



○ Featured Article

Considerations for Applying Good Clinical Practices to Phase IV Research

Dave Provost

Vice President, Global Post Approval, INC Research



As the importance of post-approval research has increased in the overall product lifecycle of drugs, biologics and devices, discussions regarding the extent to which the International Conference on Harmonisation (ICH) Good Clinical Practices (GCPs) apply to Phase IV studies have become more prevalent and more meaningful. The increased use of Phase IV studies to meet regulatory and other government agency requirements is certain to lead to increased scrutiny of these studies and thus discussions of appropriate implementation plans are critical. These discussions, however, are not straightforward. There are no regulations or guidance documents specifically intended to guide the conduct of Phase IV studies. As such, there is significant variability within the industry regarding best practices for Phase IV study implementation and how GCPs are to be applied.

Before discussing GCPs and Phase IV studies, let's begin with a few definitions to establish a common ground. Phase IV studies are those conducted after a product is approved and, most often, within the product's approved indication. They are meant to support a product's label and to help ensure a product's optimal use within the physician community. The ICH General Considerations for Clinical Trials (E8) document refers to these studies as "therapeutic use" studies. The E8 document suggests that identifying studies by their objectives (e.g., therapeutic confirmatory, therapeutic use) may be more appropriate than by their temporal phase (i.e., Phase II, Phase III) as often the trial sequence for a product in development is not a simple progression from Phase I through Phase III. For this discussion, we will refer to Phase IV studies of approved product and approved indication as "therapeutic use" studies.

Within the "therapeutic use" segment, Phase IV research models include safety studies, observational research studies (e.g., patient registries), comparative effectiveness studies, health outcomes studies (e.g., patient-reported outcomes studies, pharmacoeconomic studies), drug-drug interaction studies and various other designs intended to provide support for a product's existing labeling. This grouping can be further divided by those studies required by a regulatory authority (FDA, EMEA) as part of a product's approval vs. those that are conducted on a completely voluntary basis by the product's manufacturer or sponsor.

Some Phase IV studies are conducted with the intent to expand the currently approved indication for a product via new product doses, new modes of administration or new patient populations. Other studies seek to add one or more new indications to the product's label. Many Sponsors will consider such label expansion studies to be Phase IIIB studies or even classify them as earlier phase research depending on the study design and objectives, though some continue to categorize them as Phase IV. The E8 term "therapeutic confirmatory" will be used to refer to Phase IV studies whose objective is to demonstrate safety and efficacy beyond a product's current label.

The ICH GCP guidelines were written with a focus on pre-approval research. This focus is clear from the "Introduction" to the guidelines which state: "This guideline should be followed when generating clinical trial data that are intended to be submitted to regulatory authorities." GCPs are designed to ensure the highest level of protection for human subjects, and to help provide a scientifically sound framework for the conduct of clinical research. They are also meant to support the acceptability, by regulatory authorities, of the data collected. They are meant to help ensure that the Phase I, II and III data presented to a regulatory authority for approval and marketing authorization is unbiased and, to the extent possible, representative of a product's true safety and efficacy profile. Because of this pre-approval focus, Phase IV studies are not specifically defined or referenced within the ICH GCP Guideline or in the US Code of Federal Regulations (CFR). As such, some have considered Phase IV studies to be outside of GCPs and have conducted such studies without meaningful adherence to them.

Whether the data from a Phase IV study is intended to confirm therapeutic benefit and support an additional regulatory submission or to support therapeutic use and generate publications for the benefit of the medical community, adherence to the core tenants of the GCP Guideline is a best practice that should be followed. It is important, however, to assess the level of “to-the-letter” compliance with GCPs on a per study basis.

For example, Phase IV-therapeutic confirmatory studies are best served with full compliance to GCPs as these studies are designed to collect data that will be submitted to a regulatory authority in support of a change in product labeling. The applicability of GCPs for this type of study is specifically stated in the GCP Guideline document (see “Introduction” quote above). Making the case for full GCP compliance for these types of studies is easy and hard to counter argue.

