Strategies for Continuing 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 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 the continued presence in the marketplace. We have observed that the marketing value of a Phase IV trial diminishes with time and with 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 Operating 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.

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Second, there is a difficult-to-identify, 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 investigators are reduced.

If you have made the decision to have a continuing strategy for a Phase IV trial, 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 pharmaceutical companies use the first trial as a hypothesis-generating tool, (*i.e.* 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 (*e.g.*, the second or third protocol may use very similar techniques, but study a sub-population, probe new clinical parameters or refine the measures used in the first trial). While the first trial is more closely allied to traditional clinical indicators and research-based parameters, the second trial may examine un-researched symptoms or parameters. Trials, by their nature, capture instantaneous data; subsequent trials may provide more data on the longitudinal progression of the same or other patients.

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Of course, a second trial may use the same methods as the first, but attempt to capture a different investigator group (*e.g.*, 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.

However, a continuation of a trial is not without its challenges. 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 that 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. **CPM**

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