health outcomes and insurance reimbursements.

Distinguishing between the intent and objectives of Phase I-III clinical studies versus post-approval research is of critical importance for creating study strategies, supporting operational efficiencies, and preserving return on investment (ROI). For example, the rigor with which Good Clinical Practices (GCP) are applied is typically inversely proportional to the phase of the study. Therefore, according to this principle, post-approval research requires far less scrutiny and rigor than do registration studies.

The many and varied objectives of post-approval research studies create a unique set of challenges. For instance, post-approval research studies may:

- Be massive in sheer size and scope, requiring flexible and scalable resources.
- Have less restrictive inclusion/exclusion criteria, permitting all patients to be included in the study.
- Spark conflicting motivations from various stakeholders, including Clinical, Regulatory, Medical Affairs, and Marketing.
- Be under tremendous performance pressure to ensure return on investment (ROI), yet contend with cost constraints and tight budgets.
- Involve research-naïve physicians as well as experienced clinical research investigators, requiring more training and administration to maintain engagement.

When planning for post-approval studies, regulations also present a challenge to companies. Regulations are typically taken into consideration in the design and execution of a study, so the question “What regulations apply to Phase IV research?”
is a natural one. However, Phase IV research is not included in regulatory statutes or explicitly defined in the Code of Federal Regulations. Some quasi-regulatory agencies such as the Patient-Centered Outcomes Research Institute (PCORI) and Transcelerate are attempting to provide a framework and standards for the industry, but robust guidelines do not exist. In the absence of official guidance, companies often default to what they know: the Phase I-III regulations where everything is very clearly defined and spelled out. Unfortunately, by using the same regulatory guidelines in post-approval research that are used in registration clinical trials (Phase I-III), companies end up applying unnecessary rigor to their post-approval research. This leads to inappropriate design and execution, unnecessary processes, and increased resource requirements. The final result is that budgets are inflated and studies quickly become cost-prohibitive.

**Adopting a Post-Approval Mindset**

How should an organization respond to post-approval research’s unique objectives, distinct challenges, and lack of defined regulations? Certainly, the obligation remains to collect quality data that can defend endpoints, and to implement appropriate measures to ensure patient safety and privacy. However, beyond these basic elements, companies can and should think outside the box when it comes to post-approval research. Under mounting compliance and economic pressures, organizations can’t do the “same old, same old” and expect success. A new and innovative mindset is needed.

The first component of this new mindset is the understanding that “one size doesn’t fit all.” This does not only mean that registration study regulations need not be applied to post-approval research. It is the acknowledgement that each post-approval study is unique in and of itself. The goals of each study, the intent of the drug being researched, the size and characteristics of the patient population … all these factors and more must contribute to the development and execution of a specific post-approval operational strategy for each post-approval study.

The second component of a post-approval mindset is **flexibility**. Pre-market randomized controlled trials tend to be rigid in nature: a defined number of patients, an established number of sites, a structured set of data, etc. Post-approval research, however, has a great deal more variability. When establishing a post-approval operational strategy, organizations have to plan for change, fluctuations, unexpected patient and physician input, and more. Scalability and flexibility must therefore be built into the post-approval operational strategy from the beginning, with a full set of options at the ready should the course of the study take a surprising turn.

The third critical component of a post-approval research mindset is **patient-centricity**. Many organizations are engaging patient groups when developing their protocols. By keeping the patient’s perspective in mind when designing the protocol, the compliance and overall success of the study can be significantly improved.

---

**Case Study:** When Bioclinica was brought in to help with a client’s struggling global post-approval study of over 8000 patients, the Patient Outreach Center (POC) created outreach strategies to maximize the ROI of the study by improving patient engagement. Within the first six months of deploying the POC in this program, Bioclinica was able to increase the number of engaged patients from 31% to 46% resulting in an increase of 1132 active patients for a net increase of 14.6%. Similarly, the number of non-responders (patients who had not withdrawn consent but who weren’t providing data per the protocol) was reduced from 3323 to 2836, from 41% to 35% for a net decrease of 6%.

<table>
<thead>
<tr>
<th>14.6%</th>
<th>INCREASE in engaged patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>6%</td>
<td>DECREASE in non-responders</td>
</tr>
</tbody>
</table>

DECREASE in non-responders
INCREASE in engaged patients

**14.6%**

**6%**
increased. For example, data collection methods should be reviewed from the patient perspective to assess ease of use. Processes and tools should be adapted as necessary to make them user-friendly.

Another method of maintaining engagement is through the strategic utilization of digital technology. Patients won’t stay engaged if they receive nothing more than an occasional telephone reminder from their physician. The use of mobile applications can drive patient compliance through various features. For example, features such as calendar pop-ups to track appointments, alarm reminders for when to take medications, and alternate route alerts to avoid traffic problems on the way to a doctor’s office can significantly improve outcomes. With these features, patients are more engaged and thus become more invested in the clinical research process.