In contrast, attempting to achieve “full GCP compliance” while implementing a typical Phase IV-therapeutic use (non-submission) study would create unnecessary implementation complexities and provide minimal, if any, benefit in terms of patient protection or data quality. So, it is typically best to assess the intent of each GCP in the context of the Phase IV study being considered and develop specific rules of study conduct that support the intent if not the verbatim practice. This is best supported by a few examples.

- The monitoring of study sites is a key area in which Phase IV study implementation can differ from pre-approval research. Site monitoring, as defined in the GCP Guideline, looks to verify that study sites are following the protocol, are providing quality data to the study and that the rights of enrolled subjects are being protected. To accomplish this, the Guideline states, “In general there is a need for on-site monitoring...” The size of many Phase IV studies, however, can make regular on-site monitoring of sites an overwhelming resource and logistics burden. To address this, many Phase IV studies, especially those falling into the non-submission/therapeutic use category use centralized or in-house site management procedures to help ensure sites are kept on track. The Guideline allows for “central monitoring” in conjunction with other physician-directed support tools, so the keys to GCP compliance in this area are development of effective site management call strategies and strong site training and support materials.
- The label of each approved product defines its indicated use(s), proper dosing, mode of administration, potential adverse events, The label also provides summary information on the outcomes of the studies conducted that led to the product’s approval. With the information included in a product’s label, a practicing physician should have what he or she needs to clinically manage a patient using the product within an “approved product, approved indication” study. As such, physicians participating in non-submission Phase IV studies are well-served by a current copy of product’s label vs. an Investigator’s Brochure (IB).
- Studies of approved, marketed products do not typically present the same level of risk for physician biasing of study outcomes based on the physician’s financial interest in the product. As such, it is typical in non-submission Phase IV studies not to collect full financial disclosure information from participating physicians.
- As physicians participating in Phase IV studies do not manage investigational, unapproved product as part of their study conduct, the form FDA 1572 is often not part of the essential documents collected during the startup of the study; other tools are used to ensure each potential physician is qualified to participate.

Regardless of the type of Phase IV study being conducted, there are several critical GCPs that should always be followed:

- Every prospective Phase IV study should have a protocol. The protocol should be developed by qualified personnel, include appropriate clinical objectives and not present undue risk to those agreeing to participate.
- The protocol and all patient materials should be reviewed and approved by an Institutional Review Board (IRB)/Ethics Committee (EC) prior to the start of study enrollment.
- Every study should include an IRB/EC-approved informed consent form (ICF) that patients must sign before participating in any study-related procedures. Patients should be given as much time as they need to read the ICF, and should have the opportunity to ask study personnel questions about the study and/or the ICF before signing it.
- All participating physicians should be pre-qualified to ensure they have the appropriate training and experience to successfully participate in the study being considered.
- All participating physicians and associated study staff should be formally trained on the study protocol and study procedures, with retraining as necessary.
- Participating physicians should be contacted on a regular basis throughout the course of a study, using a combination of telephone contacts and on-site visits when appropriate, to ensure their ongoing compliance with the study protocol and implementation procedures.

In summary, Phase IV studies – whether collecting data for submission or not – should all adhere to the core constructs of the ICH GCP Guideline and evaluate individual practices on a per study basis to ensure the appropriate level of compliance and implementation effectiveness. Lack of explicit reference in the US and international GCP documents is not a “free pass” to ignore proper research methods.

At INC Research, our experience in post-approval research gives us the perspective you need in a Phase IV partner. We can help ensure that the design and implementation of your Phase IV studies meet the necessary regulatory requirements as well as the need for efficient use of resources and budgets. We understand the nuances of post-approval research and we're ready to help you succeed.

Dave Provost, Vice President, Global Post Approval at INC Research, manages operations within the Post Approval unit, as well as providing strategic consulting to clients regarding the design and implementation of their global late phase programs. He has nearly 20 years of pharmaceutical industry experience, all within the peri- and post-approval areas. He offers deep expertise in program design and implementation strategies. In addition to clinical research, Provost also has a background in health outcomes, market research and data collection and presentation technologies.