

Continuation strategies for Phase IV trials

Is the sequel better than the original?



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When our clients have sponsored a successful Phase IV trial, many consider strategies for continuing the trial or planning a sequel. But, like movies, is the sequel ever better than the original? In this article, we share our experience with successful continuation strategies for the extension of clinical trials.

There are many reasons why a follow-up post-marketing trial with similar investigators and patient types is a good idea. First is continued presence in the marketplace. We have observed that the marketing value of a Phase IV trial diminishes with time and competition with programs for other drugs, so a second trial is a natural way to extend the market effectiveness of a trial. As the French writer Alexandre Dumas said, "Nothing succeeds like success." So why not continue a successful strategy, especially when your investigators are onside? They are familiar with the processes of data collection and submission, and are comfortable working with the Clinical Research Organization (CRO) or internal group involved. Standard Operation Procedures (SOPs), technical requirements, web entry forms and other tools have already been used and do not need to be re-explained even if the protocol of the new trial is not identical to that of the original. Logistics can be streamlined, procedures refined or made easier and previous mistakes avoided while preserving all the good elements of the first trial.

Furthermore, there is a difficult-to-identify



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but often-observed phenomenon in clinical trials called "momentum." Investigators just seem to be on the lookout for eligible patients and have habituated themselves to including the trial in their day-to-day activities. Also, physicians who were unable to participate when the first initiative was launched may be able to join the second trial. The cost and time to value ratio for all participants, the sponsor and physicians are reduced.

If you have made the decision to have a continuation strategy, there are a few factors to consider. Foremost is an evaluation of how you will differentiate the sequel from the original. Consider using a survey or a closing meeting to gauge

interest in continued participation. If the interest is there, a number of strategies are possible. Many pharma companies use the first trial as more of a hypothesis-generating tool and to document practice in order to discover practical research questions. Subsequent trials investigate these questions. Physicians' insights and needs that even the sponsor was not aware of may emerge, and they can be satisfied in a follow-up initiative. For example, the second or third protocol may use very similar techniques, but study a sub-population, probe new clinical parameters or be a refinement of the measures used in the first trial. While the first trial is more closely allied to

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Can PMOS provide answers to important questions?

Drug's safety and use in real life require real-life study



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Approval to market a drug is granted based on the demonstration of adequate efficacy and safety through well-designed clinical trials. Controlled clinical trials rarely mirror the real world, however. In particular, they:

- ⊕ Include a limited number of patients;
- ⊕ Last for relatively short periods of time;
- ⊕ Under-represent patient populations;
- ⊕ Have more compliant patients;
- ⊕ Use surrogate (short-term) outcomes; and,
- ⊕ Generally lack a direct comparison with drugs in the same therapeutic class used for the same indication.

These limitations make it highly desirable to perform different research in the post-marketing phase to supplement

pivotal trials. Once a drug has disseminated in the market, a number of important questions arise. How will a drug perform once it is more widely prescribed? What safety concerns will arise when many people use a drug? How will it benefit people when compared to alternative therapies? If there are benefits, will they be worth the cost? For example, the high cost of a particular drug may limit its access to

a significant segment of the population, rendering it ineffective to society as a whole.

An important issue is how these questions can be studied. To gather evidence on the benefit or safety of an intervention in real life requires that a real-life situation be studied. This implies that the intervention should be applied in a non-controlled



manner to patients who are judged by the clinician to be appropriate candidates to receive the intervention. The frequency and duration of follow-up cannot adhere to a specific protocol, but must instead follow the clinician's routine practice. More importantly, specific patient characteristics – such as co-morbid conditions, the use of concomitant medications, and individual attributes that affect compliance – must not be controlled for the purposes of the investigation.

One approach that aims to address these issues is the Post-marketing Observational Study (PMOS). The PMOS is a non-interventional, observational study commonly undertaken to capture, in a real-world setting, more in-depth information on treatment patterns, clinical effectiveness, potential drug interactions, and patient-reported outcomes, such as adverse events, adherence/compliance, health-related quality of life (HRQOL), and satisfaction associated with a particular treatment (e.g., drug, medical device).