**Integrated Technology for Post-Approval Research**

In addition to adopting the right mindset for post-approval research, the use of appropriate technology can streamline post-approval research operations while decreasing costs and resources. When weighing the available options, companies should look for technology that will allow them to:

- Leverage flexible, scalable, customizable systems
- Access unique datasets and analytics, including real-time study metrics
- Maximize smart technology
- Support patients and protect critical data
- Enhance patient and physician compliance and engagement
- Obtain project metrics and quality/performance indicators
- Integrate datasets from multiple sources for deeper insights
- Enjoy full transparency for all stakeholders around the globe

This may sound daunting, but the good news is that companies usually do not have to build a technology platform from scratch. Many key technologies likely already exist, and layering existing technologies such as SMS text, social media, and patient forums allows a company to maximize and integrate technology which can improve the platform, enhance the patient experience in clinical research, and help support the product through commercialization and into the market.

**Post-Approval Research Mindset and Technology in Action**

To better understand how the combination of a post-approval research mindset and technology can help streamline the execution, costs, and administration of post-approval research, consider the following three examples: centralized remote monitoring, a patient outreach center, and a central data repository/portal.
Centralized Remote Monitoring

Traditional on-site monitoring is cost-prohibitive given the sheer scale of many post-approval research studies. Plus, the nature of post-approval research often requires lengthy timelines. Trials of five to ten years or more are not uncommon. Therefore, post-approval research studies benefit significantly from the implementation of a centralized remote monitoring model.

Successfully deploying centralized remote monitoring requires two things: people well-versed in a post-approval research mindset, and technology to connect all the moving parts of the study.

The people who are performing the monitoring need to understand the distinction between carrying out registration studies, where safety and efficacy are being determined, and supporting a drug post-approval, where there might be various goals. They must be sensitive to research-naïve physicians who do not have the resources to support the administrative burden of clinical research. Providing excellent service to all stakeholders should be their top priority.

Such a team of post-approval research specialists is best supported by a technology platform built with post-approval research in mind. With the use of a robust technology platform, in-house monitors can effectively decrease the site administrative burden by providing ongoing support for each protocol remotely. This keeps physicians engaged and can reduce site fatigue. This also decreases overall study costs without compromising quality, and ensures that regulatory standards for post-approval research are met.

Patient Outreach Center (POC)

As noted previously, patient-centricity is one of the pillars of a post-approval research mindset. Accordingly, establishing a patient outreach center can significantly boost patient recruitment, engagement, and retention.

A patient outreach center is not a typical call center as we know it. Staff should have a certain level of clinical competency, understand the objectives of the study protocols, and grasp the intent of patient-reported data. They need to be able to determine the answers to questions such as: How do patients want to be contacted? Why are certain patient populations disengaging? What strategies can increase patient engagement? How can the amount of electronic patient-reported data be increased?

Once again, a patient outreach center functions not only because of its people, but because of its technology. The IT infrastructure and firewalls need to be secure so that staff members can reach out directly to patients to get electronic patient-reported data. Patient data must be maintained according to strict privacy and data protection regulations.
Central Data Repository/Portal
A third area where technology that incorporates a post-approval-specific mindset can be leveraged is in the establishment of a central data repository/portal.

All too frequently, the various components of post-approval research are handled in discrete silos. For example, data managers oversee the integrity of the data collected, the pharmacovigilance group ensures that Adverse Events are reported per regulations, and project managers watch budget, time, and scope. Trying to gather these separate threads and weave them into a whole cloth is time-consuming and effort-intensive at best, and impossible at worst.

A central data repository, on the other hand, performs the collection and integration of data automatically, making it possible to gain a holistic view of multiple datasets, analyze data in real-time, and assess the study’s progress.

The repository should be available to all study stakeholders through a central portal. Ideally, this portal will have unique, customized interfaces for the different stakeholders. For instance, physicians would be able to retrieve metrics on study performance. Sponsors could access reports on efficiency, costs, compliance, etc. Contract research organizations (CROs) would be able to review safety information. The data repository and portal therefore work together to streamline both the collection and the dissemination of data.

Harnessing the Power of a Dedicated Post-Approval Research Team
Ultimately, the secret to successfully conducting post-approval research is very simple: treat post-approval research as post-approval research – not as a registration study. Phase IV is entirely distinct from Phase I-III. Approaching post-approval studies with the right mindset and supporting them with technology designed for post-approval research can increase patient compliance and data collection by 25-30% compared to traditional PRO technologies, plus reduce resource burn, translating into 15-20% overall cost savings on programs.

With the pressing need to obtain real-world data, assess product safety profiles, and support the full span of a product’s lifecycle, the ability to conduct efficient, cost-effective post-approval studies is more important than ever. It’s time to bring post-approval operational strategies into the 21st century.

**Bioclinica’s Post-Approval Research division** is comprised of a dedicated team with experience in designing and executing post-approval research. Our full-service solution includes comprehensive post-approval services, from program design and protocol development to regulatory submissions.

To learn more, contact the Bioclinica Post-Approval Research Division experts at post.approval@bioclinica.com or visit bioclinica.com.