The design of the PMOS differs in several significant ways from that of the controlled trial. Its distinguishing feature is that there is little or no control required by the protocol of factors such as patient characteristics, the methods of patient management, and the duration and frequency of follow-up. Instead, the broad eligibility criteria are based on product labelling, and physician visits or procedures are

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Clinical Trials: A Comparison

	Randomized Controlled Trial	PMOS
Objective	<ul style="list-style-type: none"> • To provide confirmatory evidence of a product's efficacy and safety 	<ul style="list-style-type: none"> • To evaluate benefit and safety of a product in a real-world situation
Principal Intent	<ul style="list-style-type: none"> • To fulfill requirements for market authorization or to provide evidence sufficient to make a pivotal claim, change the label or support a new indication 	<ul style="list-style-type: none"> • To assess the performance and safety of a product in larger and special populations over longer periods of time • To provide continuous re-evaluation of a product's benefit/risk ratio to gain insights into post-marketing safety, clinical effectiveness, healthcare resource utilization and patient out-of-pocket expenditures
Design Features	<ul style="list-style-type: none"> • Complex study protocols • Small number of patients • Uses a comparator • Complex case report forms • Use of surrogate endpoints • Strictly mandated procedures • Rigid eligibility criteria, which may not reflect the general population • Relies on experienced investigators 	<ul style="list-style-type: none"> • Simplified study protocols • Large number of patients • No comparator used • Abbreviated case report forms • Data collection of clinically meaningful endpoints • Few protocol-mandated physician visits or procedures • Broad eligibility criteria based on product labelling • Relies on community-based physicians

Patient registries: The ethics of data collection and use

Both mandated and private registries require high standards



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One of the newest tools helping the pharmaceutical industry commercialize drugs is the disease or drug registry. A registry is a cohort of patients who are followed longitudinally in an observational manner. Registries collect a wealth of valuable patient data and in some cases have advantages over clinical trials. For example:

- ☑ Registries are typically less costly;
- ☑ They contain a much larger number of patients;
- ☑ They collect real-world data;
- ☑ They track actual outcomes; and,
- ☑ They are more flexible in terms of research objectives, which might evolve over time.

Registries have inherent weaknesses and strengths. On the one hand, they are not controlled, comparative studies, so they may not provide definitive, rigorous answers to research questions. On the other hand, because of the breadth of patients captured, registries are often very useful in generating hypotheses, highlighting trends and providing impetus for more specific research efforts. They also generate data that reflects the actual clinical use of a product over large numbers of patients, providing a more realistic view of patterns and outcomes of drug use. Such information is convincing and can influence payers, physicians and even patients.

Probably most familiar are drug registries mandated by federal regulatory agencies to monitor a specific adverse drug reaction in an otherwise safe drug, such as those for Accutane® in the U.S. or Clozaril®. However, a registry can also focus on a disease. Disease-based registries can collect valuable epidemiological, treatment practice or outcome data.

Historically, registries were hospital- or government-driven initiatives. However,



companies are interested in sponsoring registries for their drug or a key therapeutic area in order to partner with key opinion leaders and collect important information about the practice environment and their products. Unlike clinical trials, in which practice guidelines and ethical considerations have been clearly established, the principles governing these registries are not as well defined.

for the reasons outlined above, many “private,” that is, non-government-funded, agencies such as pharmaceutical

However, as shown in Table 1, these registries are similar in many respects to

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Table 1. Mandated vs. Non-Mandated (Private) Registries

	Mandated Registry	Non-Mandated (Private) Registry
Sponsor	<ul style="list-style-type: none"> • Manufacturer or central agency as mandated by a regulatory body 	<ul style="list-style-type: none"> • Professional organization or company
Primary Objective	<ul style="list-style-type: none"> • To collect epidemiological/safety data 	<ul style="list-style-type: none"> • To collect epidemiological/safety/efficacy/disease data that will be used for research objectives
Examples	<ul style="list-style-type: none"> • Clozaril® Support & Assistance Network • Central Cancer registries • Canadian Blood and Marrow • Transplant Group (CBMTG) registry • U.S. Accutane® pregnancy registry 	<ul style="list-style-type: none"> • Fastrak thrombolytic hospital registry
Guidelines	<ul style="list-style-type: none"> • North American Association of Central Cancer Registries: Standards for Cancer Registries Volume III • Should use Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans 	<ul style="list-style-type: none"> • No specific guidelines or legislation • Should default to use Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans
Ethical Issues	<ul style="list-style-type: none"> • Should be reviewed by an ethics committee • Participation of stakeholders mandated by legislation • Consent not necessary • Confidentiality protected 	<ul style="list-style-type: none"> • Should be reviewed by an ethics committee • Consent necessary • Confidentiality protected
Data Access/Ownership	<ul style="list-style-type: none"> • Patient owns data • Sponsor or central registry owns database and controls access 	<ul style="list-style-type: none"> • Patient owns data • Sponsor or central registry owns database and controls access

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determined by clinical judgment or best practice. Other differences between the controlled trial and the PMOS are worth noting. Treatments in the PMOS are generally not provided by the sponsor, but are reimbursed either by the regular third-party payers or the patient. The protocols in the PMOS are generally simplified, the data recorded are obtained from community-based physicians and are usually less detailed and outcome measures are usually well-accepted clinical indicators of treatment effect rather than standardized outcomes observed in controlled trials. Because of these features, the PMOS requires less monitoring to ensure data quality and patient safety, and patient recruitment tends to be easier and faster. These factors permit large amounts of data to be collected at a significantly lower cost, a potential that seems to be underused.

In recent years, because of increased concern regarding the safety of approved medications, the focus of observational studies has been to identify risk-management signals earlier in a product's life cycle. However, observational studies can deal with a number of other important questions of interest to health providers. The data may be used to identify special patient

populations for whom the effectiveness of a product may be altered, or who are at higher risk for adverse reactions (e.g., women who are pregnant or lactating, children, the elderly, people with impaired organs, etc.) and can identify the occurrence of serious but, as yet, unlabelled events, drug-drug interactions, product abuse or misuse, and the effects of long-term exposure. The PMOS is also a valuable planning tool to evaluate current treatment patterns, product utilization and associated costs.

A properly designed and executed PMOS can provide valuable information to regulatory agencies and patients regarding the safety and effectiveness of a product, and can also reveal the factors that influence physicians and patients to prefer one course of treatment over another. The appropriate use of this information can allow sponsors to convey information that could influence the beliefs and practices of healthcare providers and inspire patient confidence. In turn, this can increase market share through ethically and scientifically sound methods.

For more information about post-marketing observational studies, contact Thomas Jaeger at 1.800.811.9880, ext. 129, tjaeger@phase4health.com.

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mandated ones, and require the same level of rigour regarding privacy and consent.

As a general rule, therefore, when designing a registry, sponsors should have an ethics review conducted prior to setting up the registry and initiating any research involving registry data. Patients should also sign an informed consent form that specifies how their data will be used. These measures will help ensure that data in the registry can be used at a later date for research purposes. It is also helpful to form a registry advisory board at the outset that will, among other functions, determine foreseeable uses for the data, specify what data will be collected and how to manage access to the data and review requests for research that will use the data. By following these guidelines, sponsors will help ensure that their registry is conducted in an ethical manner and that it is properly designed to collect data that will be useful for future research and health initiatives.

For information about drug registries, contact Dimitris Polygenis at 1.800.811.9800, ext. 121, dpolygenis@phasehealth.com, or Nabil Tadros, ext. 109, ntadros@phase4health.com.

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traditional clinical indicators and research-based parameters, the second may examine un-researched symptoms or parameters.

Trials by their nature capture "instantaneous" data so that subsequent trials may provide more data on the longitudinal progression of the same or other patients.

Of course, a second trial may use the same methods as the first, but attempt to capture a different investigator group. For example, you could target investigators who dropped out or showed initial interest, but could not participate. For a successful trial that has

yielded interesting data, you could expand the target investigators to include more primary care-oriented sites. If your trial has an important or relevant methodology, many of those who prescribe or might prescribe your product will be interested in participating.

A continuation of a trial is not without challenges, however. We all want to avoid the "I liked the first one better than the sequel" perception. Therefore, either the content or the target audience must change. You should ask a new clinical question, target different physicians or include some element that will retain the interest of the first group. In one Phase IV trial we conducted, the "original" investigators collected an expanded group of

clinical parameters, allowing them to stay involved and study richer data.

Phase IV trials require a great investment of time, energy and resources to get going. All companies should consider maximizing the return on their investment by continuing existing trials. Done correctly, the sequel is not just a rehash of the original, but a logical, well-thought-out continuation of an already worthwhile project.

For more information about continuation strategies for Phase IV trials, contact Dr. Ravi Deshpande at 1.800.811.9880, ext. 102, rdeshpande@phase4health.com.

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